



Alzheimer's
Australia
Living with dementia



Quality Dementia Care:

Understanding Younger Onset Dementia

Commissioned by Alzheimer's Australia
Prepared by Melbourne Neuropsychiatry Centre,
Royal Melbourne Hospital



Quality Dementia Care Series: Understanding Younger Onset Dementia

April 2008

This publication was supported by funding from the Australian Government Department of Health and Ageing, under the National Dementia Support Program. The opinions expressed in this document are those of Alzheimer's Australia and not necessarily those of the Australian Government.

Foreword

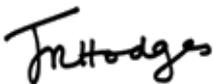
It is a great pleasure to be asked by Alzheimer's Australia to write a brief preface to this outstanding booklet which I am sure will provide a much needed resource for all health professionals involved in the care of people with younger onset dementia as well as family members. The team from the Melbourne Neuropsychiatry Centre, Royal Melbourne Hospital are to be complemented for writing such an authoritative yet accessible booklet.

Younger onset dementia is a profoundly incapacitating, and ultimately fatal, disease which presents enormous problems for the whole family but has for too long been overshadowed by other neurological disorders. This booklet will help it gain a more rightful place by raising the profile of the disease amongst the medical profession and perhaps improve funding for both research and care of this devastating disorder.

There have been enormous advances in our understanding of dementias in general, but particularly Alzheimer's disease and frontotemporal dementia, which have been my own area of particular interest for almost two decades. We can now much more accurately separate and diagnose different forms of dementia which is an essential prelude to providing accurate information to families. Sadly there is still no drug that can reverse the course of the dementias although we do now have drugs that alleviate the symptoms and perhaps slow the rate of decline. It is of my own view, that the most fundamental developments have been in the field of genetics, which has in turn shed light on the underlying cell mechanisms in dementia, and in brain imaging which has revolutionised diagnosis and tracking of the dementias. Both of these areas are well covered in this booklet.

It is really self-evident that younger onset dementia is an awful condition and affects people at the prime of life when they are looking forward to their long earned retirement and also often have dependent children and living parents. The diagnosis in the early stages can be particularly difficult. Most general practitioners receive very few patients with young onset dementia. It is not surprising the diagnosis can be missed and that initial symptoms are attributed to stress or depression. Although there have been enormous advances in the scientific aspects of dementia there remains no substitute for the opinion of a skilled clinician who spends time with the person and their family.

The publication of the booklet coincides with my move from Cambridge to take up a Federation Fellowship at the Prince of Wales Medical Research Institute (POWMI), Sydney where there are excellent neuropathology, genetic and neuroimaging research groups. It is an ideal milieu for developing a multi-disciplinary research team comprising of clinical and research psychologists, occupational and speech therapists working in close co-operation with basic scientists all focusing their efforts on this important medical topic. I am proud to be part of this team and think we are well placed to make substantial progress over the next few years.



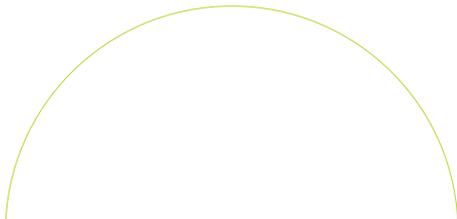
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Purpose of this booklet

The Alzheimer's Australia Quality Dementia Care Series provides complex information in an accessible form for use by people living with dementia, families, carers and health professionals.

***Understanding Younger Onset Dementia** is a practice- and evidence-based booklet summarising the neuropathology and characteristics of the different dementias occurring in younger adults under 65 years of age. This booklet provides information of assistance to health professionals and others on the different types of dementia diagnosed in younger people and explains many of the characteristics of the associated changes that occur with younger onset dementias.*

The content has been partly determined by workshop presentations by the staff at the Neuropsychiatry Unit of the Royal Melbourne Hospital to people with younger onset dementia, families, carers and professionals and the work of Dr Adrienne Withall. The remaining material has been derived from medical journal and other scientific publications.

Acknowledgements

Alzheimer's Australia would like to acknowledge the authors Dr Ramon Mocellin (neuropsychiatrist), Dr Amelia Scholes (neuropsychologist) and Dr Dennis Velakoulis (neuropsychiatrist) of the Melbourne Neuropsychiatry Centre, Royal Melbourne Hospital, the University of Melbourne and Melbourne Health. The contribution of Dr Adrienne Withall (psychologist and research fellow) of the Primary Dementia Collaborative Research Centre is also acknowledged. The authors would like to acknowledge the assistance of colleagues in the Neuropsychiatry Unit including Ms Joanne Bevilacqua, Ms Kathryn Miller and Dr Mark Walterfang. We are grateful for the comments of Prof John Hodges and the Alzheimer's Australia National Consumer Committee on the document.

Melbourne
Neuropsychiatry
Centre



1. What is younger onset dementia?

Dementia is a brain disorder causing progressive change and degeneration in cognitive mental functions, such as memory, language, rational thinking and social skills, as well as behaviour, emotion and personality. Most brain disorders causing dementia occur in the elderly but dementia can also occur in younger people.

Younger onset dementia, early onset dementia and presenile dementia are all terms that refer to dementia developed before the age of 65. Younger onset dementia has gradually become preferred because early onset dementia can also refer to people in the early stages of dementia at any age. Based on available research evidence, of which more is required, about five percent of all those with dementia (about 10,000 people in Australia) are under 65 years of age.

Younger onset dementia may be caused by Alzheimer's disease, frontotemporal lobar degeneration, stroke, Parkinson's disease, Lewy bodies and other neurological conditions, many of which are described in this booklet. Since dementia is rare in younger people, symptoms of these diseases may be difficult to diagnose accurately and initial misdiagnosis may delay appropriate treatment and care. Brain injury, HIV-AIDS and alcohol may also cause dementia in younger people, however dementia in these cases usually occurs within the context of an obvious cause and is thus more readily diagnosed and treated.

2. Diagnosing Dementia

Dementia can often be difficult to diagnose as it shares many features with normal ageing and other common conditions. Depression, for example, may be a symptom of dementia or may cause symptoms similar to dementia. As a result, depression may need to be diagnosed and treated before dementia can be accurately identified. Younger onset dementia can be particularly difficult to diagnose simply because it is less common and often caused by rare, unfamiliar medical conditions. Dementia in younger people can also cause different symptoms to those observed in older people.

The diagnosis of dementia in younger people is often longer and more protracted than for older people. Diagnosis can be complex and require extensive investigation. It may take a long time, even several years, causing individuals and their families a great deal of anxiety. Many people visit several specialists and hospitals and undergo multiple tests and brain scans before finally being diagnosed. Such delays not only compound anxiety, but they also delay treatment and affect disease progression. Good communication between families and health professionals during this process is essential to help families cope with changes that are difficult to understand.

Diagnosis may be both a shock, and a relief. A diagnosis of dementia is usually a shock to younger people because it is commonly regarded as a disease of the elderly. As such, it is important to communicate this diagnosis sensitively to help people adjust more quickly to their changed circumstances. Insensitive diagnosis may cause anger towards the diagnosing doctor and difficulties accepting the diagnosis. Once a diagnosis is made, most people feel they can move forward and learn more about the dementia and how to live with it. Some people may prefer to discuss 'memory loss' but they need to understand that such memory loss is not benign and will progressively worsen.

Diagnosis and assessment of younger onset dementia often involves a number of health professionals. A general practitioner will often be the first medical contact, but diagnosis is usually made by medical specialists such as neurologists, neuropsychologists, geriatricians, psychiatrists, old age psychiatrists or neuropsychiatrists using assessments and input from other health professionals. Specialist opinion is essential, not only for correct diagnosis, but also to ensure there are no other treatable medical conditions.

The assessment team

General Practitioners are often the first point of contact for families and people with dementia and may be responsible for initial identification of a problem and referral for specialist assessment. They may remain a significant primary contact point for medical support for the person and their family throughout the illness.

Neurologists/Geriatricians/Psychiatrists/Old Age Psychiatrists/Neuropsychiatrists specialise in neurological and/or psychiatric medical conditions and provide the primary source of specialist medical expertise for people with dementia, their families and GPs. They may be responsible for co-ordinating and/or referring other specialist services.

Neuropsychologists specialise in brain-behaviour relationships. They integrate information from a range of validated, standardised tests with information on the person's pre-illness intellectual functioning, developmental, medical, psychiatric and family history. They also include information about behaviour, mental state and personality.

Occupational therapists measure a person's ability to function in their own environment. This functional assessment can take place in the person's own home or workplace to assess levels of support and risk and plan strategies to help the person stay safely in their home as long as possible. Occupational therapists are also involved in driving assessments.

Social workers are primarily responsible for ensuring people and their families have access to the information and resources they need to support them during the illness. Social workers may also undertake a psychosocial assessment to identify areas of need and plan for change. Services

and support vary but may include carer services, respite opportunities, recreational activities and accommodation options. Social workers may also be involved in arranging guardianship and administration orders.

The medical assessment

Particularly in the early stages of dementia, there are no definitive tests that will identify that dementia is present, or the type of dementia, with absolute certainty. A clinical diagnosis of dementia is made on the basis of information gathered from all sources. Despite detailed assessment the diagnosis may sometimes remain uncertain. Sometimes a re-assessment in six to twelve months is necessary to see if symptoms have changed or if any new symptoms have arisen. It is important that people with dementia and their families attend these re-assessments and are followed-up by the assessment team.

Specialist medical assessment of dementia includes a detailed personal history of symptoms and medical problems and a family history of any disorders in other family members. This information is provided by the person, family and carers. Neurological examination (for example, testing reflexes, muscle strength, eye movements) and some testing of memory, language and other cognitive functions are also conducted.

Cognitive screening and testing examines changes in a person's cognitive functions such as memory, orientation and planning. Cognitive screening is performed when a person complains of impaired memory and cognition. Screening at this stage evaluates global, or overall, cognitive function often using the Mini-Mental State Examination (MMSE). Newer tests which are briefer and perhaps easier to administer include the General Practitioner Assessment of Cognition (GPCOG), Memory Impairment Screen and the AD8 Dementia Screening Interview although these are not sensitive to early stage dementia particularly frontotemporal lobar degeneration. More intensive cognitive testing is conducted by a neuropsychologist to evaluate performance across a range of skills including memory, language, orientation, attention, visuospatial skills, speed of information processing and higher order executive functioning. People with dementia can be aware of their cognitive difficulties and may find such

assessments confronting. A supportive and stress-free environment is beneficial during testing.

Blood investigations look for medical conditions that may explain and/or contribute to symptoms. These may include tests of thyroid, kidney and liver function, levels of calcium, phosphate and vitamin B12, as well as the presence of syphilis and HIV, depending on the findings of the medical specialist's assessment.

Genetic blood testing is available for some types of dementia. Many familial dementias are younger onset and family members are often concerned about dementia being inherited. While some genes have been clearly implicated in familial Alzheimer's and frontotemporal dementia, most people with familial dementia inherit it in a complex fashion with genetic contributions from a number of different genes. The best known of these is the apolipoprotein E gene (APOE). If a genetic disorder is suspected, a referral to specialist genetic counsellors should precede any testing. Such counselling is needed to address the complex issues that genetic testing raises for people with dementia and their families.

A lumbar puncture may be required to rule out alternative causes of symptoms if the dementia has been of rapid onset or is associated with unexplained seizures or neurological findings. This test is usually performed by a radiologist and requires the removal of a small amount of spinal fluid through an injection in the lower back.

Structural brain scans are an essential component of dementia assessment. Computerised tomography (CT) uses X-Rays, while magnetic resonance imaging (MRI) uses magnetic fields to provide an image of the brain structure i.e., what the brain looks like, whether there are any areas of stroke, white matter disease or areas of brain shrinkage (atrophy) (Figure 1).

Functional brain scans examine the activity of the brain. **Positron emission tomography (PET)** and **single photon emission computerised tomography (SPECT)** use labelled radioactive chemicals to assess the brain's energy use by measuring blood flow or metabolism in the brain (Figure 2). Different patterns of energy use are associated with different types of dementia. Newer types of PET scans also provide images of the



Figure 1. Normal MRI scan of the head

different types of abnormal protein that collect in the brain.

Psychiatric assessments may also be needed if the person's cognitive changes are caused or exacerbated by the impact of conditions such as depression, paranoia or irrational thoughts. If mental health problems are the cause of the cognitive changes then the effects may be transient and treatable.

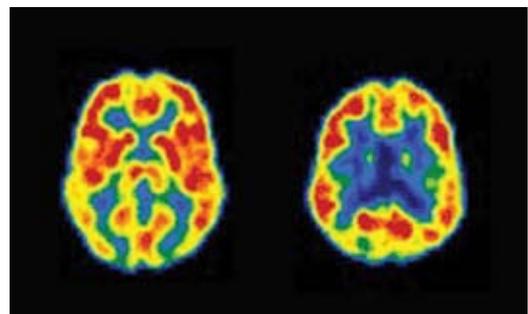


Figure 2. Normal SPECT scans of the brain

Red represents high blood flow, blue, low blood flow.

However if the condition is secondary to the dementia then the cognitive changes are more likely to be permanent and other treatments and interventions will have to be explored.

Functional assessments are conducted by an occupational therapist and may include tests

measuring the performance of 'activities of daily living' and 'instrumental activities of daily living'. Activities of daily living include familiar, basic functions such as bathing, dressing and toileting. Instrumental activities of daily living are the more complex, multi-step home and community-based tasks such as shopping, cooking meals, coping with finances and bills, driving and attending organised recreational/social activities. Functional assessments measure how the person functions in their normal environment, and identify strategies to minimise risk (such as mobility aids and environmental modifications) and to maximise strengths (such as identifying roles and routines that optimise existing skills). This assessment and subsequent recommendations can assist the family to cope and enable the person with younger onset dementia to remain at home longer where they typically function at their best due to familiarity and routine. Specific driving assessments may also be conducted to assess driving safety and may recommend restrictions to licences.

3. Causes of dementia

Many dementias are due to the abnormal accumulation of proteins, such as tau, in the brain. These proteins are needed for brain cells to function normally. The proteins are manufactured, used and then broken down by processes within the brain cells. Malfunctions at any stage of this 'production line' lead to abnormal accumulations in and around the neurons of the brain. The proteins clump together and interfere with brain cell function and connections, eventually leading to cell death. This cell death is evident as atrophy on structural scans of the brain. In addition to causing physical changes to brain cells these proteins also affect the neurotransmitters that neurons use to communicate.

Causes of dementia

Brain cells make a large number of proteins, such as amyloid or tau, by assembling them from raw materials (amino acids). These proteins are broken down again and the raw materials recycled for other proteins (A). If too much protein is made (B) or not enough is broken down (C) then protein can collect in the cell (D) (Figure 3). This may block other functions of the cell or be toxic to the cell, eventually causing the brain cell to die (E). It is thought that many dementias are caused by abnormal collection of protein in this way.

Although dementia is often associated with abnormal functioning of specific proteins, the same protein abnormality can cause a diverse range of symptoms in different people and at different ages. The characteristic symptoms tend to depend upon the areas of the brain affected. It is not clear why some proteins accumulate in different brain regions and, as yet, protein changes are difficult to identify through brain imaging or blood tests.

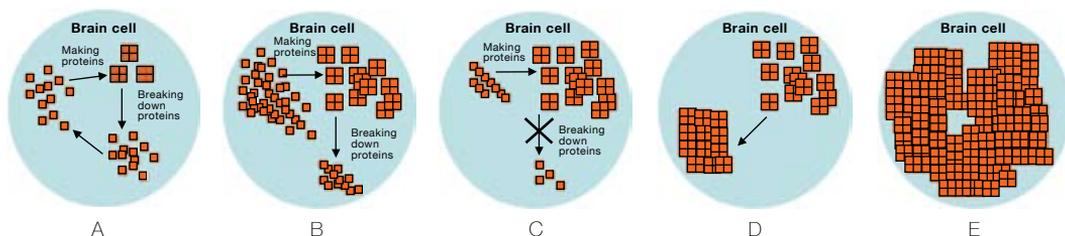


Figure 3. Proteins and dementia

Different dementias, associated proteins, brain regions and major symptoms

| | Protein/Pathology | Brain regions (Figure 4.) | Early symptoms |
|--|---|---|---|
| Alzheimer's disease | Amyloid | Hippocampus Temporal lobes Parietal lobes | Memory |
| Vascular dementia | None - blood vessel blocked or bleeding | White matter Grey matter | Determined by location of stroke |
| Frontotemporal dementias (including Pick's disease) | Tau | Frontal lobes Temporal lobes | Personality, behaviour, judgement and psychiatric changes |
| Parkinson's disease/ Lewy body dementia | Synuclein | Basal ganglia Hippocampus | Slowing of movement and memory |
| Huntington's disease | Huntington | Caudate nucleus Frontal lobes | Involuntary movements, personality, behaviour and psychiatric changes |
| Creutzfeldt-Jakob disease | Prion | All regions | Rapid cognitive, psychiatric and neurological changes |

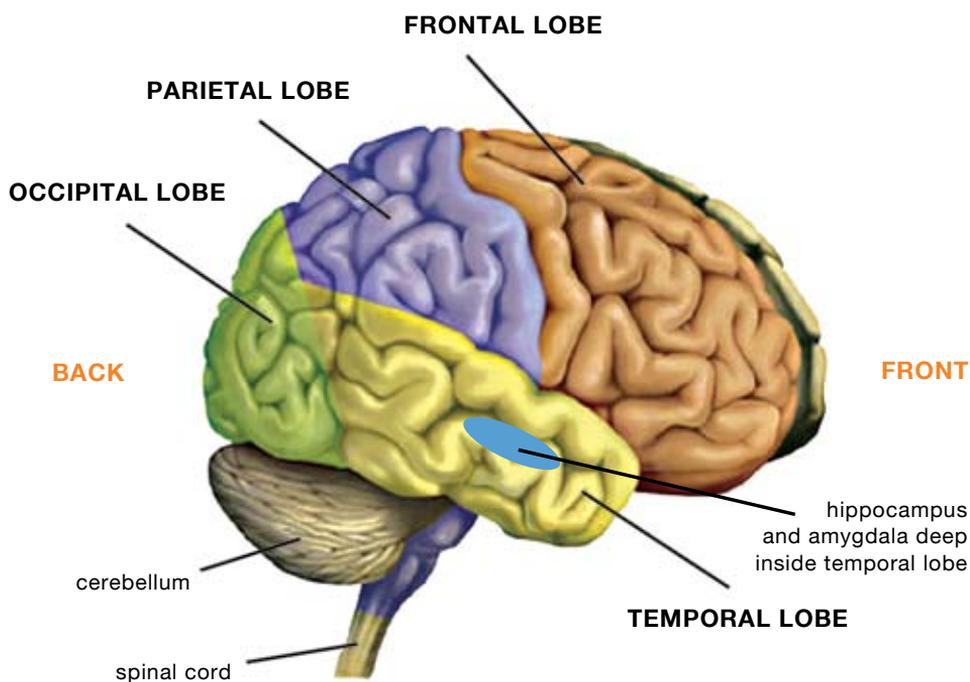


Figure 4. The major brain regions

Although protein build-up follows general patterns in different regions of the brain in particular dementias, these patterns vary considerably. Brain pathology may develop in more than one brain region at a time as the illness progresses causing symptoms to change. Disturbances in behaviour often occur and change throughout the course of dementia. For example, people may obsessively collect things in the early stages of a frontal dementia but then cease. Some of the dementias observed in younger people are characterised by behavioural symptoms which may present prior to any changes in memory or judgement. A person's response to being unwell, their personality, relationships, environment and previous level of functioning will all influence the severity and nature of their symptoms.



4. Medical treatment of dementia

Psychosocial treatment that monitors and modifies behaviour and environment around the person with dementia, to support them through changes, is an essential component of medical treatment. Common behaviour patterns associated with different dementias are described in the sections relating to types of dementia. Further information on strategies for supporting and responding to these patterns can be found in other Alzheimer's Australia publications. At present there are no medications to cure dementia; however, some medications may reduce the symptoms of dementia and delay its progression.

Acetylcholinesterase inhibitors

Some dementias, such as Alzheimer's, are characterised by low levels of the neurotransmitter acetylcholine in the brain. Blocking the enzyme acetylcholinesterase, which breaks down acetylcholine, with inhibitors can increase acetylcholine levels and improve nerve transmission in some brain regions. Commonly used cholinesterase inhibitors are donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl).

These medications may assist some people with Alzheimer's disease by reducing the rate of memory loss, allowing them to live independently for longer. Some people report improved memory, motivation and daily functioning. Cholinesterase inhibitors may also assist with advanced dementia symptoms such as agitation and wandering.

NMDA antagonists

Glutamate is another neurotransmitter associated with learning and memory. Glutamate enhances cognition at moderate levels by binding with the N-methyl-D-aspartate (NMDA) receptor. However excess glutamate, and excessive NMDA receptor stimulation, can damage neurons. Memantine (Ebixa) prevents too much glutamate being released by blocking the receptor. Although some research has found memantine benefits Alzheimer's disease and vascular dementia, it is mainly used in combination with cholinesterase inhibitors. While still requiring more research, this combination may assist with some dementia behaviours and improve independent functioning.

Antidepressant medications

Depression is a very common illness, and people diagnosed with dementia face an increased risk of depression. Not only is the diagnosis of dementia stressful in itself but even in early dementia the brain becomes more vulnerable to neurotransmitter changes related to mood. Carers of a person with early onset dementia also need to be monitored for depression as a result of the diagnosis and demands of the illness. Antidepressants may be prescribed in the early stages of dementia to treat apathy and low energy levels, ensuring that depression is controlled prior to a formal diagnosis

of dementia. Antidepressants may also treat low mood or labile emotions (where the person laughs or cries too easily or inappropriately) in Alzheimer's disease and frontal temporal dementia.

Antidepressants modify the neurotransmitters serotonin and noradrenaline. Selective serotonin re-uptake inhibitors (SSRIs) increase circulating levels of serotonin in the brain, and include sertraline (Zoloft), citalopram (Cipramil) and paroxetine (Aropax). Mirtazapine (Avanza) and venlafaxine (Effexor) increase levels of circulating noradrenaline.

Antipsychotic medications

Antipsychotic medications act via a complex mechanism to alter levels of the neurotransmitter dopamine in the brain. Antipsychotics may be used to treat hallucinations and delusions that can arise with dementia as well as less specific symptoms such as agitation and aggression. Newer antipsychotics such as olanzapine (Zyprexa), risperidone (Risperdal) and quetiapine (Seroquel), may have fewer side effects than the older 'typical' types but still need to be monitored carefully. Other management techniques such as environmental modification are essential if these medicines are used.

Mood stabilising agents

People with dementia sometimes experience mood swings and may benefit from mood stabilising medications. Lithium and valproate (Epilim) have been shown to improve elevated mood and mood fluctuations. Valproate (more commonly used in epilepsy) can also be helpful with aggression and agitation in advanced cases of dementia. Again, monitoring for side effects and using behavioural and environmental modification as adjunct treatments are very important.

5. Types of younger onset dementia

Types of dementia diagnosed in younger people, in approximate order of frequency, are:

- 5.1 *Alzheimer's disease (AD)*
- 5.2 *Vascular dementia (VaD)*
- 5.3 *Frontotemporal lobar degeneration (FTLD)*
- 5.4 *Alcohol-related dementia (ARD)*
- 5.5 *Parkinson's disease with dementia (PDD)*
- 5.6 *Dementia with Lewy bodies (DLB)*
- 5.7 *Huntington's disease (HD)*
- 5.8 *Multiple sclerosis (MS)*
- 5.9 *HIV-related dementia (HIV)*
- 5.10 *Other rare causes of younger onset dementia:*
 - *Creutzfeldt-Jacob disease (CJD)*
 - *Dementia after head injury*
 - *Dementia in Down syndrome*
 - *Homocystinuria*
 - *Vasculitis*
 - *Wilson's disease*
 - *Porphyria*
 - *Adrenoleukodystrophy*
 - *Lipid storage diseases*
 - *Mitochondrial disorders*
 - *Dentatorubralpallidolusian atrophy (DRPLA)*
 - *Neuroacanthocytosis*

Summary of neuropsychological features of younger onset dementias

| | Alzheimer's disease | Vascular dementia | Frontotemporal lobar degeneration | Alcohol related dementia | Parkinson's with dementia | Dementia with Lewy bodies | Huntington's disease | Multiple sclerosis | HIV related dementia |
|---------------------------|---------------------|-------------------|-----------------------------------|--------------------------|---------------------------|---------------------------|----------------------|--------------------|----------------------|
| Memory storage | •••• | ••• | | •••• | | • | | ••• | •• |
| Memory retrieval | | | •••• | •• | •• | | •• | | ••• |
| Attention | •• | •••• | ••• | •• | ••• | •••• | •••• | ••• | ••• |
| Language | •••• | •••• | •••• | | •• | •• | •• | ••• | • |
| Verbal skills | •• | •• | ••• | • | ••• | •• | •• | ••• | • |
| Visuospatial skills | ••• | ••• | • | •• | •• | •••• | •• | •• | |
| Information processing | •• | ••• | •• | ••• | ••• | •••• | ••• | ••• | ••• |
| Executive function | •• | ••• | •••• | ••• | ••• | •••• | •••• | ••• | •••• |
| Behaviour and personality | •• | ••• | •••• | •• | •• | ••• | •••• | ••• | ••• |

•••• *greatly affected*

••• *moderately affected*

•• *slightly affected*

• *mildly affected in some*

5.1 Younger onset Alzheimer's disease

Alzheimer's disease was first named in 1910 by neuropsychiatrist Emil Kraepelin, after his co-worker Alois Alzheimer (*Figure 5*) described the typical pathological brain changes associated with the disease. Alzheimer's original description of the disease was based on a 51 year old woman who had developed memory problems as her first symptoms. Following this description, Alzheimer's disease was used to describe people with younger onset dementia. Only since about 1960 has the term begun to be used across all ages and now it is most often identified with much older people. Increasing age and conditions that increase the risk of vascular damage such as diabetes, hypertension, high cholesterol and smoking have been linked to the development of Alzheimer's disease. Some researchers have proposed a role for diet, aluminium, vitamins and minerals in Alzheimer's disease but their exact role is uncertain.

The risk of Alzheimer's disease increases with age. Up until the age of 45 it is extremely rare (although cases as young as 31 have been reported) but after this age, risk doubles every five years. In general, younger onset Alzheimer's disease accounts for around ten percent of all cases.

Pathology

Alzheimer's disease is associated with the deposition of amyloid protein outside brain cells and its accumulation into plaques. In some people with Alzheimer's disease, the plaques will form in the walls of blood vessels (amyloid angiopathy) and lead to brain haemorrhages. Tau protein also accumulates inside brain cells where it forms neurofibrillary tangles. Together these processes kill cells and result in atrophy of the brain; first in the temporal lobes (especially the hippocampus) and parietal lobes then spreading to other brain regions. Both the hippocampus and the neurotransmitter acetylcholine are vital in the laying

down of new memories. As a consequence, people with Alzheimer's disease are often better at remembering past events but struggle to learn new information. While it is unclear whether plaque formation leads to tangles and to acetylcholine changes or whether the formation of tangles themselves cause the main symptoms, memory loss symptoms are often relieved by acetylcholinesterase inhibitor drugs.

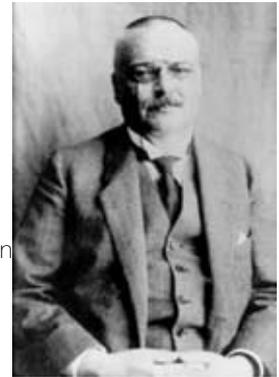


Figure 5. Alois Alzheimer

Genetics

Most Alzheimer cases are not genetic and are known as sporadic Alzheimer's.

Familial Alzheimer's is inherited either through gene mutations which cause Alzheimer's directly or through the inheritance of genes (such as the apolipoprotein E (APOE) gene), which increase the risk of developing later onset Alzheimer's indirectly.

In contrast to genes which increase the risk of Alzheimers, people with a causative mutation will inevitably develop the disease and have a 50/50 chance of passing on the mutation to each offspring. Only five to ten percent of Alzheimer's cases have one of these clear genetic causes, but since the age of onset in such familial cases is invariably under 65 (sometimes as young as the 30s or 40s) genetic mutations are responsible for up to a quarter of people with younger onset Alzheimer's disease. There are a number of different causative mutations (Table below) of which presenilin 1 is, by far, the most common.

Genes, chromosomes and types of inheritance of familial Alzheimer's disease

| Affected gene | Chromosome | Effect of mutation | Number of known mutations | Mode of inheritance |
|---------------------------|------------|--------------------|---------------------------|---------------------|
| Amyloid precursor protein | 21 | Amyloid production | 6 | Autosomal dominant |
| Presenilin 1 gene (PS-1) | 14 | Unknown | 45 | Autosomal dominant |
| Presenilin 2 gene (PS-2) | 1 | Unknown | 2 | Autosomal dominant |



Symptoms

The symptoms of younger onset Alzheimer's disease are very similar to those seen in older people with Alzheimer's disease. The greatest difference relates to the interpretation of these symptoms in younger people. In an older person, memory loss immediately raises a suspicion of Alzheimer's disease in the minds of doctors and the general population. However in a younger person Alzheimer's disease is very unlikely to be considered and other commoner problems of younger adults are considered, for example, depression, stress, marital or family problems.

The main features of younger onset Alzheimer's disease include memory loss, language dysfunction and problems with spatial orientation. There may be associated emotional and behavioural problems such as agitation, wandering, poor sleep, apathy, depression and hallucinations.

The most prominent early sign in younger onset Alzheimer's disease is memory loss. This exceeds the forgetfulness expected normally or under stress (or, in older onset Alzheimer's, with ageing). A person with Alzheimer's disease may frequently

forget entire conversations rather than just occasionally forgetting a name, a word or specific details in a conversation. Atypical presentations of younger onset Alzheimer's disease may include a marked word finding deficit (for example, searching for words to the point that conversations become difficult) or spatial difficulties (for example, getting lost, putting things together in the wrong way, or dressing problems).

The diagnosis of Alzheimer's disease is usually based on histories provided by both the person and their family, the pattern of clinical findings including the progression of disease and the results of neuropsychological testing. Evidence of brain atrophy from structural brain scans may also provide important clinical information. As yet there is no gold-standard test that can conclusively confirm a diagnosis of Alzheimer's disease whilst a person is alive. Only post-mortem brain changes can provide a conclusive diagnosis and, as a result, people meeting the criteria for this illness are given the diagnosis of probable Alzheimer's disease.

Alzheimer's disease: cognitive and behavioural changes

KEY FEATURES

- *Worsening of short-term memory, especially for details of recent events.*
- *Language difficulties such as problems finding the right word and with comprehension.*
- *Increasing disorientation with respect to geographical location and time.*
- *Problems with motivation and initiating tasks.*

Memory and learning

Difficulties learning or storing new information.

- Visual and verbal memory loss—forgetting conversations, requests and directions.
- Difficulty storing new memories (beyond thirty minutes) but retain past memories and emotionally and personally meaningful events.
- Memory is not prompted by reminders but strong associations can sometimes help (for example, linking a word to an action or familiar event).

Attention

Not all people suffer from attentional problems in the early stages.

- Alertness and sustained attention are not usually affected until later stages.
- Difficulty with divided attention (doing two things at once), selective attention (knowing what to attend to) and shifting attention (from one task to another).
- Less able to hold auditory information in attentional store (like phone numbers).

Language skills

Use of language is usually appropriate, but sentences may remain unfinished or the person might get stuck trying to find a word.

- Commonly suffer from difficulties finding words unless prompted.
- 'Circumlocutory' speech—talking around topic, can't think of the word, speech seems 'empty' of meaning.
- Verbal fluency may be affected with restricted quantity and/or rate observed
- Writing and reading are often impaired.
- Comprehension sometimes affected early on but the basic principles of language remain intact (such as syntax and lexical structure).

Verbal skills

No difficulties usually apparent in early stages.

- Well-learned verbal knowledge usually preserved in early stages.
- Verbal processing such as reasoning ability may reduce in later stages.

Visuospatial and nonverbal skills

Difficulties apparent in early stages, such as drawing, using maps or making things.

- May find it hard to use a map and may become disoriented even in familiar places.
- Difficulties copying a demonstrated action and with sequencing unfamiliar processes. Increasing difficulties carrying out familiar tasks in the correct order.
- Making things or putting things together becomes hard even for handy or crafty people. Drawing (especially copying) becomes difficult.

Information processing speed

Slow to respond to questions and carry out tasks.

- Slower response to questions caused by slower processing speeds.
- Tasks also carried out more slowly.

Executive or higher order functioning

Usually only mild difficulties apparent in early stages.

- Retain self-awareness and insight initially.
- Increasing difficulties in reasoning, abstraction, judgement and mental flexibility.
- Difficulty understanding information unless with examples or demonstrations.
- Difficulty moving onto a new topic in conversation, adapting to a new situation or following movie storylines.

Behaviour and personality

Behaviour change not typically an early sign although behaviour may change to compensate for cognitive changes.

- Embarrassment, depression, apathy, social withdrawal, reduced appetite, poor sleep and reduced spontaneous speech may occur as a reaction to brain changes.
- May become emotional, irritable, frustrated or angry about their symptoms.
- Memory problems can lead to suspicion and paranoia as they try to make sense of their confusion (for example, may think a misplaced item is stolen).
- Personality changes, social interactions and daily functioning are affected by disease.

5.2 Vascular dementia

Vascular dementia is a progressive cognitive decline caused by stroke or vascular lesions in the brain. Vascular lesions occur where the brain's blood supply has been disrupted by either an ischaemic or haemorrhagic lesion causing infarcts or areas of cell death. The causes of vascular dementia are therefore essentially the same as the causes of strokes. As these infarcts can occur in different areas of the brain the features of vascular dementia are much less stereotyped than frontotemporal lobar degeneration or Alzheimer's disease.

Risk factors for stroke include hypertension, smoking, hypercholesterolemia, diabetes mellitus, cardiovascular disease (angina and heart attacks), increasing age and obesity. The risk of stroke is also increased in pregnancy and migraine. Additional risk factors in younger people include kidney failure, amphetamine and cocaine use, as well as systemic lupus erythematosus causing inflammation of arteries.

Vascular dementia occurs in both older and younger populations but is a particularly significant cause of younger onset dementia. It seems likely that vascular dementia in the young is related to more common stroke risk factors, while cases in the elderly are caused by rarer conditions. Vascular dementia can occur together with other types of dementia such as Alzheimer's disease and is then referred to as mixed dementia.

Pathology

Infarcts can occur in any area of the brain depending on which arteries are affected. A single infarct may produce a very specific cognitive deficit with or without neurological deficits such as weakness on one side of the body or speech disturbances. Vascular dementia however can occur much more subtly when a succession of smaller infarcts over a period of time occurs in the deep white matter of the brain. The white matter of the brain is vital in information transmission since it is composed of interconnecting and myelinated neuronal fibres. Such infarcts are due to narrowing of smaller arteries which penetrate deep into the brain and are referred to as lacunar infarcts. The resulting multiple small infarcts can produce a

vascular dementia, once referred to as multi-infarct dementia or Binswanger's disease. Occasionally these infarcts may occur without any of the typical stroke deficits such as weakness or speech disturbance. Such multiple small infarcts may produce the structural brain changes referred to as white matter hyperintensities.

Genetics

There are a number of genetic disorders that cause high cholesterol levels, abnormalities in blood clotting (either clots forming too easily or not easily enough), sickle cell anaemia (in which red blood cells are abnormally shaped) and a rare condition called cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). CADASIL may cause vascular dementia in people as young as 25 years.

Symptoms

Although the symptoms of vascular dementia are variable, this diagnosis might be considered when vascular risk factors are present, there is a history of stroke and/or when neurological features of stroke (such as weakness, gait or language problems) occur.

Cognitive changes are often referred to as "patchy" as they involve different areas of the brain. They also often occur in a stepwise pattern which is different to the gradual and steady decline observed in Alzheimer's disease. Although memory and language dysfunction can occur, involvement of frontal lobes or white matter fibres can also produce features that are very similar to frontotemporal lobar degeneration such as personality change, apathy, emotional lability or poor planning and judgement (*Figure 6*).

Neurological deficits such as weakness, reduced vision and lack of insight mean that people with vascular dementia may require higher levels of care at an earlier stage than those people with other types of dementia.

Neuropsychologically, vascular dementia differs from Alzheimer's disease in having greater impairment of attention, executive functioning and psychomotor speed but with better preservation of

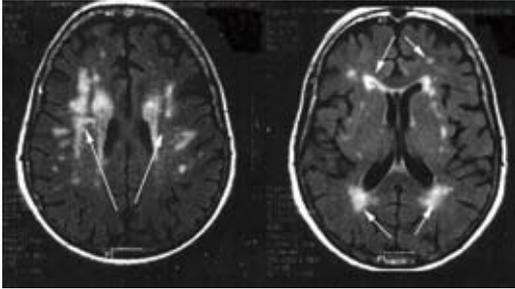


Figure 6. Vascular dementia
MRI scans of the brain showing extensive white matter changes in the subcortical areas of the brain often associated with vascular dementia (arrows)

memory. However vascular dementia can often occur in conjunction with Alzheimer's disease which further complicates diagnosis. Moreover, people who show cortical (grey matter) and subcortical (deep white matter) pathology together, or subcortical pathology alone, generally demonstrate greater impairment than those who only show cortical pathology. This is evident as a particularly more marked decline in regard to attention, psychomotor speed, executive functioning and language abilities.

Vascular dementia: cognitive and behavioural changes

Vascular dementia is highly variable and may not include these characteristics.

KEY FEATURES

- *Presence of vascular risk factors.*
- *Often stepwise progression of symptoms with periods of relative stability.*
- *Slowed motor speed, impaired attention, some short-term memory impairment.*
- *Impaired planning and organisation with marked perseveration.*
- *Frequently accompanied by depression and apathy.*

Memory and learning

Similar to Alzheimer's but not as severe early on.

- Benefit from recognition prompts and reminders more so than in Alzheimer's.

Attention

Prominently and widely affected especially if there is white matter involvement.

- Similar to Alzheimer's but focussed attention not usually as impaired.

Language skills

A range of difficulties can occur but word finding problems tend to be common.

- Slurred speech, naming problems and lack of verbal fluency.
- Simplified speech, some grammar difficulties and shortened phrase length may occur.

Verbal skills

No difficulties usually apparent in early stages.

- General knowledge and vocabulary tend to be initially well-preserved.
- Abstract verbal reasoning preserved in early stages and declines slowly.

Visuospatial and nonverbal skills

Difficulties often seen in early stages—similar to Alzheimer's disease.

- More prominent constructional problems when there is white matter involvement.

Information processing speed

Slowed processing and output.

- Slowed motor output and mental processing deficits more marked than Alzheimer's.

Executive or higher order functioning

Prominent but variable deficits apparent in early stages.

- Executive deficits (planning and organisation) often more prominent than memory deficits initially with complex organisational skills more likely to be impaired than abstract reasoning and problem-solving.
- Perseveration and difficulty inhibiting habitual responses. Poor error monitoring.

Behaviour and personality

Depression common, resulting from cognitive and functional change.

- Depression may produce loss of interest, apathy, withdrawal and poor sleep.
- Insight, personality and sociality often maintained except with frontal cortical lesions.
- Personality and behaviour changes may be caused by awareness of other cognitive and functional deficits. May tend to complain about physical symptoms or changes.

5.3 Frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) refers to a spectrum of clinical disorders that are characterised by atrophy of the frontal and temporal lobes (often asymmetrically) as well as areas with swollen brain cells. Unlike Alzheimer's disease, frontotemporal lobar degeneration features various different underlying patterns of protein-containing inclusions in brain cells. Frontotemporal lobar degeneration is a characteristic dementia of younger people with relatively few cases occurring in people over 65.

In 1892 Czechoslovakian psychiatrist Arnold Pick first described the typical clinical features associated with focal atrophy of the brain. Microscopic brain changes (Pick bodies, which are clumps of abnormal tau proteins) were reported a few years later. Classification of these disorders has evolved considerably since then but Pick's disease is still used as an alternative label for frontotemporal lobar degeneration. Frontotemporal lobar dementia is sometimes classified by the clinical profile at presentation, the underlying subtype of pathology, the presence (or not) of a family history, or whether there is a causative gene mutation.

At a clinical level most patients can be classified into one of three major subtypes:

- **frontotemporal dementia (FTD)** which affects behaviour,
- **semantic dementia (SD)** which affects meaningful speech, or,
- **progressive nonfluent aphasia (PNFA)** which affects speech production.

Frontotemporal dementia (also known as the behavioural variant) is the commonest of the three types and is characterised by early changes in personality and behaviour. Loss of insight and social awareness are prominent and a range of inappropriate and altered behaviours such as sexual disinhibition, apathy, aggression, petty theft, hoarding, ritualistic behaviour and compulsions may be observed. Patients typically show frontal atrophy on brain imaging.

People with both semantic dementia and progressive nonfluent aphasia have early problems with language before frontal symptoms develop.

Those with semantic dementia, although able to speak fluently, have progressive word finding difficulties with a loss of semantic information (conceptual knowledge) about objects, people and the meaning of words caused by the asymmetric atrophy of the anterior temporal lobes. In progressive nonfluent aphasia the main symptom is difficulty with language production causing halting, distorted and slowed speech caused by damage to the key language areas of the brain, which may be difficult to see on MRI scans.

A number of other syndromes overlap considerably with frontotemporal lobar degeneration. Two disorders with Parkinson-like features are particularly relevant: **corticobasal degeneration (CBD)** and **progressive supranuclear palsy (PSP)**.

People with **corticobasal degeneration** typically develop problems with movement such as apraxia and limb rigidity, often affecting one side more than the other. They often exhibit fine jerky movements (myoclonus) and their limbs may appear to behave as if they have a life of their own (alien limb phenomena). As the disease progresses, their personality and language may also change, sometimes even before the physical symptoms appear. Atrophy of the frontal and parietal lobes is seen on brain imaging.

In **progressive supranuclear palsy (PSP)** there is involvement of the trunk and neck as well as difficulty looking up or down (vertical gaze palsy). Limb and neck rigidity are characteristic. Unexplained falls are very common in the early stages and most patients become apathetic and have problems with planning and organisation.

Frontotemporal lobar degeneration may also share similarities with **motor neurone disease (MND)**. Motor neurone disease (also known as amyotrophic lateral sclerosis) is a progressive disorder associated with changes in the upper and lower motor neurones causing muscle weakness, wasting and involuntary twitching. Some patients with either behavioural or aphasic frontotemporal lobar dementia may develop typical features of motor neurone disease, including difficulty swallowing, slurred speech, wasting and weakness

of limb muscles. Similarly, some patients with motor neurone disease develop features of frontotemporal lobar dementia. The dementia progresses rapidly and may be associated with prominent delusions.

Frontotemporal lobar degeneration may sometimes run in families and some of these families have a gene mutation involving either the MAPT (tau) gene or the progranulin gene, both of which are located on chromosome 17. The symptoms of people with familial chromosome 17 linked frontotemporal dementia are indistinguishable clinically from those without a family history.

Pathology

All cases, regardless of the clinical presentation, or the presence of a gene mutation, share certain pathological features, namely focal atrophy or neuronal loss in the grey matter, gliosis (brain scarring following cell death) and the appearance of microscopic vacuoles in the brain also referred to as spongiform changes. Special staining reveals two major subtypes depending on whether the major abnormality is a build up of the microtubular associated protein tau or the presence of ubiquitin-positive (but tau-negative) intraneuronal inclusions. Tau positive cases include those with classic Pick bodies and cases with tau gene mutations, corticobasal degeneration and progressive supranuclear palsy. Ubiquitin positive pathology is found in those with frontotemporal dementia-motor neurone disease and is also found in most cases of semantic dementia and those with pregranular gene mutations (Figure 7).

Genetics

About twenty to thirty percent of patients with frontotemporal lobar dementia have a family history of dementia, although in some cases this may be coincidental from the high incidence of dementia

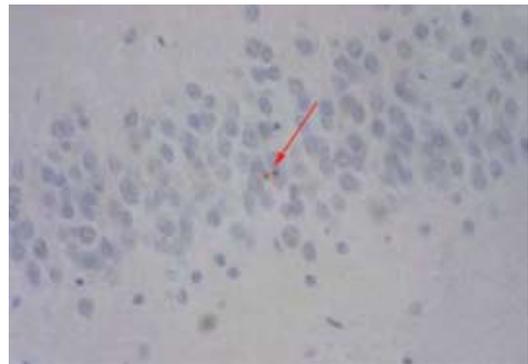


Figure 7. Photograph of microscopic appearance of the brain of a person with frontotemporal lobar dementia stained to show ubiquitin.

The two small brown dots (red arrow) are accumulations (known as inclusions) of ubiquitin protein inside brain cells.

generally. First-degree relatives of a person with frontotemporal lobar dementia may be three and a half times more likely to develop the disorder than members of the general population. Of those with a family history, a few will have a gene mutation which causes the condition. Two major causative gene mutations occur on chromosome 17. The first mutation, found in the late 1990s, involves the microtubule associated protein tau (MAPT) gene which is associated with tau positive pathology in the brain. In 2006 a second major locus close to MAPT was discovered, the progranulin (PGRN) gene. Patients with progranulin gene mutations have ubiquitin-positive but tau-negative pathology. Familial motor neurone disease has been linked to chromosome 9 but little else is known about the mechanisms involved. The same genetic abnormality in a family may cause different clinical features in different family members, including age of onset.

Pathology of frontotemporal lobar degeneration

| | Neuronal loss | Gliosis | Spongiform changes | Inclusions |
|--|---------------|---------|--------------------|------------------|
| Frontotemporal dementia | Yes | Yes | Yes | Tau or Ubiquitin |
| Semantic dementia | Yes | Yes | No | Ubiquitin |
| Progressive nonfluent aphasia Corticobasal degeneration | Yes | Yes | Yes | Tau |
| Motor neurone dementia associated with frontotemporal lobar degeneration | Yes | Yes | No | Ubiquitin |

Symptoms

Frontotemporal lobar degeneration generally begins between the ages of 45 and 65 and is relatively uncommon after 65. Very early in the course of the illness family and friends may notice increased levels of anxiety, pre-occupation with health problems or mood problems. Later, the more characteristic changes in personality and social interactions emerge. The symptoms associated with frontotemporal lobar degeneration relate to the role of the frontal and temporal lobes. The frontal lobes have a key role in executive functioning, including goal setting, problem solving, organisation, sequencing and regulating behavioural functions. The frontal lobes are also involved in the control of social interactions, personality and emotions. The temporal lobes are predominantly concerned with language and memory including storing word and object meanings (or semantic memory), retrieving names, day-to-day memory and face and object identification.

Symptoms of the common behavioural variant of frontotemporal lobar degeneration generally include problems with behaviour control such as disinhibition and impulsivity. Disinhibition in particular can lead to substantial caregiver distress since, as mentioned earlier, some people may become hypersexual, be overfamiliar or aggressive towards strangers or begin to shoplift. People may lack motivation, lose empathy or have problems regulating food intake, preferring sweet foods. They

may have problems with organisation, planning and the initiation of new action plans resulting in repetitive behaviours or inflexibility. Personal hygiene and self-care may be neglected as the disease progresses.

Those with semantic dementia complain of a “loss of memory for words” with problems naming objects and people. This may be coupled with more subtle impairment in word comprehension and general knowledge. People with progressive nonfluent aphasia may develop a distressing inability to communicate fluently due to frequent pauses, stammering, dysarthria and grammatical errors.

As the dementia progresses new symptoms develop while others disappear. They do not always occur together or in the same order. In the later stages people may become mute or display grasp reflexes (involuntary grabbing of objects placed in the hand). A range of motor phenomena are seen including Parkinsonian features such as tremor, rigidity and slowed movements (akinesia), muscle twitches (apraxia) and features of motor neurone disease (muscle weakness and wasting). They may stop walking and lose bowel and bladder control. These changes ultimately lead to the need for full nursing or residential care. The mean survival from diagnosis is in the order of five to eight years although the prognosis is highly variable and some people with frontotemporal lobar degeneration can live for up to fifteen years after initial diagnosis.

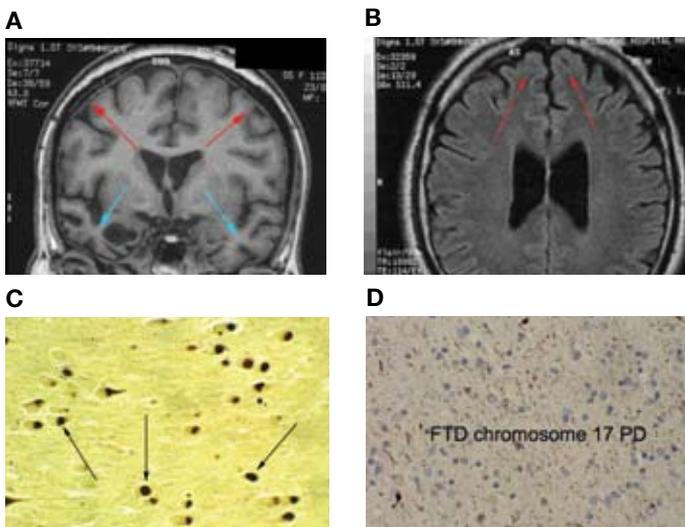


Figure 8. Frontotemporal dementia

A MRI scan of a person with FTD showing shrinkage (atrophy) of frontal (red arrow) and temporal lobes (blue arrow).

B MRI scan of a person with FTD with more prominent frontal lobe atrophy (red arrow)

C Microscopic appearance of the brain of a person with FTD stained with silver stain to demonstrate Pick bodies (black arrow)

D Microscopic appearance of the brain of a person with familial FTD (related to chromosome 17) stained to reveal accumulations of tau protein inside the brain cells.

Frontotemporal lobar degeneration: cognitive and behavioural changes

People with the same clinical subtype of frontotemporal lobar degeneration may display markedly different symptom profiles. While many of the frontal symptoms are shared by all of the frontotemporal lobar degeneration dementias, there are particular features that clinicians will look for in making a specific diagnosis.

Behavioural variant frontotemporal dementia

KEY FEATURES

- Personality and behaviour changes include loss of emotional reactivity, insight and abstract reasoning.
- Disinhibition, aggression and/or ritualistic behaviour may occur.
- Planning, organisation and mental flexibility reduced.
- Memory essentially intact but may have difficulty retrieving memories.

Semantic dementia

KEY FEATURES

- Language difficulties, especially word-finding and comprehension.
- Fluent but empty speech.
- May have problems with visual recognition such as for unfamiliar objects or faces.
- Memory and behavioural symptoms evident later.

Primary progressive aphasia

KEY FEATURES

- Language difficulties, especially with word-finding, speech production, reading and writing. Reduced and hesitant speech.
- Problems with abstract reasoning and mental arithmetic, memory and behavioural symptoms evident later.

Memory and learning

Memory storage usually intact but difficulties accessing information when needed.

- Generally no early memory difficulties (particularly memory storage).
- Memory retrieval problems—may seem absent-minded rather than amnesic.

Attention

Difficulties in maintaining focus over time and easily distracted.

- Problems in maintaining attention are most common. Initially focussed but distractible.

Language skills

Variable difficulties constructing, using and understanding language.

- Word finding difficulties due to a difficulty accessing the word or word meaning. Reduced fluent, spontaneous speech. Speech slow, delayed or tangential.
- Circumlocutory speech, mimicry or repetition. 'Empty' speech, stock phrases or 'sayings' more frequent. Specific deficits including neologisms, agrammatic and paragrammatic speech, phonemic and semantic paraphasia and primary non-fluent progressive aphasia. Can affect reading and writing.
- Comprehension usually intact early on, except in semantic dementia where word meanings and object and face recognition are lost. Marked familiarity effects. Diminishing comprehension exacerbates confusion and irritability.

Verbal skills

Difficulties in reasoning logically and understanding abstract ideas.

- Well-learned verbal knowledge (such as vocabulary and general knowledge) preserved in early stages, but processing may be compromised.
- Abstract reasoning causes difficulty processing and relating conceptual ideas, leading to confusion in unfamiliar, complex or abstract situations.
- Reasoning around daily experience initially intact but deteriorates over time.

Visuospatial and nonverbal skills

Skills are usually well-preserved initially.

- Apparent visuospatial problems often due to executive function and attention deficits.

Information processing speed

Generally well preserved initially.

- Slow completion of complex or higher order/executive tasks.

Executive or higher order functioning

Most commonly observed deficits occurring reasonably early in illness.

- Difficulty planning and organising complex, multi-faceted activities.
- Impulsivity may cause the person to rush and act or speak without thinking.
- Disinhibition—may say or do inappropriate things.
- Difficulties in thinking flexibly or shifting between ideas and steps in an activity, causing rigid thinking and repetitive or apparently obsessive behaviours.
- Perseveration, or continuing an action even though no longer appropriate—giving same answer to a different question.

Behaviour and personality

Early changes in behaviour and personality may obscure diagnosis.

- Lack of self-control—risk-taking, aggression, hypersexuality, frustration and irritability.
- Withdrawal or apathy (not necessarily depression) may include reduced motivation, interest and emotional expressivity. Reduced activity and spontaneous speech.
- Express emotions that are inappropriate or incongruent with their own feelings.
- Personality changes and uncharacteristic behaviour.
- May become uncaring or overly affectionate towards their caregiver (and family).

Overlap syndromes: cognitive and behavioural changes

Corticobasal ganglionic degeneration (CBD)

KEY FEATURES

- *Unstable posture and gait with prominent and often asymmetric limb apraxia.*
- *Parkinsonian with stiffness and/or rigidity and alien hand phenomena.*
- *Word finding problems and speech dysfluency.*
- *Difficulties with mental arithmetic, executive function, slowed information processing and some memory.*
- *Prominent irritability, depression and/or apathy.*

Depression and irritability common with expressive language and executive deficits.

- Executive dysfunction and behavioural/personality change often identified early.
- Depression and irritability common but less often anxiety and agitation.
- Difficulties in spelling and calculation are also sometimes seen.
- Problems sequencing and controlling complex motor functions can lead to problems in handwriting, drawing and constructional difficulties as well as in using tools.
- Memory storage deficits (not retrieval).

Progressive supranuclear palsy (PSP)

KEY FEATURES

- *Postural and gait instability as well as slowed and/or slurred speech.*
- *Blurred vision and inability to maintain and/or shift gaze.*
- *Poor mental flexibility, slowed information processing and memory difficulties.*
- *Irritability, depression and/or apathy.*

Deficits similar to Parkinson's disease but more severe at the outset.

- Greater cognitive deficit from the outset and more severe decline than Parkinson's disease. Similar memory retrieval deficits.
- Language deficits not major, but may have reduced speech fluency and initiation.
- 'Visual grasping' is a notable feature—cannot tear gaze away from something.
- Tend not to have deficits in skilled movements in early stages (unlike CBD).
- Apathy common and disinhibition occurs sometimes but rarely anxiety or agitation.

Motor neurone disease associated with frontotemporal dementia

KEY FEATURES

- *Muscle weakness, atrophy, slowed and slurred speech and dysphagia.*
- *Personality changes, such as emotional lability and apathy, evident early.*
- *Language output problems as seen in progressive nonfluent aphasia.*
- *Poor mental flexibility, slow information processing and some memory issues.*
- *Rapid progression.*

Similar pattern to frontotemporal lobar degeneration although variable.

- Early personality and behaviour change including emotionality, paranoia and apathy.
- Word finding difficulties associated with slurring and difficulty swallowing.
- Slowed information and motor processing are typical signs as well as rigid thinking.
- Visuospatial skills often preserved at first with insight and judgement deteriorating later and initial memory deficits becoming more widespread.
- Psychotic features may be seen with bizarre delusions and/or hallucinations.

5.4 Alcohol related dementia

Alcohol related dementia (ARD) results from chronic use of excessive alcohol and is more prevalent amongst younger people than older people.

While small amounts of alcohol may ward against dementia, chronic use produces the reverse pattern. Chronic alcohol use may be a factor in up to a quarter of younger onset dementia cases although rates are currently declining, mostly due to the addition of folate into foods.

Pathology

Large doses of alcohol and its metabolite acetaldehyde are toxic to neurons, lead to vascular and liver disease and vitamin B1 (thiamine) deficiency. All of these processes result in cell death in particular cortical regions. Neuropathologically, alcoholism causes neuronal loss and cortical atrophy as well as arteriosclerotic changes and an accumulation of glial cells or astrocytes which appear where massive neuronal loss occurs in the brain.

The brain stem, mamillary bodies and cerebellum are particularly vulnerable to thiamine deficiency and, when damaged, result in impaired muscle coordination and control as well as cognitive changes. The mamillary bodies, in particular, coordinate the flow of information between the

amygdala and hippocampus and damage results in memory deficits, particularly in the emotional meaning of events.

Symptoms

The neurological symptoms of alcohol related dementia include a wide-based gait and peripheral nerve damage (mostly affecting the feet) as well as cognitive changes including hepatic encephalopathy, Wernicke's encephalopathy and Korsakoff's syndrome.

Hepatic encephalopathy is a complication of cirrhosis in which brain damage occurs due to the liver's inability to adequately filter neurotoxins. Wernicke's encephalopathy describes a triad of neurological symptoms that are caused by severe thiamine deficiency. In addition to alcohol use, Wernicke's encephalopathy may occur with severe anorexia or severe vomiting in pregnancy. Korsakoff's syndrome is often considered to be the neuropsychiatric aspect of Wernicke's encephalopathy and includes confabulation, retrograde amnesia, executive dysfunction and failure to learn new information.

Alcohol related dementia: cognitive and behavioural changes

KEY FEATURES

- *Cognitive deficits tend to stabilise with abstinence from alcohol.*
- *Unable to learn—confabulation, executive and visuospatial dysfunction.*
- *Slowed and poorly controlled motor function.*
- *Apathy, disinhibition and impulsive behaviours common.*

Memory and learning

Characterised by a prominent inability to learn new material.

- *Unable to learn new information but retains old skills (retrograde amnesia with temporal gradient).*
- *Executive dysfunction and inability to self-monitor leads to confabulation ‘filling the gaps’. Interviewing is vital to confirm details if this diagnosis is suspected.*

Attention

Alertness is impaired although registration of auditory material is usually acceptable.

- *Normal immediate auditory attention (such as remembering a phone number).*
- *Alertness and orientation to time and place often impaired—distractible.*

Language skills

Language functioning generally remains intact.

- *Reading, writing and comprehension retained although verbal fluency may decline.*

Verbal skills

Reduced abstract and logical reasoning.

- *Impaired abstract verbal reasoning but well-learned verbal knowledge preserved.*

Visuospatial and nonverbal skills

Many people with ARD have impaired visuospatial function.

- *Visuospatial impairment common as on non-verbal tests like Clock Drawing Test.*

Information processing speed

Psychomotor skills can be impaired.

- *Motor function and control are usually impaired due to cerebellar atrophy.*

Executive or higher order functioning

Executive deficits are widespread.

- *Lack of mental flexibility and impaired problem solving—decreased spontaneity.*
- *Difficulties with planning and organisation including poor judgement.*

Behaviour and personality

Behaviour and personality change are relatively common.

- *Apathy and its symptoms including reduced affect, initiative and social withdrawal.*
- *Agitation, anxiety and/or depression may occur—also disinhibition and impulsivity.*

5.5 Parkinson's disease with dementia

Parkinson's disease is a relatively common disorder characterised by tremors, rigidity, slowness and instability causing impaired balance and falls.

Parkinson's may be confused with other movement disorders such as progressive supranuclear palsy and corticobasal ganglionic degeneration, and with Lewy body dementia (next section).

Usually Parkinson's disease begins after the fifth decade but earlier onsets have been described particularly with familial cases. Some people with Parkinson's disease also develop dementia. People with Parkinson's disease and dementia have higher morbidity and mortality and are more likely to be placed in a nursing home than people with Parkinson's disease alone.

Pathology and genetics

Parkinson's disease is associated with both genetic and environmental factors. Familial inheritance of younger onset Parkinson's disease (including adolescent cases) is usually associated with a mutation on the Parkin gene, however genes for the proteins alpha-synuclein and ubiquitin are also occasionally implicated. The condition may also be caused by pesticides, illegal drugs contaminated with MPTP (see *Glossary*) and even severe influenza.

Parkinson's disease has two key pathological characteristics; loss of dopaminergic neurons in the substantia nigra of the brain stem and the presence of Lewy bodies. Lewy bodies are collections of

proteins including ubiquitin and alpha-synuclein. These protein collections may reduce dopamine levels, affecting movement, cognition and motivation. Increasing dopamine levels in the brain using levodopa is the major treatment available.

Symptoms

Cognitive impairment is relatively common in Parkinson's disease and most will have problems such as slowed thinking and poor planning. Dementia develops in up to forty percent of people with Parkinson's disease, often well after the neurological movement symptoms. Symptoms of dementia in Parkinson's disease include attention and executive function deficits accompanied by slowed thought processes, personality and behavioural changes. Risk factors for dementia in Parkinson's disease are age (with few cases below 50 years), disease duration, early cognitive problems, depression, slowed motor initiation and increased muscle tone and stiffness and hallucinations and/or psychosis.

Parkinson's disease with dementia: cognitive and behavioural changes

Parkinson's disease does not necessarily result in dementia, but when it does depression may make these cognitive changes worse.

KEY FEATURES

- *Postural and gait instability, jerky movements, stiffness, tremor and/or rigidity.*
- *Speech becomes soft, slurred, flat and hesitant.*
- *Marked slowing of motor and cognitive function.*
- *Poor attention, broad and severe executive dysfunction.*
- *Apathy and depression are common early on.*

Memory and learning

Memory is often intact early in the disease course.

- Learning of new information less impaired than for people with Alzheimer's.
- Memory retrieval problems may arise from deficits in organising memories.
- Recognise material but can't recall it (seem absent-minded rather than amnesic).
- Cannot learn unrelated information (like a random word list).

Attention

Attention and arousal are commonly affected.

- Fluctuating attention relatively common.
- Attentional problems on complex tasks, particularly shifting between different steps.
- Impaired sustained attention—difficulty staying on task and easily distracted.
- Difficulties performing mental arithmetic where using mental storage.

Language skills

Most language functions are spared.

- Speech is often slowed and phrase length and output quantity is often reduced.
- Difficulties naming objects more likely due to executive impairments.
- Verbal fluency difficulties noticeable.

Verbal skills

Similar pattern to that in frontotemporal lobar degeneration.

- Well-learned verbal knowledge is usually preserved in the early stages.
- Impaired executive function may cause problems with abstract reasoning.

Visuospatial and nonverbal skills

These skills are initially well-preserved with increasing impairment over time.

- Difficulties with complex visuospatial tasks increase as disease progresses.

Information processing speed

Slowing is a hallmark of Parkinson's.

- Slow and inefficient mental processing and output is common.
- Slowed motor function with respect to both speech and manual output is common.

Executive or higher order functioning

Similar to frontotemporal lobar degeneration but with earlier and more severe difficulties.

- Rigid thinking—get 'stuck' on a particular idea, belief, approach or topic.
- Reduced mental flexibility especially if motor skill is required.
- Reduced inhibition—cannot suppress habitual or over-learned responses.
- 'Overloads' when completing tasks requiring combined motor output and higher order thinking.
- Problem solving and logical deduction skills intact early on but progressively decline.

Behaviour and personality

Behavioural problems associated with executive deficits may be seen later.

- Apathy and/or depressive features common early on—including reduced motivation, interest, emotional expression, initiation of action and spontaneous speech.
- May say or behave inappropriately or show irritability and frustration.
- Hallucinations, anxiety and agitation may also occur.

5.6 Dementia with Lewy bodies (DLB)

Dementia with Lewy bodies was relatively unknown until about twenty years ago but has been increasingly recognised recently, particularly in older people. It is closely related to dementia with Parkinson's disease. Lewy bodies may be the second most common cause of dementia in people over 65 and account for ten to fifteen percent of cases, more often in men. The average age of onset is 75 years, however an age range of 50–80 is reported.

Pathology

The presence of Lewy bodies (*see Glossary*) is the only current neuropathological criteria for diagnosis. Lewy bodies, identical to those in Parkinson's disease, are found throughout the brain particularly the neocortex, limbic system and brainstem, concentrating in the substantia nigra. They reduce dopamine levels, although not to the extent observed in Parkinson's disease. It is not known exactly how Lewy bodies damage the cortex but they seem to disconnect cortical regions by impeding the transport of proteins necessary for cell survival. Most people with DLB also have plaques, similar to those in Alzheimer's, although tau pathology is rare. Cholinergic deficits are also observed in both Alzheimer's and DLB. DLB alters the structure of the amygdala early in the disease, and in the hippocampus later in the disease. DLB can be seen as pathologically intermediate between Alzheimer's and Parkinson's disease.

Genetics

The few genetic studies of DLB have reported cases where the disorder appeared to pass from one generation to the next in families with alpha-synuclein gene mutations. Dementia with Lewy bodies and Parkinson's disease may be inherited similarly and share similar genetic risk factors. Most cases, however, appear to be sporadic.

Symptoms

The diagnosis of DLB may be difficult because of similarities with Alzheimer's disease and vascular dementia. Brain scanning alone is usually not helpful and there are no other diagnostic tests available. Key features distinguishing DLB from Alzheimer's include fluctuating mental state, Parkinsonian features, bradykinesia and visual hallucinations. Early incontinence is another supporting symptom. Cognitive and functional ability in DLB also

deteriorates faster than in other dementias.

DLB is also difficult to distinguish from dementia with Parkinson's disease. Motor deterioration is usually the first symptom of Parkinson's disease while the motor symptoms of DLB often emerge twelve months after the first signs of dementia. Some people with DLB will not have motor symptoms until years after the cognitive problems have begun as the Lewy bodies occur in the cortex early in the disease and only progress to the brain stem later on.

Accurate diagnosis is vital for this type of dementia since it responds well to treatment with cholinesterase inhibitors but risks adverse effects from some antipsychotics. People with DLB should not be prescribed older, typical antipsychotic medications such as haliperidol (Haldol) or chlorpromazine (Thorazine) as these are associated with increased mortality through sedation, falls and neuroleptic malignant syndrome. Atypical antipsychotics should also be used with caution and in small doses.

DLB is often characterised by fluctuating cognitive functioning where a person varies dramatically in how they present within the same day or between days. Although fluctuations also occur in other dementias, variations caused by DLB appear as an apparent interruption in the person's stream of awareness or attention. For example, a sudden episode of confusion and inability to complete a task may be followed by a return to normal functioning. These episodes are usually spontaneous with no apparent external trigger. In other dementias, such fluctuations are often triggered by fatigue, poor memory or changed environment. DLB often features this distinct pattern of 'good' and 'bad' days.

The cognitive features of DLB include visuospatial deficits, reduced attention, slowed reaction time and information processing, inability to initiate activities, poor planning skills, reduced problem solving and abstract reasoning. People with DLB may also have unstable blood pressure and falls. Visual hallucinations (often recurrent, vivid and colourful) may occur as well as delusions and misidentification of objects, relatives or strangers. DLB is often associated with suspiciousness, depression and sleep and dream disorders.

Dementia with Lewy bodies: cognitive and behavioural changes

KEY FEATURES

- *Fluctuating mental state* —sudden bouts of reduced alertness and/or confusion.
- *Slowing, rigidity, tremors and loss of facial expression.*
- *Prominent visuospatial and perceptual disturbances; hallucinations common.*
- *Poor abstract reasoning and judgement, and executive deficits.*

Memory and learning

Fluctuating alertness and confusion inhibits memory storage.

- Recognition prompts are often not effective in helping improve retrieval.
- Delayed recall may not be impaired allowing some retention of information.

Attention

Prominent fluctuations of attention.

- Decreasing alertness, frequent drowsiness or lethargy and increased napping.
- Sudden but transient episodes of confusion (can last a day) with no apparent trigger.
- Attentional impairment is widespread not specific.

Language skills

Language skills usually intact.

- Speech may be disorganised during periods of fluctuating cognition.
- Verbal fluency may be affected with slow or delayed speech.
- Relatively intact language function helps people present well and mask problems.

Verbal skills

Abstract thinking usually a marked deficit.

- Well-learned verbal knowledge preserved in the early stages.
- Verbal processing, such as reasoning ability, is often reduced.
- Difficulties processing conceptual ideas and may take things too literally.
- Reasoning around daily experiences often remains intact initially but does deteriorate.

Visuospatial and nonverbal skills

Visuospatial and perceptual problems are common.

- Difficulties discriminating visual information from a background. Hard to see details.
- Perceptual difficulties when an object is unfamiliar or obscured.
- Difficulties integrating simple visual material into a cohesive image.
- May have difficulties recognising familiar people and family members.
- Visual hallucinations from visuo-perceptual difficulties and fluctuating attention.

Information processing speed

Slowing is a key feature.

- Slow motor output, information processing and response times.

Executive or higher order functioning

Deficits are quite common.

- Executive functions requiring quick and adept speed of processing most affected.
- Initiation problems often seen.

Behaviour and personality

Behaviour and personality problems more common than with Alzheimer's disease.

- Hallucinations and delusions very common
- Sensitivity to antipsychotic medication can make management difficult.
- Depression common as well as apathy including reduced motivation, interest, initiation of action, expression of emotion and spontaneous speech.
- May be paranoid, anxious, irritable and/or confused although this fluctuates.

5.7 Huntington's disease

Huntington's disease is a rare genetic disorder characterised by abnormal involuntary movements, personality change and cognitive impairment.

Pathology and genetics

The gene that causes Huntington's disease is located on chromosome 4 and is passed on in an autosomal dominant fashion meaning that all carriers will eventually develop the disorder and there is a fifty percent chance of children inheriting the gene. Genetic testing is available for Huntington's disease and families with affected individuals should be referred for specialised counselling before any testing takes place.

The abnormal gene produces the protein huntingtin which accumulates inside neurons in the frontal lobes and basal ganglia and causes cell death, particularly in the caudate and putamen (*Figure 9*). Problems with these structures lead to uncontrolled and uncoordinated movements. The caudate also mediates information to the frontal lobes and damage may cause problems controlling frustration and aggression, as well as difficulties with insight and the ability to prioritise tasks.

Symptoms

Huntington's disease most commonly becomes symptomatic between 30 and 45 years of age although about five to ten percent of cases are diagnosed during adolescence and another five percent are older than 60 years. This degenerative disorder progresses over fifteen to twenty years although people with Huntington's may survive for as long as thirty years after diagnosis. People with Huntington's often require special care and support because of the complex nature of their symptoms.

Initial symptoms sometimes include motor signs such as twitching or tremors in their arms or legs, mood symptoms such as depression and apathy or cognitive changes such as impairments of their short-term memory.

Motor symptoms associated with Huntington's disease include involuntary, sudden jerking movements (chorea), a wide based walk with 'prancing' steps, poor balance, clumsiness and difficulties with coordination. Other associated

problems include slurred speech, difficulties swallowing and moving the head and eyes and trouble with their handwriting. As the disease progresses, rigidity and spasticity become more noticeable.

The main personality and psychiatric symptoms of Huntington's disease include noticeable apathy, anger, irritability, impulsiveness, psychosis and suspiciousness of and lack of concern for others. Both depression and elevated mood (mania) may occur.

Dementia in Huntington's disease is characterised by slowed psychomotor speed, impaired judgement and decision making ability and difficulty planning and performing complex tasks. Detailed information regarding Huntington's disease is available from The Australian Huntington's Disease Association (www.ahda.com.au).

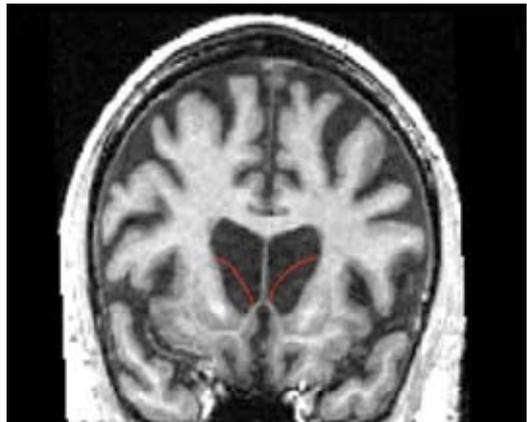


Figure 9. Huntington's disease
MRI scan showing atrophy of both heads of the caudate nuclei typical of Huntington's disease. The red dotted lines show the area that is usually occupied by the caudate nucleus.

Huntington's disease: cognitive and behavioural changes

KEY FEATURES

- *Jerky movements, tremors, poor balance, lack of coordination and slurred speech.*
- *Reduced psychomotor speed and distractibility accompanied by problems with planning, mental flexibility and judgement.*
- *Depression, irritability, emotional lability, aggression and impulsivity.*

Memory and learning

Recall often impaired early on although encoding and storage are reasonably intact.

- Problems with learning and memory early on.
- Problems with retrieving memories, as opposed to acquiring them.
- Better at recognising information than recalling it.
- Visual memory often remains intact.

Attention

Attentional decline one of the earliest cognitive signs, especially for complex tasks.

- Attentional skills affected, particularly concentrating and shifting attention.
- Distracted and/or confused when required to multi-task.
- Can get stuck on a topic and find it difficult to shift to a new one.
- Eventually all functions become impaired including immediate auditory attention.

Language skills

No difficulties usually apparent in early stages but slurring noticeable over time.

- Marked language disturbance is not a typical early sign but this can vary.
- Slurring of speech is very common and typically develops with disease progression.
- Speech output becomes increasingly limited over time.
- Problems in verbal fluency common, such as spontaneous speech or word generation.
- Comprehension typically intact but executive deficits can cause problems.

Verbal skills

No difficulties usually apparent in early stages.

- Abstract verbal reasoning initially intact declining much later in disease.
- Vocabulary tends to remain intact.

Visuospatial and nonverbal skills

Some difficulties in putting things together and attending to visual details can occur.

- Visuospatial skills (constructional abilities and attention to visual details) can decline.
- Sequencing and spatial orientation problems are not typical early signs.

Information processing speed

Slowness on motor tasks is a common finding.

- Mental processing is often slowed particularly for complex tasks.

Executive or higher order functioning

Difficulties in planning and thinking flexibly are often seen.

- Planning is a significant problem early on and declines rapidly.
- Judgement, decision making and mental flexibility problems also evident.



Behaviour and personality

Irritability and depression common (similar to frontotemporal lobar degeneration).

- Behavioural and personality change can be an early sign or not present until later
- Depression, aggression, heightened emotionality and apathy are particularly common.
- Suspiciousness, elevated mood, psychosis, agitation and suicidal ideation may occur.
- Irritability and a reduced concern for others can present early on.

5.8 Multiple sclerosis (MS)

Multiple sclerosis is an inflammatory disease of the central nervous system causing neurological, emotional and cognitive deficits. Multiple sclerosis often begins between 20 and 40, more commonly in women than men. Many people initially suffer discrete episodes called relapsing remitting multiple sclerosis. Within ten years, about half of people develop secondary progressive multiple sclerosis. A smaller group (about fifteen percent of cases), progressively decline without any remission (primary progressive MS).

Pathology and genetics

Multiple sclerosis is an autoimmune disease. The body's immune system destroys the myelin coating in the white matter of the brain and in the spinal cord. Myelin is crucial for efficient electrical conduction and nerve function and damage causes nerve signals to slow. The brain scans showing areas of demyelination (known as plaques) are usually diagnostic (*Figure 11*). Multiple sclerosis is not considered to be inherited however there may be a familial component since first and second degree relatives have a slightly higher risk of developing the disease.

Symptoms

Multiple sclerosis is associated with changes in sensation and vision, unsteadiness and balance problems. Muscle weakness, bowel and bladder dysfunction may also occur. Emotional problems are also common including emotional instability (such as inappropriate euphoria, psychosis, irritability and anxiety) as well as fatigue and depression. These last two symptoms may contribute to cognitive problems.

About half of people with multiple sclerosis are cognitively impaired, with the progressive form of multiple sclerosis having more severe impairment. Impairment varies depending on where the lesions are located in the brain. Commonly reported cognitive problems include slowed thinking, impaired attention, memory loss (in particular short-term memory) and language disturbance. Planning skills, judgement and abstract thinking may also be reduced along with processing speeds. Further detailed information is available from the Multiple Sclerosis Society of Australia (www.msaustralia.org.au).



Figure 11. Multiple sclerosis
MRI scan showing multiple discrete lesions (white spots) which represent areas of destroyed white matter (plaques). Those involving the corpus callosum (arrows) are typical of MS.

Multiple sclerosis (MS): cognitive and behavioural changes

The cognitive deficits associated with multiple sclerosis vary depending on the type of multiple sclerosis and the stage of the disease. Typically, general intellectual skills and language remain intact until advanced stages whilst memory, attention, processing speed and executive function deteriorate earlier.

KEY FEATURES

- *Changes in sensation, weakness, poor balance and incoordination.*
- *Visual problems, such as blurred vision, also occur.*
- *Slowing of motor and cognitive function.*
- *Sustained attention, short-term memory, problem solving and abstract reasoning are often impaired.*
- *Depression, fatigue and emotional lability.*

Memory and learning

Problems with encoding and retaining information in memory often seen over time.

- Memory deficits are common—reduced ability to encode information in memory.
- Information retention over time even more severely impaired with significant loss of the previously encoded material.

Attention

Registration of auditory material may be impaired and attention declines.

- Immediate auditory attention span may be reduced by more information.
- Problems with attention and concentration present early and decline with disease.
- Alertness and orientation to date, time, person and place often becomes impaired.

Language skills

Language functioning generally intact although can have a sudden onset of difficulties in expression.

- Acute language dysfunction (word finding difficulties and reduced fluency).
- Many show no language problems at all.

Verbal skills

Reduced abstract or logical reasoning.

- Abstract verbal reasoning can become impaired.
- Vocabulary and structured verbal skills intact until disease progresses.

Visuospatial and nonverbal skills

No difficulties usually apparent in early stages.

- Abilities tend to remain intact or only decline with disease progression.
- Construction, perceptual ability and complex visual sequencing issues emerge later.

Information processing speed

Slowed information processing speed is an early characteristic.

- Slowed mental processing can be an early sign in some cases.
- Motor slowing can occur but can complete tasks if given extra time.

Executive or higher order functioning

Executive deficits often an early cognitive sign and decline with disease.

- Deficits in mental flexibility can occur causing perseveration.
- Planning and organisation difficulties.
- Difficulties self-monitoring causing missed errors and difficulty learning from errors.
- Difficulties initiating actions or conversations.
- Judgement can decline.

Behaviour and personality

Behaviour and personality change can be the initial sign in some cases or these features may remain intact until more advanced progression.

- Depression and fatigue commonly affect behaviour, personality and cognition.
- Anxiety can occur and even some 'hysterical' types of reactions.
- Marked personality change ranging from social withdrawal to disinhibition.
- May show psychiatric features such as paranoia or suicidal ideas.

5.9 HIV-related dementia

Human immunodeficiency virus (HIV) is an infectious disease that suppresses the immune system and may cause cognitive impairment in its later stages. HIV causes acquired immunodeficiency syndrome (AIDS) in most infected individuals. About ten thousand Australians currently have AIDS, mostly men in their thirties and forties.

Pathology

HIV is a retrovirus that attacks white blood cells (lymphocytes). HIV can be transmitted from an infected person through sexual contact, sharing syringes and/or needles, in-utero or via blood transfusions. HIV causes brain inflammation, leading to an accumulation of glial cells, neuron loss and white matter changes. This virus accumulates mostly around subcortical structures, such as the basal ganglia and caudate, giving rise to similarities with other subcortical dementias. The virus may also affect frontal cortical regions.

The frequency of HIV dementia (also known as AIDS dementia complex and HIV encephalopathy) increases as the disease progresses and the immune system deteriorates. It is also believed to increase with age. The prevalence of HIV dementia has recently reduced somewhat with the introduction of highly active retroviral therapy.

Symptoms

HIV dementia causes cognitive, behavioural and motor changes. Symptoms may be overlooked in early stages and many are not diagnosed until daily activities are impaired. Cognitive symptoms typical of HIV dementia include lack of concentration, forgetfulness, slowed information processing, impaired judgement and problem solving. Depression and apathy including reduced motivation and spontaneity are common as well as irritability and, more rarely, psychosis or mania.

Motor symptoms may be mild initially but become evident as problems with balance and fine motor control including clumsiness and an awkward or unsteady gait. Changed handwriting can be an early diagnostic sign. Neurological examination may reveal primitive reflexes (frontal release signs) usually suppressed by the frontal lobes and over-responsive reflexes (hyperreflexia) commonly in the legs. Both bladder and bowel incontinence can be another sign of loss of motor control, particularly in the later stages.

HIV-related dementia: cognitive and behavioural changes

KEY FEATURES

- *Distractibility and slow speed, memory problems and executive dysfunction.*
- *Motor symptoms include poor balance, coordination, writing and continence.*
- *Depression, fatigue, irritability and apathy are common.*

Memory and learning

Memory problems are common and present early in the disease.

- Difficulty learning new material but do not forget as quickly as in Alzheimer's.
- Memory deficits are common (retrieval problem not storage).

Attention

Problems with concentration and attention can be an early sign.

- Struggle to maintain their concentration and to shift attention between tasks early on.
- May complain of distractibility and inability to fulfil daily tasks quickly and easily.

Language skills

Language functioning generally remains intact early on with a decline as the disease progresses.

- Speech initially intact but may slow and even cease over time due to motor changes.
- Writing can be difficult early on and word-finding difficulties can emerge with time.

Verbal skills

Reduced abstract reasoning becomes apparent over time.

- Abstract verbal reasoning can become impaired over time.
- Vocabulary and structured verbal skills tend to initially remain intact.

Visuospatial and nonverbal skills

Usually not impaired in the early stages.

- Visuospatial ability and construction remain intact or decline only in later stages.

Information processing speed

Slowed information processing speed noticeable early in disease.

- Slowed information processing is a characteristic sign as well as motor slowing.
- May struggle with fine motor tasks—can benefit from extra time to complete a task.

Executive or higher order functioning

Executive deficits are prominent early on and decline with disease progression.

- Reduced mental flexibility may impact on problem solving ability.
- Difficulties with planning, organisation and judgement are quite common.
- Difficulties initiating activity; for example, be less likely to initiate a conversation.
- Impaired reasoning and abstraction makes it hard to follow conversations or stories.

Behaviour and personality

Many report changes in behaviour and personality over time.

- Depression, loss of motivation and fatigue commonly affect cognitive functioning.
- Lost spontaneity, initiative, expressed emotion may cause social withdrawal.
- In rare cases, symptoms of psychosis and/or mania may emerge in later stages.

5.10 Other rare causes of younger onset dementia

Creutzfeldt–Jacob disease (CJD)

Creutzfeldt-Jacob disease is a rare and poorly understood transmissible spongiform encephalopathy caused by an abnormal form of the normal prion protein. Abnormal prion proteins accumulate in brain cells, disrupting cell function and causing cell death. The brains of people who have died from CJD are filled with holes where cells have died, giving them a spongy appearance. CJD may be **acquired** through surgery (infected instruments), tissue transplants (such as corneal grafts) or the ingestion of human hormones, although this is now very rare. CJD may also be inherited with the **familial** form caused by mutations in the gene coding for the prion protein.

The most common form of CJD is the **sporadic** form which results from the spontaneous mutation of the prion protein. It most often appears between the ages of 50–65 but can occur as early as during adolescence. **Variant CJD** is a very early onset form (usually 20 - 30 years of age) and is linked to the consumption of products from animals with bovine spongiform encephalopathy (BSE or mad cow disease).

The first symptoms of CJD are a rapid progressive dementia with neurological and psychiatric symptoms including seizures, visual disturbances, jerking muscle movements (myoclonus) and difficulties with co-ordination, balance and walking. Diagnosis can be made upon these features, but is supported by typical findings on electroencephalogram, lumbar puncture and MRI scanning. Unfortunately, in most cases the symptoms progress rapidly and people with any form of CJD may survive only for a few months.

Dementia after head injury

Dementia can be a long-term consequence of severe head injury, particularly repeated head injuries. Professional boxers are at an increased risk of cognitive impairment due to repeated head injury. Dementia may deplete a person's cognitive reserve or the resting level at which a person's mental resources 'run out', making impairments noticeable. People with this type of dementia tend to have a slower decline than with other types of dementia.

Dementia in Down syndrome

People with Down syndrome have a particularly high risk of developing a young onset dementia. By 40 virtually all people with Down syndrome have the hallmark plaques and tangles in their brain associated with Alzheimer's disease with both conditions sharing problems with the amyloid precursor gene. However, not all people with Down syndrome show symptoms of dementia. Those with lower levels of pre-existing cognitive function tend to show more decline. Dementia is most common from the age of 50 and about fifty percent of people are diagnosed with Alzheimer's disease by 65.

Homocystinuria

Homocystinuria is a group of hereditary metabolic disorders in which the enzyme that breaks down homocysteine does not function. This causes homocysteine to build up in the blood and be excreted in the urine. Homocysteine is a normally occurring amino acid, however an increased level of homocysteine is a risk factor for coronary artery disease, stroke and thrombosis. Homocystinuria is an inherited autosomal recessive condition which results in muscle weakness, vision changes, psychiatric symptoms and dementia. Although usually evident in childhood, it may also present in early adult life.

Vasculitis

Vasculitis is a treatable cause of younger onset dementia. It is very rare with one or two cases described each year. The presentation for this disease is quite varied and may resemble an acute encephalopathy with headache and confusional state, an atypical multiple sclerosis (sometimes with seizures) or a subcortical form of dementia. Neurological signs often come and go and there is no group of symptoms which are characteristic for the disease. There are also no definitive diagnostic tests. Treatment is usually with steroids.

Wilson's disease

Wilson's disease is an autosomal recessive disease which disrupts normal copper transport in the body. It occurs in approximately one in fifty

thousand people. It usually presents after childhood and before the age of 40. Accumulation of copper in the liver, brain and other organs produces a particular group of features.

The main features of Wilson's disease include liver disease, jaundice, involuntary twitching and the deposition of copper in the cornea of the eye. Cognitive and behavioural symptoms may include speech difficulties, personality changes, psychoses and mood disturbances alongside dementia with a frontal and global pattern.

Diagnosis is made from these clinical features and by the detection of biochemical changes in the blood and liver resulting from increased copper. Wilson's disease is treatable with medications that attach to copper and help remove it from the body through excretion in the urine or faeces.

Porphyria

The porphyrias are a complex group of disorders that result from disordered metabolism of heme which is an essential protein for the synthesis of hemoglobin and other important proteins. Because of enzyme dysfunction, porphyrins may accumulate in the body resulting in acute attacks of illness with characteristic symptoms including bouts of severe abdominal pain and vomiting, seizures, sensory changes, acute confusion which may mimic dementia and psychiatric symptoms. With appropriate treatment most people with porphyria do not suffer long-term cognitive problems.

Adrenoleukodystrophy

This is one of a group of genetic disorders (leukodystrophies) that cause damage to the myelin sheath which surrounds nerve cells. In this disorder high levels of fatty acids accumulate in the brain and adrenal gland because the enzyme that breaks down these fatty acids is absent or does not function in the normal manner.

The most common forms involve an abnormal gene located on the X-chromosome. As an X-linked condition, it is carried through the maternal line, but affects men more severely. It commonly starts in childhood, but the adult onset form may begin between 21 and 35. Symptoms may include progressive stiffness, weakness or paralysis of the lower limbs, impaired balance and dementia as the disease progresses.

The diagnosis is made if increased levels of fatty acids are found in the blood or skin. MRI scans may also show white matter disease. Prognosis is generally poor due to progressive neurological deterioration although some people may survive up to ten years after diagnosis.

Lipid storage diseases

Lipid storage diseases are a group of genetic disorders in which affected people either do not produce enough of an enzyme needed to break down lipids or produce enzymes that do not work properly. Lipids can then accumulate and cause damage to organs such as the brain, peripheral nervous system, liver, spleen and bone marrow. These disorders may present as a dementia in a younger person

Lipid storage disorders include metachromatic leukodystrophy, gangliosidoses, Fabry's disease, Niemann Pick disease and membranous lipodystrophy.

Mitochondrial disorders

This is a large group of complex and progressive inherited disorders of mitochondrial function. These disorders impair oxidative phosphorylation or the process by which mitochondria provide energy for cell function. Most of these disorders produce multi-organ dysfunction with a variety of neurological symptoms (including visual impairment, seizures, neuropathy, hearing deficits and dementia) and muscle disease.

Dentatorubralpallidoluysian atrophy (DRPLA)

DRPLA is a rare autosomal dominant disorder that is particularly common in Japan. The disorder resembles Huntington's disease with respect to its genetics, symptoms and prevalence. It is characterized by myoclonus, epilepsy, balance disorders, abnormal movements and dementia. Presentations are variable and age of onset varies between 10 to 70 years of age. Diagnosis is available through genetic testing.

Neuroacanthocytosis

This is an extremely rare progressive autosomal recessive disorder of unknown cause. It may begin between the ages of 20 and 50 years. Acanthocytes (spiked red blood cells) are found in



the blood stream. It produces progressive muscle weakness, abnormal movements, seizures, biting of the tongue and lips, and changes in personality, comprehension, and judgement. The diagnosis is made by blood tests and people with this disease generally survive for less than ten years after diagnosis.

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Glossary

Acetylcholine: A neurotransmitter that may occur in lower than normal levels in the brain in Alzheimer's disease and some other dementias.

Acetylcholinesterase: An enzyme that inactivates acetylcholine by breaking it down into other compounds.

Acetylcholinesterase inhibitors: Medications blocking the function of acetylcholinesterase in the brain and slowing the progress of cognitive deficits in dementias where acetylcholine is low.

Acquired CJD: A form of Creutzfeldt-Jacob disease acquired through infection from surgery, tissue transplants or ingestion of human hormones.

AD8 Dementia Screening Test: A screening test for cognitive indicators of dementia.

Adrenoleukodystrophy: One of a group of genetic disorders that damage the myelin sheath of nerve cells and causes an accumulation of fatty acids in the brain and adrenal gland.

Alzheimer's disease: A common cause of dementia.

Amnesia: A partial or total loss of memory.

Amyloid precursor protein gene: Gene involved in production of amyloid, mutations of which can contribute to Alzheimer's disease.

Amyloid plaque: A complex non-soluble collection of protein that may collect outside cells and cause disease.

Apathy: A lack of emotions, motivation or enthusiasm. A state of indifference.

Aphasia: Loss or impairment of ability to comprehend language.

Apolipoprotein E gene (APOE): a gene implicated in the complex inheritance of Alzheimer's disease.

Atrophy: Degeneration or shrinkage of all or part of an organ, such as the brain.

Attention: A person's ability to be alerted to and register sensory information around them so that they can engage in a task, such as a conversation or driving.

Autosomal genes: Genes not on the X or Y sex chromosomes.

Autosomal dominant: The genetic inheritance of trait where only one copy of the gene is required for the trait to be passed on. One in two children (irrespective of sex) of an affected parent will inherit the gene and the trait.

Basal Ganglia: A specialised group of structures deep within the brain associated with higher levels of control of voluntary movements and learning, including the *caudate nuclei*.

Binswanger's disease: See vascular dementia.

CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is a rare genetic form of vascular dementia which may affect people as young as 25.

Caudate Nucleus: A group of neurons in the basal ganglia involved in controlling movement. Known to atrophy in Huntington's disease.

Cholinergic deficit: Low levels of the neurotransmitter acetylcholine, characteristic of Alzheimer's disease and dementia with Lewy bodies.

Chorea: Sudden jerking movements associated with Huntington's disease.

Circumlocutory: A form of speech or thought that, although completely comprehensible, talks around a subject or theme without actually addressing it or providing essential detail about it.

Cognition: Mental processes including learning, comprehension, language, planning and decision-making. Functions that allow new and old information or knowledge to be processed, enabling preferences and actions to be made.

Computerised tomography (CT): Also known as computed axial tomography (CAT scan). Uses a digital geometry process to generate a three-dimensional image from a large number of two-dimensional X-ray images taken around a single axis of rotation. Used to scan brains for areas of atrophy, white matter disease or stroke.

Cortical: The outer layer, in reference to the brain the surface grey matter largely responsible for memory, attention, perceptual awareness, thought, language and consciousness.

Corticobasal degeneration (CBD): A form of frontotemporal lobar degeneration associated with apraxia and rigidity and often involving the limbs asymmetrically as well as myoclonus.

CT scan: see Computerised Tomography.

Demyelination: Loss of myelin, the insulating layer around nerves, resulting in impaired nerve function. Large areas of demyelination in the brain are called *plaques*. This is the main process by which the symptoms of multiple sclerosis are produced.

Dentatorubralpallidoluyian atrophy (DRPLA): A rare inherited disorder (more common in Japan), resembling Huntington's disease, it is characterized by myoclonus, epilepsy, balance disorders, abnormal movements and dementia.

Disinhibition: Loss of usual social and cultural inhibition resulting in unrestrained behaviour and a loss or disregard of appropriate restraints.

Distractibility: An inability to focus or restrict attention to a task, impeding task completion.

Dopamine: A neurotransmitter which assists nerve cells to communicate with one another.

Dysarthria: Slurring of speech often associated with Huntington's disease.

Dysfunction: A failure to function or operate in an expected or complete manner. It can refer to an organ of the body (i.e. bladder dysfunction) a mental disorder, or the improper behaviour of a social group (family dysfunction).

EEG: Electroencephalography is the graphic measurement of the electrical activity of the brain by scalp electrodes. Predominately used to investigate forms of epilepsy, however it can also provide general information about levels of consciousness and general brain dysfunction.

Euphoria: An intense state of happiness and well being, often out of proportion to real events.

Executive functioning: Complex thinking skills involving the integration of many pieces of information and brain functions. These skills allow us to problem-solve, plan and organise, reason through multi-component or abstract ideas logically, monitor and control our behaviour, process more than one piece of information at once and think flexibly.

Familial chromosome 17 linked frontotemporal dementia: a form of frontotemporal lobar degeneration associated with a mutation of the gene responsible for tau protein production.

Familial CJD: An inherited form of Creutzfeldt-Jacob disease.

Frontal Lobes: Part of the cerebral cortex located directly behind the forehead, primarily involved in higher cognitive functioning including planning, personality and movement.

Frontal release signs: Primitive reflexes usually suppressed by the frontal lobes but apparent with brain damage.

Frontotemporal dementia (FTD): a subvariant of frontotemporal lobar dementia commonly causing disinhibition or apathy.

Frontotemporal lobar degeneration (FTLD): or dementia, where there is degeneration in one or both of the frontal or temporal lobes of the brain. Subvariants of frontotemporal lobar dementia include FTD, progressive non-fluent aphasia and semantic dementia and Pick's disease.

General Practitioner Assessment of Cognition: An initial cognitive screening test.

Gliosis: Accumulation of specialised cells called astrocytes or glial cells (or scarring) in areas of the brain when it is damaged. Seen in many degenerative brain diseases.

Grey matter: Surface areas of the brain (and the centre of the spinal cord) dominated by unmyelinated nerve cell bodies that process information. Distinguished from the *white matter* dominated by myelinated axons or nerve cell tails that transmit information.

Haemorrhagic lesions: Occur where there are infarcts causing bleeding into or around the brain.

Hallucinations: The perception of a sensation when there is no corresponding external cause or stimulus. These perceptions can be in all the senses so that they may be seen (*visual*), heard (*auditory*), felt (*tactile*), smelt (*olfactory*) and tasted (*gustatory*).

Hepatic encephalopathy: A complication of liver failure causing cognitive changes.

Hippocampus: A region of the brain within the temporal lobe that plays a part in memory and orientation in space. One of the first regions of the brain to suffer damage in Alzheimer's disease and may be affected later in dementia with Lewy bodies.

HIV: Human Immunodeficiency Virus is a blood-borne infectious disease that damages the immune system. It allows various infectious diseases to affect different parts of the body. Dementia may result from unusual infectious diseases or direct effects of the virus on the brain.

Homocysteine: An amino acid derived from dietary methionine and which reforms into the anti-depressant S-adenosyl methionine (SAME) and anti-ageing glutathione chemicals. A build up of homocysteine can be associated with dementia as well as other conditions.

Homocystinuria: A group of hereditary metabolic disorders where the enzyme that breaks down homocysteine does not function, allowing homocysteine to build up resulting in muscle weakness, vision changes, psychiatric symptoms and dementia.

Huntingtin: A protein coded for by the Huntington's disease gene on chromosome 4 and commonly found in the brain. Its normal function is not known but the protein is abnormally long in Huntington's disease and does not appear to function normally.

Hyperflexia: Over-responsive reflexes often indicating lack of inhibition by frontal lobes.

Information processing speed: The speed at which a person can take in information around them and make sense of it, and their ability to respond to that information or carry out an activity.

Ischaemic lesions: Occurs where a cerebral artery has been blocked either by thickening of the arterial walls or a blood clot or thrombus.

Judgement: The capacity of a person to weigh up different types of information or evidence prior to making a decision. Judgement depends on a capacity to hear and/or see, understand and process information as well as the ability to communicate a decision.

Korsakoff's syndrome: A degenerative brain disorder caused by the lack of thiamine in the brain through alcohol use. Associated with Wernicke's encephalopathy.

Lacunar infarcts: Areas of neuronal death within the white matter of the brain caused by the narrowing of smaller arteries which penetrate deep into the brain.

Levy bodies: Collections of proteins in the brain, including ubiquitin and alpha-synuclein, which reduce dopamine levels and are associated with Parkinson's disease and dementia with Lewy bodies.

Limbic system: Structures in the brain involved in emotion, motivation and emotional memory.

Lipid storage diseases: A group of genetic disorders where not enough (or damaged) enzyme is produced to break down lipids. Accumulated lipids may damage the brain causing younger onset dementia.

Lumbar puncture: A diagnostic test that collects cerebrospinal fluid (CSF) for examination to assist with diagnosis of brain diseases. This is done by introducing a very thin needle through the skin of the back into the fluid surrounding the base of the spinal cord.

Magnetic resonance imaging (MRI): Uses radiofrequency waves and a strong magnetic field to determine the types of tissues present and reconstruct detailed images of internal organs and tissues. Used to identify areas of stroke, white matter disease or atrophy in the brain.

MAPT gene: Microtubule associated protein tau gene implicated in some cases of inherited frontotemporal lobar degeneration.

Memory and learning: A person's ability to store new verbal and visual information and then access this information when needed, as well as their ability to remember old information, routines and skills.

Memory Impairment Screen: A memory screening test.

Mini-Mental State Examination: A commonly used screening test for global cognitive function.

Mitochondria: Components of cells providing energy. Sometimes called the 'power plant of the cells'.

Mitochondrial disorders: A large group of complex and progressive inherited disorders which impair oxidative phosphorylation or how mitochondria provide energy. Produce multi-organ dysfunction with a variety of neurological symptoms (including visual impairment, seizures, neuropathy, hearing deficits and dementia) and muscle disease.

Motor Neurone Disease (MND): usually a progressive disorder associated with muscle wasting but without any cognitive change except, occasionally, late in disease progression.

Mood disorder: A mental illness where normal mood functioning is impaired. The most common form of mood disorder is depression. An elevation or increase in mood is called mania.

Motor neurone inclusion dementia (MNID): A subtype of frontotemporal lobar degeneration associated with bilateral frontal atrophy and with pathological changes similar to motor neurone disease.

MPTP: 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine is an accidental chemical by-product created during the production of synthetic opioids which kills neurons in the substantia nigra and may cause Parkinson's disease.

MRI scan: Magnetic Resonance Imaging is a specialised imaging technique using the magnetic properties of water molecules to produce more anatomically detailed pictures of the brain than CT scans.

Multi-infarct dementia: See Vascular dementia.

Multiple sclerosis: Inflammatory disease of the central nervous system associated with late cognitive decline.

Myoclonus: Brief, involuntary twitching or jerking of muscles (e.g. a hiccup). May be a symptom of neurological disease such as Creutzfeldt-Jakob disease and corticobasal degeneration (CBD).

Neocortex: The cortex of the cerebral hemispheres (not cerebellum).

Neologisms: A characteristic of frontotemporal lobar degeneration where words are used that do not exist and are unrelated to the intended word.

Neuroacanthocytosis: An extremely rare progressive inherited disorder featuring acanthocytes (spiked red blood cells) and producing progressive muscle weakness, abnormal movements, seizures, biting of the tongue and lips, and changes in personality, comprehension, and judgement.

Neurofibrillary tangles: Non-soluble clusters of *tau protein* seen typically in the brains of people with Alzheimer's disease.

Neurology: The medical study, assessment and treatment of illnesses involving the brain, spinal cord, nerves and muscles.

Neuron: The major class of cells in the nervous system.

Neuropsychiatry: The field of medicine and sub-specialty of psychiatry that is involved with the overlap between neurological and psychiatric disease.

Neuropsychology: The study of the brain and behaviour interface.

Neurotransmitter: Special chemicals relaying and modifying electrical signals between neurons. They include *glutamate*, *acetylcholine* and *dopamine*.

NMDA antagonists: Drugs like memantine block N-methyl-D-aspartate receptors in the brain, preventing the build up of glutamate which can lead to neuron damage.

Noradrenaline: A neurotransmitter that assists nerve cells to communicate with one another.

Occupational Therapist: A health care professional who can assess and improve an individual's capacity to function in their own home and other environments (work).

Paragrammatic speech: A characteristic of frontotemporal lobar degeneration causing disorganised grammar where random words or parts of words are left out or substituted. *'The girl ran but mother looking held back. The boys said yes. O' there. She's working another time though'.*

Paranoia: Generally a state in which a person feels they are being persecuted and/or the persecutor has the intention to harm them. Paranoia occurs in a number of mental illnesses, including dementias where memory loss is prominent.

Parietal lobe: A part of the brain behind the frontal lobes and above the temporal lobes responsible for integration of the senses.

Perseveration: An uncontrollable repetition of a word, phrase or gesture in the absence of a stimulus.

Personality: Consistent patterns of emotions, thought and behaviour unique to a particular individual, that develop in childhood and adolescence and define us as individuals.

Positron emission tomography (PET) scan: Uses a very short-lived radioactive *tracer* linked to a metabolic molecule (usually sugar) in the blood stream to provide a three dimensional image of function or metabolism in the brain (rather than its anatomical structure as in an MRI scan).

Phonemic paraphasia: A characteristic of frontotemporal lobar degeneration which causes word structures or sounds to be confused, for example 'dynamos' for 'dominoes' or 'helicopter' for 'helicopter'.

Phosphate: An essential element important in energy production, communication between cells and also for healthy bones and often linked to calcium.

Pick bodies: Sphere shaped collections of *tau protein* in neurons seen in certain types of frontotemporal dementia. First described by Czechoslovakian neurologist Arnold Pick in 1882.

Pick's disease: See frontotemporal lobar degeneration.

Plaques: The abnormal accumulation of *amyloid* protein on nerve cells in brains affected by Alzheimer's disease. Large collections are called plaques and within blood vessels, amyloid angiopathy.

Porphyrias: a complex group of disorders caused by disordered metabolism of the protein for the synthesis of hemoglobin which allows porphyrins to accumulate in the body resulting in acute attacks of illness which may include acute confusion mimicking dementia if untreated.

Post mortem: The state of a dead body or the examination of a body after death by a specialist pathologist to determine cause of death, associated disease or injury. Also referred to as an *autopsy*.

Praxis: The ability of the individual to carry out learned and familiar movements (such as combing hair or swinging a tennis racket). Also known as motor planning.

Primary non-fluent progressive aphasia (PNFA): A form of and characteristic of frontotemporal lobar degeneration also called progressive aphasia. Causes reduced fluency and word finding difficulty including paraphasic and grammatical problems but intact comprehension and word knowledge.

Prions: Proteinaceous infectious particles or abnormally-structured forms of normal proteins that convert other normal protein molecules into an abnormal structure.

Progranulin (PRGN) gene: implicated in some cases of inherited frontotemporal lobar degeneration.

Progressive supranuclear palsy (PSP): A form of frontotemporal lobar degeneration often affecting the trunk and neck and causing difficulties looking up or down (vertical gaze palsy).

Putamen: A central brain structure associated with the caudate nucleus, often damaged in Huntington's disease.

Selective serotonin re-uptake inhibitors (SSRIs): Anti-depressants which increase levels of serotonin in the brain.

Semantic dementia: A form of frontotemporal lobar degeneration associated with asymmetric atrophy of the temporal lobes.

Semantic paraphasia: A characteristic of frontotemporal lobar degeneration. Semantic paraphasics use words with the wrong meaning but that are in some way related to the intended word (e.g. substitute 'table' for 'bed' or 'mother' for 'wife').

Serotonin: A neurotransmitter which assists nerve cells to communicate with one another.

Single photon emission computerised tomography (SPECT): A scanning technique similar to PET scanning. A short-lived radioactive tracer is introduced into the blood stream without a linked metabolic molecule. SPECT scanning thus represents blood flow rather than true metabolism.

Spongiosis: A sponge-like appearance of the brain under a microscope, indicating damage or degeneration.

Sporadic CJD: A form of Creutzfeldt-Jacob disease resulting from the spontaneous mutation of the prion protein.

Sporadic: Conditions that occur spontaneously without a genetic basis.

Stroke: Brain disease caused by interrupting blood supply to part of the brain. A blockage of a blood vessel supplying an area of brain may result in death of this area (infarction). Rupture of a blood vessel may cause escaping blood to damage the surrounding brain (haemorrhage).

Subcortical area: Areas of brain beneath the cortex including basal ganglia, thalamus and hypothalamus.

Substantia nigra: A part of the basal ganglia in the brain stem responsible for dopamine production.

Synuclein: This normal brain protein (alpha-synuclein) is thought to serve an important role in transport of chemicals such as neurotransmitters within the brain cells.

Syphilis: A sexually transmitted disease that may result in dementia many years after it is contracted.

Systemic lupus erythematosus: A chronic autoimmune disease commonly resulting in inflammation and tissue damage of the heart, joints, skin, lungs, blood vessels, liver, kidneys and nervous system.

Tangential: A form of speech or thought that lacks goal direction and often includes excessive amounts of detail. Very similar to circumlocutory speech.

Tangles: Also known as neurofibrillary tangles, these are non-soluble clusters of *tau protein* seen typically in the brains of people with Alzheimer's disease.

Tau: Normal proteins associated with microtubules (microscopic tubes in the cell that form part of the cell's skeleton) in brain neurons. Tau proteins are involved with construction and stabilisation of these microtubules.

Taupathies: A group of frontotemporal lobar dementias often initially diagnosed as Parkinson's disease.

Temporal lobes: The part of the brain located on both sides immediately behind the temples and associated with memory, hearing and understanding speech.

Thiamine: Vitamin B1, the deficit of which contributes to cell death in alcohol related dementia.

Ubiquitin: A small protein found in all cells with a nucleus. It modifies other protein by binding to it and forms part of the particles seen in the neurons of people with some forms of frontotemporal lobar dementia.

Variant CJD: A form of Creutzfeldt-Jacob disease linked to the consumption of animal products infected by bovine spongiform encephalopathy (or mad cow disease).

Vascular dementia: Progressive cognitive decline caused by stroke or vascular lesions in the brain.

Vasculitis: A rare treatable cause of younger onset dementia with a varied presentation, resembling acute encephalopathy with headache and confusional state, an atypical multiple sclerosis (sometimes with seizures) or a subcortical form of dementia.

Verbal skills: Verbal intellectual skills refer to how someone processes and understands speech (for example, word meanings or reasoning). Different from language skills (including reading and writing) but do affect verbal intellectual functioning.

Visuospatial ability: A range of skills involving practical abilities (such as putting things together) and visual processing (such as finding your way around somewhere or recognising objects).

Vitamin B12: A B-group vitamin essential for the healthy production and maintenance of blood cells, nerve cells and DNA. Deficiency of this vitamin is a common cause of anaemia.

Wernicke's encephalopathy: results from damaged mammillary bodies caused by inadequate thiamine through alcoholism. Characterised by short-term memory loss. See also Korsakoff's syndrome.

White matter: The specially insulated branches of nerve cells (or *axons*) that connect and carry impulses between different neurons.

White matter disease: A disease process that affects the white matter of the brain, in particular, with degeneration of the insulating material (called *myelin*).

White matter hyperintensities: Structural brain changes caused by multiple small infarcts and characteristic of vascular dementia.

Wilson's disease: An autosomal recessive disease which disrupts normal copper transport in the body, sometimes causing dementia with a frontal and global pattern.

X-Linked: Genes located on the X-chromosome and traits or conditions passed on via the X-chromosome. X-linked traits are passed down via female carriers to male sons who develop the condition (cannot be carriers).

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April 2008