New approaches to understanding dementia

In this article...
- Causes of the main types of dementia
- How existing theories on dementia are being challenged
- How research is advancing our knowledge of dementia

Some 30 million people around the world live with dementia, a figure equivalent to about 4.5% of people over 65, and up to 10% of those aged over 70. In the UK it affects approximately 840,000 people – about 7% of the population aged over 65 (Alzheimer’s Society, 2014).

Dementia is an umbrella term for a chronic, progressive syndrome characterised by degeneration of the brain (World Health Organization, 2012) that causes a complicated set of symptoms including:
- Memory problems;
- Difficulty learning new information;
- Distorted awareness of the passage of time;
- A gradual loss of the ability to make informed decisions (Ginesi et al, 2016).

Dementia can have a devastating impact on the lives of people with the condition and their families. It also has an estimated annual financial cost of £26bn in the UK, which is predicted to rise to over £50bn in the next 30 years (Jenkins et al, 2016; Department of Health, 2015).

Causes of the main types of dementia

Alzheimer’s disease

The characteristic signs of Alzheimer’s disease are progressive memory loss, declining executive function, difficulty with language and changes in behaviour. These are caused by gradual neurodegeneration, resulting from both genetic and environmental factors.

The disease is characterised by a build-up of abnormal protein structures called “plaques” and “tangles” in the affected areas of the brain, eventually resulting in damaging lesions. The discovery that amyloid-beta protein pieces clump together into neuritic plaques (extracellular deposits of amyloid-β in the grey matter of the brain) – and that an abnormal form of the protein known as tau forms into neurofibrillary tangles (twisted intracellular threads) – led to the amyloid cascade hypothesis. This suggested the accumulation of the plaques and tangles triggered the destruction of nerve cells that eventually led to Alzheimer’s disease (Copstead and Banasik, 2013).

It seems likely that inflammatory processes and glutamate homeostasis are deregulated in Alzheimer’s disease (glutamate is key to cell metabolism and the neurotransmitter at most excitatory synapses in the brain). Studies of the...
There is a widespread loss of the brain’s neurotransmitters in Alzheimer’s disease and vascular dementia. Cholinergic neurons in the basal forebrain are lost at an early stage of Alzheimer’s disease, but degeneration may be slowed through the use of anticholinesterase inhibitors. However, the effect of these drugs is sometimes modest (in about 50% of cases) and they can have unpleasant side-effects; they should only be used after diagnosis has been confirmed (NICE, 2011).

The hippocampal circuits in the limbic area of the brain – crucial for memory and learning – are among the earliest structures to be affected by degeneration in Alzheimer’s disease; this leads to a decline in the ability to store information. Another early feature is a disrupted sense of time and place and those affected may find it difficult to prepare meals, for example, or repeat questions several times – a result of rapid memory loss and poor recall of recent events and conversations. Nurses should expect to repeat instructions to people with Alzheimer’s disease and allow more time for them to perform tasks (Jenkins et al, 2016).

Vascular dementia
Vascular (or multi-infarct) dementia is caused by impaired blood supply to the brain, possibly due to a series of micro-bleeds, transient ischaemic attacks (TIAs) or cerebrovascular incidents (strokes). Compared with Alzheimer’s disease, vascular dementia is more often characterised by attention and concentration deficits, resulting in slowness of thought and problems recalling words, for example. However, the specific deficits experienced depend on the location of the cerebrovascular disease in the brain; therefore vascular dementia is regarded as a heterogeneous disease (one with a variety of causes).

The interrupted blood supply results in focal ischaemia (where blood, oxygen and nutrients fail to reach an organ), disrupting the metabolism in brain cell mitochondria (energy-producing organelles). Cells, including neurons, rely on homeostatic surveillance mechanisms and the clearance of toxic intracellular components such as reactive oxygen species (ROS – also known as free radicals) (Martinez-Vincent and Cuervo, 2007).

In response to the hypoxic insult to brain tissue following a stroke or TIA, for example, white cells called phagocytes cross the blood-brain barrier to remove debris, but this inflammatory response also increases the production of ROS. Increased ROS levels can result in significant damage to cell structures; cumulatively, this is known as oxidative stress, which can further damage neurons (Witte et al, 2010) and in turn triggers the production of toxic levels of glutamate. The subsequent pathophysiological “cascade” contributes to the further loss of neurons and the shrinking of brain tissue (Sas et al, 2013).
Nursing Practice

Discussion

2010), which in turn leads to the signs and symptoms of vascular dementia (Fig 2).

Deregulated lipid metabolism is also emerging as a key risk factor for both stroke and vascular dementia. Human apolipoprotein E (ApoE) is an important transporter of cholesterol in the central nervous system and loss of this function – especially through inheritance of the ApoE4 allele (an allele is a variant form of a gene) – is another potential mechanism for degeneration (Rohn et al, 2014). However, this can be combated through the use of statins (cholesterol-lowering therapy).

Dementia with Lewy bodies or Parkinson’s disease dementia

Lewy bodies are microscopic structures located in the cytoplasm of neurons (generally known as inclusion bodies) and are composed of abnormal forms of the common proteins ubiquitin and α-synuclein. Lewy bodies form in the brainstem, basal ganglia and cerebral cortex and result in disruption to both cholinergic and dopaminergic pathways in the brain (Gore et al, 2015; Ballard et al, 2013).

Those affected experience visual disturbance and hallucinations, rapid eye movement sleep behaviour disorder, attention deficits and marked loss of neurons in the nigrostriatal pathway (one of the major dopamine pathways in the brain and particularly responsible for movement). Changes in these neurotransmitter systems also help to explain the frequency of psychosis, depression and profound sensitivity to neuroleptic medications (which act as dopamine antagonists) among people with this disorder (Linden, 2012; Neal, 2012).

Dementia is a progressive neurodegenerative disease that affects thinking, memory, behaviour and the ability to carry out daily activities, while Parkinson’s disease is primarily a disorder of mobility that evolves towards dementia in its later stages. The disease is related to degeneration of pigmented dopaminergic neurons of the substantia nigra region of the brain but, typically, the surviving neurons are characterised by the presence of Lewy bodies containing misfolded synuclein proteins within their cytoplasm (Copsted and Banasik, 2013).

The precise details of molecular processes occurring in dementia and Parkinson’s disease are not completely understood. Nevertheless, it is becoming increasingly clear that failure of intracellular homeostatic mechanisms to detect and destroy proteins that have not folded correctly is damaging for cells.

Indeed, neurons (which are unable to divide and replace themselves by mitosis) may be particularly prone to accumulating aberrant proteins. In addition, the quality control mechanisms may become less efficient with age, resulting in the remodelling of neuronal interconnections seen in Alzheimer’s disease, Parkinson’s disease and Lewy body dementia (Bourdenx et al, 2015).

Frontotemporal dementia

Frontotemporal dementia refers to a diverse group of conditions that are sometimes misdiagnosed as mental health problems and/or associated with neurological problems. Frontotemporal dementia manifests in two distinct ways:

- A subtype characterised by language difficulties;
- A behavioural subtype.

About half of those affected exhibit progressive aphasia (impaired language comprehension), while the remainder experience a distinct profile of symptoms including changes in personality and social behaviour, loss of insight and empathy, neglect of responsibilities, and a diminished ability to self-care (NHS Choices, 2015).

One of the contributing factors of frontotemporal dementia (and Alzheimer’s disease) is thought to be the hyperphosphorylation of tau, a protein found in the cytoskeleton in the neurons of the central nervous system. This leads to the misfolding of tau and the formation of protein aggregates and tangles in the brain, although (as with Alzheimer’s disease) its significance is unclear (Tenreiro et al, 2014).

The average age of onset of frontotemporal dementia (52.8 years) and the often impulsive behaviour associated with the condition mean it can be particularly stressful compared with other forms of dementia for carers and families as well as those affected (Bristow et al, 2008). Carers of people with frontotemporal dementia often report higher levels of distress (Caceres et al, 2016), and as a result require a great deal of support.

New concepts of dementia

Excitotoxicity

It is clear that dementia is caused by an interplay between genes, lifestyle and environmental factors (Ferencz and Ritsen, 2015), but until recently it was assumed that the death of neurons caused neurotransmitter loss. However, alternative theories now suggest that neurotransmitter depletion, rather than being an effect of neurodegeneration, may also be a cause (Alisky, 2006).

The regulation of extracellular concentrations of the neurotransmitter molecule glutamate seems to be critical for normal brain function, particularly in processing speed and cognitive function. This is because glutamate contributes to long-term potentiation (increase in the strength of nerve impulses) and synaptic plasticity among key neural structures that are important for memory and learning (Rudy et al, 2015). However, nervous tissue (brain, spinal cord and nerves) becomes vulnerable when too much glutamate is produced by presynaptic neurons, or when the ability of astrocytes (a type of cell found in the nervous system) to clear glutamate from the synaptic cleft is exceeded. When glutamate reaches pathological levels it promotes overstimulation of neurons through a damaging cascade called excitotoxicity. Uncontrolled levels of glutamate may erode the integrity of...
inter-connected neural networks leading to progressive neurodegeneration (Stambl er, 2015).

**Neuroinflammation**

With a rapidly ageing population, it is imperative to identify factors associated with cognitive decline and this is why mechanisms of brain inflammation (neuroinflammation) not caused by infective agents are attracting increasing interest. Microglia (macrophage-like cells found in the central nervous system) are scavenging cells that normally clear damage, debris or infective agents; however, they can become hyperactive (reactive microgliosis) when neurons are damaged, and this appears to trigger a vicious cycle that is then toxic to neighbouring neurons, resulting in a perpetuating cycle of neuron death.

Neuroinflammatory processes such as reactive microgliosis, oxidative damage and mitochondrial dysfunction (Pasqualetti et al., 2015), have been identified as a potential pathophysiological mechanism in dementia and, while atypical and different from the acute or chronic inflammation that occurs elsewhere in the body, is thought to accelerate the loss of neurons and white matter in the brain (white matter contains nerve fibres and is found in the deeper tissues of the brain) (Trollor et al., 2012).

**Conclusion**

Although the exact causes of dementia are still not fully understood, research into molecular biology and new concepts such as protein misfolding, neuroinflammation and excitotoxicity are advancing our knowledge of the causes of conditions like Alzheimer’s disease. The extent to which the mechanisms described here are involved in neurodegeneration is yet to be established, but processes such as neuroinflammation and excitotoxicity may act as a catalyst for other ongoing pathophysiological changes characteristic of dementia. NT

**References**


Bit.ly/DementiaNormalAgeing


Neurology and Neuroscience Reports; 15: 4, 17.


Sas K et al (2010) Dementia, stroke and migraine - some common pathological mechanisms. Journal of the Neurological Sciences; 299: 1-2, 55-65