LECTURE 06: MPTP Metabolism and PD Neurodegeneration Selectivity. CONTINUED

Other treatments

Muscles and nerves that control the digestive process may be affected by PD, resulting in constipation and gastroparesis (food remaining in the stomach for a longer period than normal). A balanced diet, based on periodical nutritional assessments, is recommended and should be designed to avoid weight loss or gain and minimize consequences of gastrointestinal dysfunction. As the disease advances, swallowing difficulties (dysphagia) may appear. In such cases it may be helpful to use thickening agents for liquid intake and an upright posture when eating, both measures reducing the risk of choking. Gastrostomy to deliver food directly into the stomach is possible in severe cases.

Levodopa and proteins use the same transportation system in the intestine and the blood–brain barrier, thereby competing for access.When they are taken together, this results in a

reduced effectiveness of the drug. Therefore, when levodopa is introduced, excessive protein consumption is discouraged and well balanced Mediterranean diet is recommended. In advanced stages, additional intake of low-protein products such as bread or pasta is recommended for similar reasons. To minimize interaction with proteins, levodopa should be taken 30 minutes before meals. At the same time, regimens for PD restrict proteins during breakfast and lunch, allowing protein intake in the evening.

Repetitive transcranial magnetic stimulation temporarily improves levodopa-induced dyskinesias. Its usefulness in PD is an open research topic, although recent studies have shown no effect by rTMS.Several nutrients have been proposed as possible treatments; however there is no evidence that vitamins or food additives improve symptoms.There is no evidence to substantiate that acupuncture and practice of Qigong, or T'ai chi, have any effect on the course of the disease or symptoms. Further research on the viability of Tai chi for balance or motor skills are necessary. Fava beans and velvet beans are natural sources of levodopa and are eaten by many people with PD. While they have shown some effectiveness in clinical trials, their intake is not free of risks. Life-threatening adverse reactions have been described, such as the neuroleptic malignant syndrome.

Alzheimer's disease (AD)

NEUROSCIENCE

Also known in medical literature as **Alzheimer disease**, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. It was first described by German psychiatrist and neuropathologistAlois Alzheimer in 1906 and was named after him.

Most often, AD is diagnosed in people over 65 years of age, although the less-prevalent early-onset Alzheimer's can occur much earlier. In 2006, there were 26.6 million sufferers worldwide. Alzheimer's is predicted to affect 1 in 85 people globally by 2050.

Although Alzheimer's disease develops differently for every individual, there are many common symptoms. Early symptoms are often mistakenly thought to be 'age-related' concerns, or manifestations of stress. In the early stages, the most common symptom is difficulty in remembering recent events. When AD is suspected, the diagnosis is usually confirmed with tests that evaluate behaviour and thinking abilities, often followed by a brain scan if available.

As the disease advances, symptoms can include confusion, irritability and aggression, mood swings, trouble with language, and long-term memory loss. As the sufferer declines they often withdraw from family and society.Gradually, bodily functions are lost, ultimately leading to death. Since the disease is different for each individual, predicting how it will affect the person is difficult. AD develops for an unknown and variable amount of time before becoming fully apparent, and it can progress undiagnosed for years. On average, the life expectancy following diagnosis is approximately seven years. Fewer than three percent of individuals live more than fourteen years after diagnosis.

The cause and progression of Alzheimer's disease are not well understood. Research indicates that the disease is associated with plaques and tangles in the brain.Current treatments only help with the symptoms of the disease. There are no available treatments that stop or reverse the progression of the disease. As of 2012, more than 1000 clinical trials have been or are being conducted to find ways to treat the disease, but it is unknown if any of the tested treatments will work. Mental stimulation, exercise, and a balanced diet have been suggested as *possible* ways to delay symptoms in healthy older individuals, but they have not been proven as effective.

Because AD cannot be cured and is degenerative, the sufferer relies on others for assistance. The role of the main caregiver is often taken by the spouse or a close relative. Alzheimer's disease is known for placing a great burden on caregivers; the pressures can be wide-ranging, involving social, psychological, physical, and economic elements of the caregiver's life. In developed countries, AD is one of the most costly diseases to society.

Characteristics

The disease course is divided into four stages, with progressive patterns of cognitive and functionalimpairments.

Pre-dementia

The first symptoms are often mistakenly attributed to ageing or stress.Detailed neuropsychological testing can reveal mild cognitive difficulties up to eight years before a person fulfils the clinical criteria for diagnosis of AD.These early symptoms can affect the most complex daily living activities. The most noticeable deficit is memory loss, which shows up as difficulty in remembering recently learned facts and inability to acquire new information.

Subtle problems with the executive functions of attentiveness, planning, flexibility, and abstract thinking, or impairments in semantic memory (memory of meanings, and concept relationships) can also be symptomatic of the early stages of AD.Apathy can be observed at this stage, and remains the most persistent neuropsychiatric symptom throughout the course of the disease. The preclinical stage of the disease has also been termed mild cognitive impairment,but whether this term corresponds to a different diagnostic stage or identifies the first step of AD is a matter of dispute.

Early

In people with AD the increasing impairment of learning and memory eventually leads to a definitive diagnosis. In a small portion of them, difficulties with language, executive functions, perception (agnosia), or execution of movements (apraxia) are more prominent than memory problems.AD does not affect all memory capacities equally. Older memories of the person's life (episodic memory), facts learned (semantic memory), and implicit memory (the memory of the body on how to do things, such as using a fork to eat) are affected to a lesser degree than new facts or memories.

Language problems are mainly characterised by a shrinking vocabulary and decreased word fluency, which lead to a general impoverishment of oral and written language.In this stage, the person with Alzheimer's is usually capable of adequately communicating basic ideas. While performing fine motor tasks such as writing, drawing or dressing, certain movement coordination and planning difficulties (apraxia) may be present but they are commonly unnoticed.As the disease progresses, people with AD can often continue to perform many tasks independently, but may need assistance or supervision with the most cognitively demanding activities.

Moderate

Progressive deterioration eventually hinders independence; with subjects being unable to perform most common activities of daily living. Speech difficulties become evident due to an inability to recall vocabulary, which leads to frequent incorrect word substitutions (paraphasias). Reading and writing skills are also progressively lost.Complex motor sequences become less coordinated as time passes and AD progresses, so the risk of falling increases.During this phase, memory problems worsen, and the person may fail to recognise close relatives. Long-term memory, which was previously intact, becomes impaired.

Behavioural and neuropsychiatric changes become more prevalent. Common manifestations are wandering, irritability and labile affect, leading to crying, outbursts of unpremeditated aggression, or resistance to caregiving.Sundowning can also appear.Approximately 30% of people with AD develop illusionary misidentifications and other delusional symptoms. Subjects also lose insight of their disease process and limitations (anosognosia). Urinary incontinence can develop.[25] These symptoms create stress for relatives and caretakers, which can be reduced by moving the person from home care to other long-term care facilities.

Advanced

During this last stage of AD, the person is completely dependent upon caregivers.Language is reduced to simple phrases or even single words, eventually leading to complete loss of speech.Despite the loss of verbal language abilities, people can often understand and return emotional signals. Although aggressiveness can still be present, extreme apathy and exhaustion are much more common results. People with AD will ultimately not be able to perform even the simplest tasks without assistance.Muscle mass and mobility deteriorate to the point where they are bedridden, and they lose the ability to feed themselves. AD is a terminal illness, with the cause of death typically being an external factor, such as infection of pressure ulcers or pneumonia, not the disease itself.

Cause

The cause for most Alzheimer's cases is still essentially unknown (except for 1% to 5% of cases where genetic differences have been identified). Several competing hypotheses exist trying to explain the cause of the disease. The oldest, on which most currently available drug therapies are based, is the

cholinergic hypothesis, which proposes that AD is caused by reduced synthesis of the neurotransmitteracetylcholine. The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency have not been very effective. Other cholinergic effects have also been proposed, for example, initiation of large-scale aggregation of amyloid, leading to generalised neuroinflammation.

In 1991, the *amyloid hypothesis* postulated that amyloid beta (Aβ) deposits are the fundamental cause of the disease.Support for this postulate comes from the location of the

gene for the amyloid beta precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (Down Syndrome) who have an extra gene copy almost universally exhibit AD by 40 years of age.

Also APOE4, the major genetic risk factor for AD, leads to excess amyloid buildup in the brain.[41] Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology with spatial learning deficits.

An experimental vaccine was found to clear the amyloid plaques in early human trials, but it did not have any significant effect on dementia.Researchers have been led to suspect non-plaque Aβ oligomers (aggregates of many monomers) as the primary pathogenic form of Aβ. These toxic oligomers, also referred to as amyloid-derived diffusible ligands (ADDLs), bind to a surface receptor on neurons and change the structure of the synapse, thereby disrupting neuronal communication. One receptor for Aβ oligomers may be the prion protein, the same protein that has been linked to mad cow disease and the related human condition, Creutzfeldt-Jakob disease, thus potentially linking the underlying mechanism of these neurodegenerative disorders with that of Alzheimer's disease.

In 2009, this theory was updated, suggesting that a close relative of the beta-amyloid protein, and not necessarily the beta-amyloid itself, may be a major culprit in the disease. The theory holds that an amyloid-related mechanism that prunes neuronal connections in the brain in the fast-growth phase of early life may be triggered by ageing-related processes in later life to cause the neuronal withering of Alzheimer's disease. N-APP, a fragment of APP from the peptide's N-terminus, is adjacent to beta-amyloid and is cleaved from APP by one of the same enzymes. N-APP triggers the self-destruct pathway by binding to a neuronal receptor called death receptor 6 (DR6, also known as TNFRSF21).DR6 is highly expressed in the human brain regions most affected by Alzheimer's, so it is possible that the N-APP/DR6 pathway might be hijacked in the ageing brain to cause damage. In this model, beta-amyloid plays a complementary role, by depressing synaptic function.

A 2004 study found that deposition of amyloid plaques does not correlate well with neuron loss.This observation supports the *tau hypothesis*, the idea that tau protein abnormalities initiate the disease cascade.In this model, hyperphosphorylated tau begins to pair with other threads of tau. Eventually, they form neurofibrillary tangles inside nerve cell bodies.When this occurs, the microtubules disintegrate, collapsing the neuron's transport system.This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells.

Herpes simplex virus type 1 has also been proposed to play a causative role in people carrying the susceptible versions of the apoE gene.

Another hypothesis asserts that the disease may be caused by age-related myelin breakdown in the brain. Iron released during myelin breakdown is hypothesised to cause further damage. Homeostatic myelin repair processes contribute to the development of proteinaceous deposits such as amyloid-beta and tau.

Oxidative stress and dys-homeostasis of biometal (biology) metabolism may be significant in the formation of the pathology.

AD individuals show 70% loss of locus coeruleus cells that provide norepinephrine (in addition to its neurotransmitter role) that locally diffuses from "varicosities" as an endogenous antiinflammatory agent in the microenvironment around the neurons, glial cells, and blood vessels in the neocortex and hippocampus.[57] It has been shown that norepinephrine stimulates mouse microglia to suppress Aβ-induced production of cytokines and their phagocytosis of Aβ.This suggests that degeneration of the locus ceruleus might be responsible for increased Aβ deposition in AD brains.

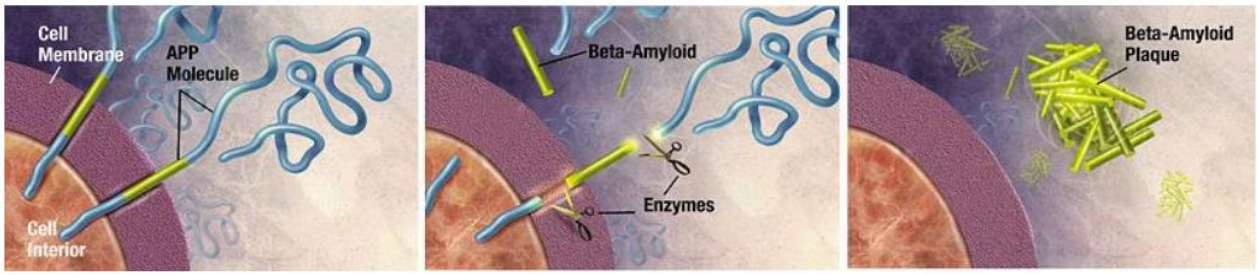
Pathophysiology

Neuropathology

Alzheimer's disease is characterised by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus.Studies using MRI and PET have documented reductions in the size of specific brain regions in people with AD as they progressed from mild cognitive impairment to Alzheimer's disease, and in comparison with similar images from healthy older adults.

Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in brains of those afflicted by AD.Plaques are dense, mostly insoluble deposits of amyloid-betapeptide and cellular material outside and around neurons. Tangles (neurofibrillary tangles) are aggregates of the microtubule-associated protein tau which has become hyperphosphorylated and accumulate inside the cells themselves. Although many older individuals develop some plaques and tangles as a consequence of ageing, the brains of people with AD have a greater number of them in specific brain regions such as the temporal lobe.Lewy bodies are not rare in the brains of people with AD.

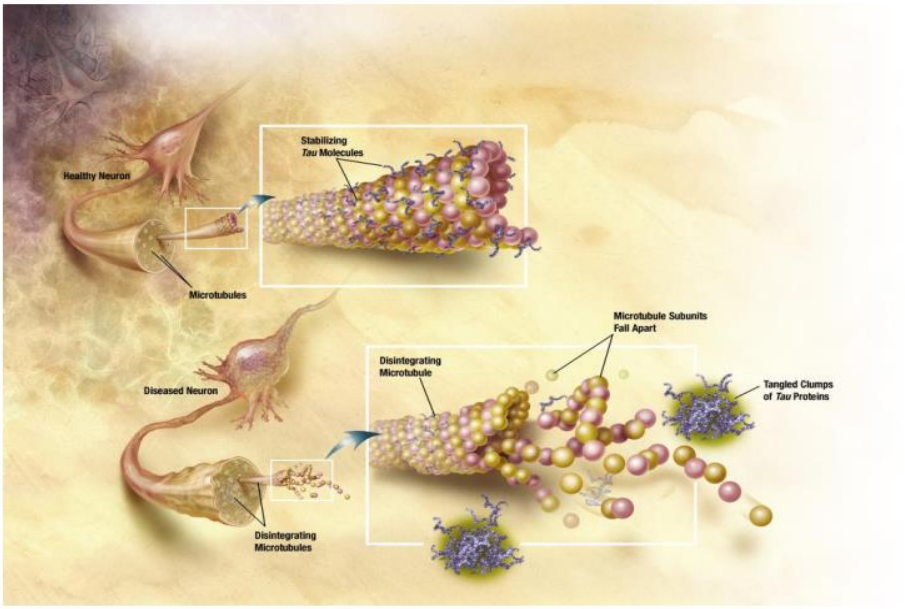
Biochemistry



Enzymes act on the APP (amyloid precursor protein) and cut it into fragments. The beta-amyloid fragment is crucial in the formation of senile plaques in AD.

Alzheimer's disease has been identified as a protein misfolding disease (proteopathy), caused by accumulation of abnormally folded A-beta and tau proteins in the brain.Plaques are made up of small peptides, 39–43 amino acids in length, called beta-amyloid (also written as A-beta or Aβ). Beta-amyloid is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that penetrates through the neuron's membrane. APP is critical to neuron growth, survival and post-injury repair.In Alzheimer's disease, an unknown process causes APP to be divided into smaller fragments by enzymes through

proteolysis.One of these fragments gives rise to fibrils of beta-amyloid, which form clumps that deposit outside neurons in dense formations known as senile plaques.



In Alzheimer's disease, changes in tau protein lead to the disintegration of microtubules in brain cells.

AD is also considered a tauopathy due to abnormal aggregation of the tau protein. Every neuron has a cytoskeleton, an internal support structure partly made up of structures called microtubules. These microtubules act like tracks, guiding nutrients and molecules from the body of the cell to the ends of the axon and back. A protein called *tau* stabilises the microtubules when phosphorylated, and is therefore called a microtubule-associated protein. In AD, tau undergoes chemical changes, becoming hyperphosphorylated; it then begins to pair with other threads, creating neurofibrillary tangles and disintegrating the neuron's transport system.

Disease mechanism

Exactly how disturbances of production and aggregation of the beta amyloid peptide gives rise to the pathology of AD is not known.The amyloid hypothesis traditionally points to the accumulation of beta amyloid peptides as the central event triggering neuron degeneration. Accumulation of aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cell's calciumionhomeostasis, induces programmed cell death (apoptosis).It is also known that Aβ selectively builds up in the mitochondria in the cells of Alzheimer's-affected brains, and it also inhibits certain enzyme functions and the utilisation of glucose by neurons.

Various inflammatory processes and cytokines may also have a role in the pathology of Alzheimer's disease. Inflammation is a general marker of tissue damage in any disease, and may be either secondary to tissue damage in AD or a marker of an immunological response.

Alterations in the distribution of different neurotrophic factors and in the expression of their receptors such as the brain derived neurotrophic factor (BDNF) have been described in AD.