Subtypes Of Dementia

Currently there are around 50 million people diagnosed with dementia, with 10 million newly diagnosed annually. Although it mostly affects elderly people, it is not a normal part of ageing. Dementia is a term used to describe progressive cognitive disturbance leading to the loss or impairment of independent function. It can originate from a variety of diseases that have primary or secondary effects on the brain. The symptoms vary from forgetfulness and becoming lost in familiar places to near total dependence and inactivity. Dementia has a significant economic, physical, emotional and social impact not only on the patient, but also on the family and carers.

Dementia can be subdivided into different sub-types, Alzheimer's disease(AD) is the most common form. Other major forms include dementia with Lewy bodies, vascular dementia, frontotemporal dementia, Creutzfeldt-Jakob disease, HIV associated dementia and alcohol-related brain damage. However, the boundaries between the types of dementia are indistinct and often two or more types are present in patients.

AD is known to cause dementia in elderly people and in individuals with Down's syndrome who survive until the age 50. It is characterized by various pathological markers, such as amyloid plaques surrounding neurons containing neurofibrillary tangles, vascular damage as a result of extensive plaque deposition and loss of neuronal cells. Amyloid plaques are extracellular deposits of beta-amyloid peptide(A-beta). Neurofibrillary tangles are intracellular cytoplasmic bundles of microtubule-associated phosphorylated protein "tau". The main risk factor for Alzheimer's is the age, that is how finding a treatment is more and more relevant with the increase in life expectancy. AD can be familial, with an early onset of a disease due to mutations in amyloid precursor(APP) gene, PS1 and PS2 genes. Late-onset familial AD and sporadic AD are mainly associated with polymorphisms of the apolipoprotein E (apoE) gene. Studies show that inheritance of APOE and TREM2 gene variants are associated with increased risk of AD.

Vascular dementia(VD) is caused by disruption or decrease of blood supply to the area of the brain due to diseased blood vessels. The vessels may have decreased blood carrying capacity or be blocked due to atherosclerosis, brain hemorrhages or transient ischemic attacks, caused by small clots preventing the oxygen flow to brain tissue. Vascular dementia is mostly diagnosed in the elderly population and slightly more often in males. Some of the risk factors include diabetes, history of strokes or heart disease in both the patient and the family, poor physical health – lack of exercise, obesity, excessive use of alcohol or poorly managed long-term health condition.

The other type of dementia is frontotemporal(FTD). It appears to have a higher percentage of familial cases than AD, and involves frontal and temporal lobes of the brain. It is sometimes referred to as Pick's disease. FTD is characterized by progressive neuronal loss, in particular spindle neurons, while the other neuron types remain intact. Common symptoms include apathy, significant changes in social and personal behaviour, lack of emotions and difficulties with language. However, memory, perception and special skills are preserved in patients with FTD, whereas in other types of dementia they are usually affected. Risk factors for FTD are poorly understood, but some studies suggest that head injury, diabetes and autoimmune

diseases can increase the risk of developing FTD.

Lewy bodies dementia(LBD) is the term which covers Parkinson's dementia and dementia with Lewy's bodies. These two forms of dementia are characterized by an abnormal deposit of alpha-synuclein protein in the brain. Its main features are fluctuating attention and cognition, visual hallucinations, some cardinal features of parkinsonism and REM sleep behavior disorder. It also usually affects the autonomic nervous system, so the patient may experience changes in heart and gastrointestinal function. LBD is the most commonly misdiagnosed form of dementia. It usually develops after the age of 50.

Creutzfeldt-Jakob disease(CJD) and HIV-associated represent rapidly and slowly progressive dementias respectively. CJD is a disease caused by prions, and it leads to a fatal degenerative brain disorder. It is rarely inherited, and mostly presents with spongiform encephalopathy. HIV-associated dementia is caused by neuronal damage by the HIV virus. In purely HIV-associated dementia subcortical pathologic changes result from infiltration of infected macrophages or microglial cells into deep grey matter. Incidence is inversely proportionate to CD4 count.

Recently, a new form of dementia, limbic-predominant age-related TDP-43 encephalopathy, LATE, was discovered. It is said to be mimicking AD. It was found that many individuals with classical features of AD without the amyloid plaques or fibrillary tangles. Instead, the symptoms and signs are caused by deposits of TDP-43 protein in the brain. TDP-43 is the protein regulating gene expression. It has been found that a prelevant mutation causes the protein misfolding, leading to amyotrophic lateral sclerosis and frontotemporal lobar degeneration. It can also accumulate in the hippocampus, which is the memory center, causing the symptoms similar to Alzheimer's. Identification and distinguishing LATE and AD will lead to more targeted drug development. It could also explain why there has been so little progress in finding the treatment for Alzheimer's, because LATE may respond to a different therapy.

In March Biogen and Eisai announced that Aducanumab is likely to be ineffective in battling AD. In patients with AD the usual pathological finding is the shrinkage of the brain cortex, leading to enlargement of ventricles and widening of sulci. There are two types of lesions found in the AD patients: amyloid plaques and fibrillary tangles. Amyloid plaques are extracellular deposits of beta-amyloid peptide(A-beta). A-beta peptide is normally produced in the brain, and studies suggest that it acts as an antioxidant involved in metal ion homeostasis. It is also thought to trigger toxic events, such as tau phosphorylation. Increased A-beta is caused by over-expression of APP gene in cases of Down syndrome, head injury and mutations in APP or gamma-secretase genes. There are two hypothesises in regards to AD – amyloid and tau hypothesis. The amyloid hypothesis states that A-beta aggregation triggers the cascade of events that lead to AD, including the aggregation of phosphorylated tau proteins into neurofibrillary tangles, inflammation and oxidative stress leading to neuronal dysfunction and death. Individuals with Down syndrome can experience neuronal changes later in life with formation of plaques similar to AD, because their A-beta protein is overexpressed. This link between amyloid beta and neurodegeneration provides researchers with a therapeutic target. In contradiction to that the tau hypothesis postulates that formation of tau tangles precedes amyloid plaque formation, and that tau aggregation and phosphorylation are the primary reason for neuronal degeneration in AD. However, clinical trials involving the glycogen synthase kinase 3 beta, a protein that initiates tau phosphorylation did not show significant clinical benefits. The drug, Aducanumab, was a human, high-affinity IgG, that would bind to aggregated forms of A-beta, preferentially to parenchymal over vascular amyloid. It showed reduction in size of plaques

in APP-transgenic old mice after thirteen-week administration. However, in phase 3 human trials Aducanumab proved to be ineffective.

In some trials the failure was partially blamed on the recruitment of APOE4 gene carriers, who are genetically predisposed to a rapid progression. The studies showed that APOE gene is responsible for predisposition to the development of sporadic/late-onset AD. Three polymorphisms in APOE gene e2, e3, e4 result in a single amino mutations in ApoE protein. APOEe2 is associated with decreased risk of developing AD, whereas APOEe4 is associated with increased risk. ApoE is a lipoprotein expressed in many organs, with the highest expression in the liver, followed by the brain. It exists mainly as a part of lipoprotein complexes. Having one copy of APOEe4 allele increases the risk of developing AD by 3-fold. It has been also suggested that the presence of one or two APOEe4 alleles shifts the onset age earlier by a decade in comparison to non-carriers with late-onset AD.

The other protein linked to AD is TREM2. It is a transmembrane receptor, which is expressed on myeloid cells 2. Recent studies have discovered that variations in TREM2 can triple the risk of developing AD for an individual. Its involvement supports the theory of inflammatory and immune pathways in development of AD, rather than being the consequence of the disease. TREM2 variations which are associated with AD induce partial loss of TREM2 protein and thus alter the behaviour of microglial cells in the plaque-associated region. Microglia’s neuroinflammatory and phagocytic role in the pathogenesis of AD has been suggested alongside with its role in clustering and limiting the spread of amyloid plaques.

Alzheimer’s disease continues to be the most common cause of dementia, with very little success rate in drug production. However, the increasing rate of developing a better understanding of AD pathogenesis and genetic factors that affect it, as well as discovering new forms of dementia, allows for a more targeted and potentially more financially effective therapy development.