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BRAIN DISORDERS ASSOCIATED WITH DEMENTIA

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Abstract

This paper addresses the mental decline and dementia of patients suffering from brain disorders. The most common of these neurological illnesses is Alzheimer's disease, characterized by a progressive atrophy of cortical brain areas. Alzheimer's disease accounts by far for the largest part of all dementias and is presently one of the most serious disorders, causing an immense burden on patients and society. Vascular dementia is noticed when the brain's supply of blood is disrupted by strokes or other vessel pathologies and just as in Alzheimer's this leads to cortical atrophy with almost identical symptoms. Since the distinction between Alzheimer's and vascular dementia is a gradual one, mixed pathologies are rather common. Rarer causes of dementia are frontotemporal dementia, with pathologies mainly in frontal and temporal brain regions, Parkinson's disease with atrophy in basal ganglia which leads to motor disturbances and at times to mental decline, Lewy body dementia caused by abnormal deposits in the brain resulting in considerable damages of neural cells, and Huntington's disease, a genetic disorder with widely dispersed brain atrophy characterized by mixed Alzheimer's and Parkinson's symptoms. Presently, for the most part the cease of the progressive course of all these disorders is not possible. The last two disorders mentioned in this paper are normal pressure hydrocephalus, with a reduced absorption of ventricular fluid, and Korsakoff's syndrome, caused by a deficiency of vitamin B_1. In normal pressure hydrocephalus a brain shunt may reverse the pathological symptoms, while a vitamin B_1 diet could improve the symptoms of Korsakoff's syndrome. Diagnosis, symptoms and pathologies of all disorders are presented in this paper.

Keywords: brain disorder, dementia

Abstrak

Tulisan ini membahas penurunan mental dan demensia pada pasien yang menderita brain disorder. Penyakit paling umum dari penyakit neurologis adalah penyakit Alzheimer, ditandai dengan atrofi progresif area otak kortikal. Alzheimer menyumbang bagian terbesar dari terjadinya demensia dan saat ini merupakan salah satu gangguan yang paling serius, menjadi beban besar pada pasien dan Masyarakat. Demensia vascular terjadi ketika pasokan darah dalam otak terganggu oleh stroke atau patologi lain, seperti halnya Alzheimer ini menyebabkan atrofi kortikal dengan gejala yang hampir sama. Karena perbedaan antara Alzheimer dan demensia vaskular adalah bertahap, kombinasi dari patologi ini agak umum. Penyebab demensia yang jarang adalah demensia frontotemporal, dengan patologi terjadi utamanya di bagian otak frontal dan temporal, penyakit Parkinson dengan atrofi di ganglia basal yang menyebabkan gangguan motorik dan pada saat bersamaan terjadi penurunan

mental, Lewy body dementia disebabkan oleh deposit yang abnormal dalam otak yang mengakibatkan kerusakan sel saraf, dan penyakit Huntington, kelainan genetic yang tersebar luas pada atrofi otak ditandai dengan kombinasi Alzheimer dan gejala Parkinson. Saat ini, untuk menghentikan perkembangan progresif semua gangguan ini tidak mungkin. Dua gangguan terakhir dalam tulisan ini adalah normal pressure hydrocephalus*, berkurangnya penyerapan cairan ventrikel, dan sindrom Korsakoff, yang disebabkan oleh kekurangan vitamin B1. Dalam* normal pressure hydrocephalus, brain shunt *dapat membalikkan gejala patologis, sedangkan diet vitamin B1 dapat meningkatkan gejala sindrom Korsakoff. Diagnosis, gejala dan patologi dari semua gangguan disajikan dalam tulisan ini.*

Kata kunci: brain disorder, dementia

Dementia is not a specific disease. It is an overall term for a wide range of symptoms accompanying brain disorders causing a long-term and gradual decline in intellectual and or other cognitive functions. The essence of a dementia is a worsening of mental abilities, such as thinking, reasoning, insight, memory and executive functions, which is severe enough to reduce a person's performance in everyday activities. Side symptoms are often emotional and personality alterations, problems with language and a decrease in motivation. For diagnosis of dementia it is obligatory that the decline in the person's mental abilities is far greater than what could be expected due to ageing. In the DSM-5, dementia is classified as a cognitive disorder when more than one cognitive dysfunction is noted. The diagnosis is usually based on the history of the illness and on cognitive testing with brain imaging and somatic investigations in order to rule out other possible causes. The mini-mental state examination (MMSE) is a test generally used to screen cognitive impairments, indicating putative cognitive deficits, which have to be confirmed by neuropsychological assessments. The most common type of dementia is Alzheimer's disease which makes up more than 50% of all dementias (Figure 1). Other types include vascular dementia and frontotemporal dementia. Less common types of dementia are Parkinson's disease dementia, Lewy body dementia, Huntington's disease, normal pressure hydrocephalus (NPH) and Korsakoff's syndrome. More than one type of dementia may exist in the same person, whereby Alzheimer's disease is often co-occurring with other types of dementia, in particular with vascular dementia.

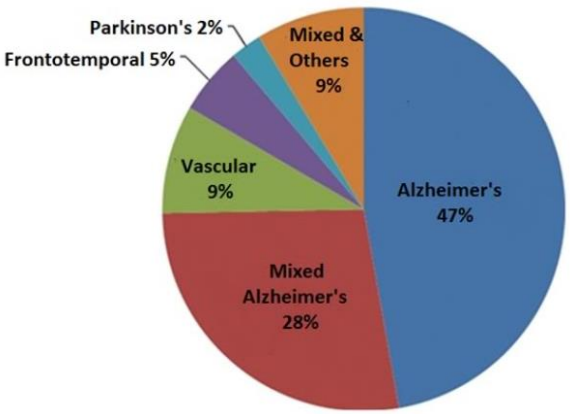

Figure 1. Prevalence of types of dementia. Data are from the Framingham Study of Seshadri and colleagues (1997). The category 'mixed Alzheimer's' consists mostly of patients with a mix of symptoms of both Alzheimer's and vascular dementia. Lewy body dementia is in this graph presented under the category 'mixed & others', just as Huntington's disease, syndrome of Korsakoff and normal pressure hydrocephalus.

Alzheimer's Disease

Alzheimer's disease is the most common form of dementia and previously indicated as senile dementia. Alois Alzheimer (1864-1915) was a German psychiatrist who discovered and diagnosed the disease that bears his name now. Alzheimer had a practice in the University Psychiatric Clinic at Munich (Germany) under the famous psychiatrist Emil Kraepelin, the grandfather of schizophrenia. In 1901, Alzheimer examined patient Auguste Deter, a 51-years old woman with strange behavioral symptoms and a fast loss of short-term memory (Figure 2). Her condition rapidly deteriorated into a severe dementia. This patient was treated by Alzheimer for years and is now recognized as the first patient diagnosed with the disease of Alzheimer. In 1906, Auguste Deter died and the German neurologist performed autopsy on the patient's brain. He identified a number of pathological conditions including shrinking of the cortex and the presence of neurotic plaques and neurofibrillary tangles (Figure 3). Plaques and tangles were distinctly enough to warrant a diagnosis of senile dementia which later become known as Alzheimer's disease.

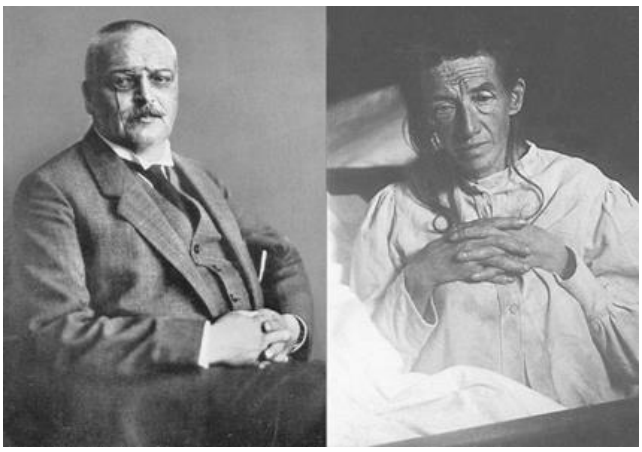

Figure 2. The German neurologist and psychiatrist Alois Alzheimer (1864-1915) (left) and his first patient Auguste Deter (1850-1906).

Clinical Symptoms of Alzheimer's Disease

A common symptom in the early-stage of Alzheimer's is memory loss expressed in forgetting of recent obtained information. Also the ignorance of important dates or events, the over-and-over asking for the same information are signs of an early stage of dementia. Family and friends begin to notice the memory difficulties, such as the forgetting of familiar words and the location of everyday objects. The short-term memory loss is the most obvious symptom of Alzheimer's, but troubles with visual-spatial orientation resulting in getting lost and problems with familiar tasks at home or at work, start also to appear. This early-stage of Alzheimer's is followed by the middle-stage in which reasoning, judgment, and insight deteriorates. This results in withdrawal from work and social activities. The patient becomes unable to recall his own address and telephone number, is confused about which day it is, needs help to choose proper clothing, and have trouble by controlling bladder and bowels. Changes in sleep patterns, such as sleeping during the day and restlessness at night can occur, just as an increased risk of getting lost. The personality of an Alzheimer patient might change. He can be frustrated or angry, moody or euphoric and often behaves in an unexpected way.

Suspiciousness and delusions with compulsive, repetitive behaviors such as hand-wringing, tissue shredding or continuous playing with small objects might occur. Many patients show the 'sundowning' syndrome, an increased agitation with mood swings occurring in the late afternoon when the sun is setting. The middle-stage in Alzheimer is typically the longest stage and can last for many years. As the disease progresses, the person with Alzheimer's will require a great level of care. In the late-stage of the disease, patients lose the ability to respond to their environment, to carry on a conversation and, eventually, to control their movements. They may still utter words or phrases, but communicating is extremely difficult and finally impossible. As memory and other cognitive skills continue to worsen (especially executive functions), gross personality and behavioral changes take place and individuals need extensive help with all daily activities. In the late-stage patients require full-time, around-the-clock assistance with personal care. They need high levels of assistance with all activities. In this stage Alzheimer's patients become increasingly vulnerable to the side-effects of the disease, such as to impairments of immune functions, to inability to ambulate, to incontinence and to aspiration. They often die suddenly as a consequence of these complications resulting in severe infections, especially in pneumonia.

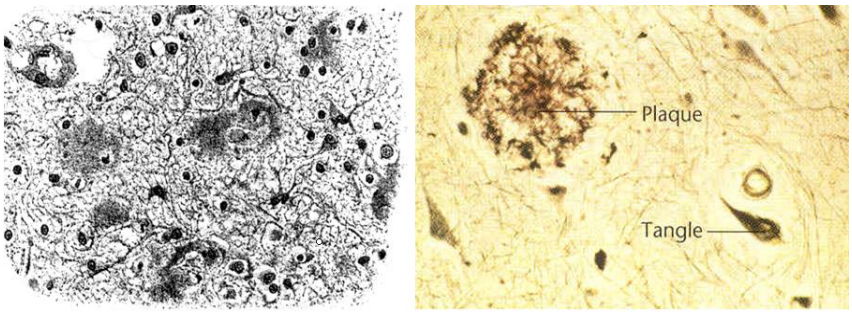

Figure 3. Left: The oldest picture of a cortex of a senile person published in 1898 by the Austrian neurologist Emil Redlich (1866-1930). Sclerotic plaques in the atrophied cortex of a senile individual with gross mental defects and confusions are shown in this photograph. Also some tangles can be identified. Right: The cerebral cortex of an Alzheimer patient showing a plaque and a tangle, the hallmarks of Alzheimer's disease. A plaque is a sign of neuronal degeneration composed of the protein beta-amyloid, consisting of waste products of neurons and glia cells, axons and dendrites. Another waste product from degenerative structures within neuronal cell bodies are the twisted tangles from tau-protein. [Source: J.W. Kalat, Biological Psychology, Wadsworth, 2009].

Neuropathology of Alzheimer's Disease

The brain of a patient with Alzheimer's disease commonly shows a marked atrophy, with widened sulci and shrinkage of the gyri. In the majority of cases, every part of the cerebral cortex is involved; however, the occipital pole is relatively spared, while the prefrontal cortex and the posterior parietal cortex are mostly affected. Also the inferior temporal cortex is widely attacked, due to atrophy of the hippocampus and to a lesser degree of the amygdala. Microscopically, there is shrinkage of cortical neurons, with a

significant loss of cells. The marked shrinkage of the dendritic trees of neurons, with a considerable loss of synapses, is the pathological substrate (Figure 4). Cell degeneration and loss lead to waste products as expressed in sclerotic plaques and fibrillary tangles (Figure 3). These pathological structures are regarded as the neurologic hallmarks of Alzheimer's, although these lesions are not completely unique to Alzheimer's. They can also be found in other neurodegenerative disorders, such as predominantly in the temporal lobes in semantic dementia, and even in healthy individuals, though in much less density. Classic neurotic plaques are spherical structures consisting of a central core of fibrous amyloid protein that is surrounded by degenerating nerve structures. Because beta-amyloid forms insoluble clumps in the brain, it has been postulated that they initiate a cascade of events leading to neuronal dysfunction and death. The accumulation of beta-amyloid is critical to the pathogenesis of Alzheimer's. Neurofibrillary tangles are the other characteristic pathological changes seen in Alzheimer's. Tangles are mostly found inside neurons and are composed of paired helical filaments of tau protein. Deposition may cause disruption of common neuronal architecture with subsequent neuronal cell death. Plaques and tangles are not evenly distributed across the cortex in Alzheimer's, but are concentrated in vulnerable neural systems. The pathological criterion for the diagnosis of Alzheimer's at autopsy requires the demonstration of a sufficient number of plaques and tangles on microscopic examination. Because of the presence of amyloid in plaques, the role of this protein and its precursor peptide (the amyloid precursor protein), is widely investigated, although the exact role in the pathogenesis of Alzheimer remains unclear. The most consistent biochemical change associated with Alzheimer's has been the well-documented decline in cholinergic activity that has inspired many attempts to treat this disease with cholinergic drugs.

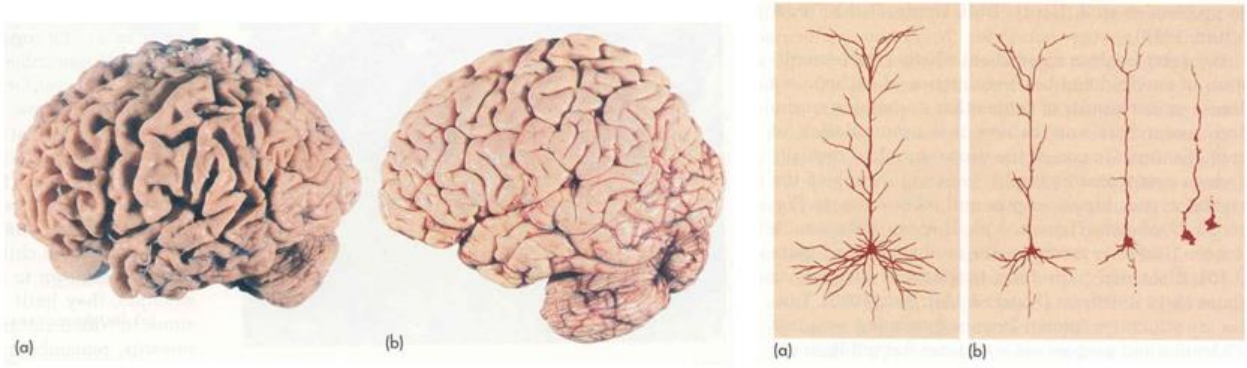

Figure 4. Brain atrophy in Alzheimer's disease. Left: The cerebral cortex of a patient (a) has widened sulci and shrunken gyri in comparison with those of a normal person (b). Right: Atrophy is due to neuronal degeneration and cell loss. A cell in the prefrontal cortex of a normal brain (a). Cells from the same area of the cortex in Alzheimer's disease at various stages of deterioration (b). Note the shrinkage of the dendritic tree. [Source: J.W. Kalat, Biological Psychology, Wadsworth, 2009].

Hypotheses Regarding Alzheimer's Disease

The oldest hypothesis of Alzheimer dementia is the cholinergic hypothesis (Bartus et al., 1982), and most drug therapies are still based on this hypothesis. The cholinergic hypothesis proposes that Alzheimer's is caused by a reduced synthesis of the neurotransmitter acetylcholine. Decreased levels of acetylcholine in the brain are believed to be responsible for the typical symptoms of Alzheimer's disease. This hypothesis got an extra boost when publications appeared that smoking may prevent the development of Alzheimer's. Later papers, however, made clear that smoking just doubles the risk on dementia, probably by the negative effects on blood vessels. This could mask the eventual positive effects of smoking by the stimulating effects of nicotine on the cholinergic system. The cholinergic hypothesis is the leading hypothesis but has not maintained general support, because medications intended to treat acetylcholine deficiency have not been very effective in Alzheimer's. Medication is only delaying the deterioration and is not a cure of the disease. Despite this, almost all patients are treated with drugs increasing the level of acetylcholine. Two drugs are in use: galantamine and rivastigmine. Both belong to a class of drugs called cholinesterase inhibitors. These inhibitors block the action of acetylcholinesterase, the enzyme responsible for the destruction of acetylcholine. Galantamine and rivastigmine increase the concentration of acetylcholine in the brain by blocking the enzyme. The increase in acetylcholine is believed to be responsible for the improvement of symptoms of Alzheimer's.

In 1991, the amyloid cascade hypothesis (Hardy and Higgins, 1992) postulated that extracellular beta-amyloid deposits are the fundamental cause of the disease. Support for this postulate comes from the location of the gene for the amyloid precursor protein on chromosome 21 and the apoE4 gene on chromosome 19. In particular, these two genes make people more risk full for the development for Alzheimer's. Especially the apoE4 gene, synthesizing a specific isoform of apolipoprotein, is a major genetic risk factor. Scientists estimate that apoE4 is implicated in about 20 to 25 percent of late onset Alzheimer's. While most isoforms of these proteins enhance the breakdown of beta-amyloid, the apoE4 isoform is not effective in this process, leading to an excess of beta-amyloid in the brain. Further evidence is delivered by the finding that mice with a mutant form of the human amyloid precursor protein gene, develop amyloid plaques and a brain pathology reminding Alzheimer's. The amyloid cascade hypothesis fails however to explain some aspects of Alzheimer's, such as the poor correlation between plaque load and the degree of dementia. Therefore, an additional hypothesis, the tau-hypothesis (Braak and Braak, 1991), has been postulated that might fill this gap. This hypothesis proposes that tau-protein abnormalities precede the cascade of amyloid, since hyperphosphorylated tau begins early to pair with other threads of tau. Eventually, this leads to the formation of neurofibrillary tangles inside the nerve cell bodies. When this occurs, the microtubules disintegrate, destroying the structure of the skeleton of the neuron with a cascade of amyloid. This results in a malfunction in neurons and ends finally in the death of the cells.

Oxidative stress may be significant in the formation of the pathology. Free radicals, mostly originating as by-products of the action of mitochondria in the cell, mediate oxidative cell injury and cell death. Mitochondrial oxidative phosphorylation is the major source of free radicals. The oxidative damage that ensues, attacks the structural and functional integrity of neurons. Alzheimer's seems associated with a dysfunction of neurons due to free radical productions. Moreover, it is characterized

by a deficiency of antioxidant capacity. The free radicals thus are able to produce cellular damages unchecked by antioxidants. This is the 'oxidative stress' hypothesis of Alzheimer's (Markesbery, 1997). The use of antioxidants to limit the activity of free radicals as a therapy for Alzheimer's is extensively evaluated over the past decade. Perhaps the most widely studied is the antioxidant vitamin E, a candidate because of its powerful activity. Also vitamin D has been shown to have strong potencies as an antioxidant. Omega-3 fatty acids are in use to attack the inflammation induced by the free radicals by strengthening the cellular membrane. All three substances, however, are not the ultimate panacea for Alzheimer's disease.

Living with Alzheimer's Disease

In all simplicity it can be stated that the affected cortical parts of the brain are responsible for the cognitive and mental defects and disorders, whereas the damaged hippocampus causes memory problems and the impaired amygdala induces the emotional swings. The changes in the brain start long before the first clinical signs such as short-term memory loss, are expressed. When clinical signs are noticeable, the affection of the brain is already in such an advanced stage that a therapy only can help in delaying the disease. Researchers hope to discover an easy and accurate way to detect Alzheimer's before irreversible brain damage has occurred. They believe that biological markers offer one of the most promising pathways. By using modern scanning techniques biomarkers such as the plaques (beta-amyloid level) and tangles (tau-protein level), indicating the presence of the disease can be identified in an early stage. Research on new strategies for an earlier diagnosis is among the most active areas in Alzheimer's science. Because early detection with biological markers on a structural level are not yet sensitive enough, diagnostic indicators focus on a functional neuropsychological level. A sensitive test to detect early dementia of the Alzheimer type is the Visual Association Test (VAT) of Lindeboom et al. (2002) (Figure 5). This test detects with high specificity a great proportion of patients with Alzheimer's a year before the actual diagnosis can be achieved. A low score on this test is uncommon in patients with another type of dementia.

Figure 5. The visual association test of Lindeboom and colleagues (2002), a brief learning task based on memory recall. The test materials consist of six familiar drawings (left part) shown to the person who has to name the objects. Secondly, each object is coupled to a non-associated other familiar object, for example, the ape now holds an umbrella. The six coupled pairs are presented again to the person who has to name now both objects of each pair (right part). Later, the six original single drawings are presented again to the person and now he has to name the associated objects of the

second presentation. A score of 2 or lower (maximum 6, which is a normal score for healthy persons) strongly points to Alzheimer's.

Life expectancy for Alzheimer patients vary for each patient, but the average life duration after diagnosis is approximately 10 years. In some cases, however, it can be as short as 3 years or as long as 20 years. There is a direct connection between brain abnormalities and the length of life. When cortex atrophy is too severe, e.g. when cortical thickness drops under 4 mm, death follows (Figure 6, left part). Alzheimer's can be undiagnosed for several years. In fact, the average length of time between the beginning of the early symptoms and the establishment of the diagnosis is estimated on 3 years. Alzheimer is an old people disease but it is not a normal part of ageing, although the greatest risk factor is increasing age (Figure 6, right part). The majority of people with Alzheimer's is 65 or older. However, Alzheimer's is not only a disease of old age since up to 5 percent of patients have early-onset Alzheimer's, often appearing when someone is in his early 40s or mid-50s. There are two categories of genes that are implicated in the development of Alzheimer's (Bertram et al., 2010). The upper mentioned risk genes, such as the apoE4 gene, increase the likelihood of developing Alzheimer's, although it is not certain that those people who have this gene will develop the disease. The estimation is that these risk genes are involved in about 20 to 25 percent of late-onset Alzheimer's. The second category consists of the deterministic genes, which cause Alzheimer's in everybody who inherited these genes. In a few hundred extended families these rare Alzheimer genes are found, which genes are responsible for these familiar early-onset Alzheimer forms.

Worldwide there are more than 50 million Alzheimer patients. A number that is fast increasing given the increase in the average age of humans. Alzheimer's place a great burden on caregivers, especially given its debilitating and dehumanizing nature. Caring for someone with Alzheimer's has a great impact on every aspect of the caregiver's life. As a patient with Alzheimer's loses one mental or physical ability after another, a caregiver faces tests of patience, problem solving and resiliency. Maintaining the emotional and physical fitness is crucial for caregivers. The continuous care makes that Alzheimer's is a highly costly disease. It is estimated that almost half of the total nursing fees are for Alzheimer patients, due to the combination of the high costs for nursing and the lengthy stay of nursing. Medical society should make a major step forward in designing tests to predict a very early onset of the disease, facilitating the development of treatments which could prevent the progression of the disease.

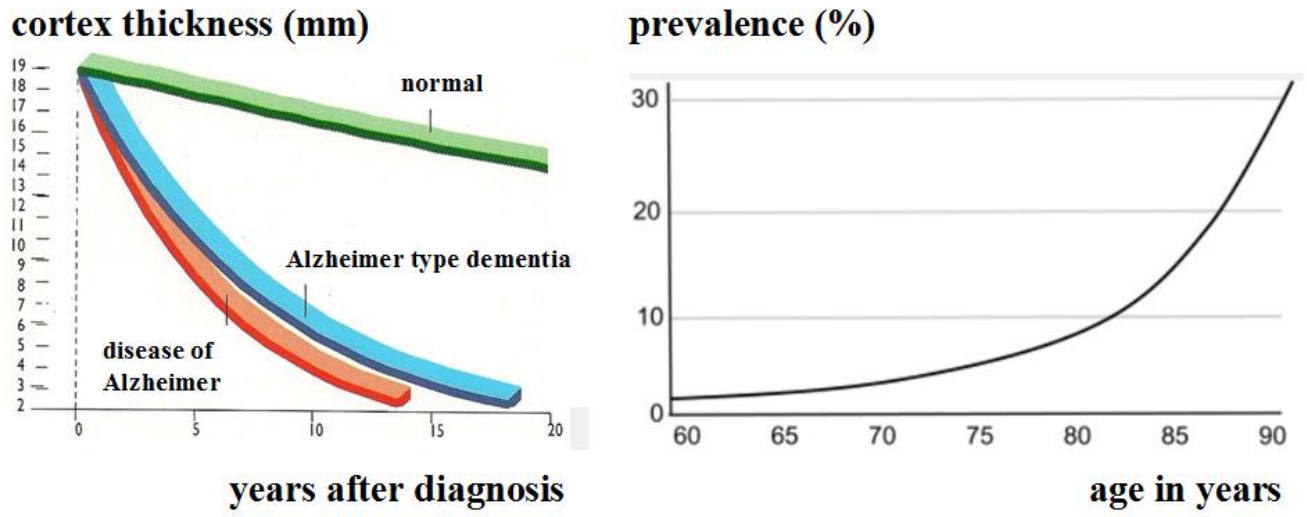

Figure 6. Left: average life expectancy is about 10 years after diagnosis of Alzheimer's or Alzheimer type dementia, mostly vascular dementia. Death comes when the atrophied cortex thickness is strongly reduced. Right: Global prevalence of Alzheimer's disease in percentage as a function of age. From this graph it is evident that Alzheimer's is an old people's disease. Approximately 30% of people of 90 years show clear symptoms.

Vascular Dementia

Vascular dementia is characterized by a progressive decline in memory and cognitive functioning caused by a blockage or reduction in the blood flow to the brain. When the blood supply to the brain is interrupted by diseased vessels, brain cells are deprived of oxygen and vital nutrients, often causing damage to the cortex, the brain area which is involved in learning, memory and language. Vascular dementia is the second most common type of dementia after Alzheimer's disease, accounting for up to 40 percent of dementia cases in older adults. Depending on the person and the severity of the vessel obstruction, vascular dementia might start gradually but mostly more sudden and more stepwise compared to Alzheimer's, and can range from mild to severe. Currently, there is no cure for vascular dementia, but there are steps to prevent vessel obstructions and strokes. Moreover, there are ways of living such as sufficient mental and physical activities, to compensate for cognitive losses, slowing the development of dementia. Vascular dementia is a heterogeneous entity with a large pathological spectrum consisting of cortical and subcortical ischemic damages resulting from local large- or small-vessel occlusions. Symptoms of vascular dementia include memory deterioration, though often less significant than in Alzheimer's. Moreover, impairments in other cognitive domains, such as in language, executive functions and spatial orientation, may occur. Psychiatric disturbances such as depression and apathy are common in this type of dementia. The worsening of cognitive abnormalities might have a major impact on daily living of patients as well as on their family and caregivers.

Epidemiological studies have recently established that vascular dementia and Alzheimer's disease are more closely linked than was previously thought. Vascular dementia and Alzheimer's share a number of vascular risk factors,

including atherosclerosis, high blood pressure and diabetes. Alzheimer patients have a higher risk for stroke, with about 30 to 50 percent of Alzheimer's displaying evidence of strokes at autopsy. The exact role of stroke in the disease of Alzheimer remains to be investigated. In any case vascular dementia and Alzheimer's cannot be longer considered as strictly separated conditions. Mixed dementias with post-mortem pathological evidence for both vascular dementia and Alzheimer's seem much more common in the elderly than the pure forms of dementia. The clinical criteria to distinguish mixed dementia from vascular dementia and Alzheimer's remain to be clearly defined. There is some evidence that cholinesterase inhibitors, such as rivastigmine and galantamine, may have a role in the treatment of vascular dementia. These agents have proven symptomatic efficacy in Alzheimer's disease, and their use in vascular dementia has justification given the high prevalence of dementia with mixed pathologies. It is recommended to treat patients also for the cerebrovascular risk factors (Kirshner, 2009).

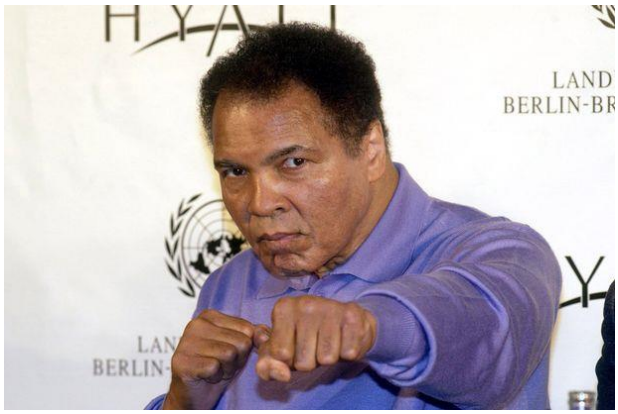

Figure 7. This is the legendary American boxer Muhammad Ali, born as Cassius Clay (1942-2016). Ali suffered from Parkinson's disease which he got already at the end of his long boxing career. It is estimated that he got more than 25,000 punches to his head, while he fought without a helmet. The repeated blows caused multiple infarctions, leading to dementia pugilistica. It is still under discussion whether the disease of Parkinson he got, was the direct result of the trauma to the head causing the dementia or the medicines he got for that, or that it was just a fate that hit him The photo is taken from the Daily Mirror from 2014.

A form of vascular dementia is known under the name multi-infarct dementia (Figure 7). This type of dementia is caused by a series of minor strokes. A stroke or infarction is the interruption or blockage of the blood flow to a part of the brain. Multi-infarct implies many small strokes with many, mostly small areas of, usually permanent, damage. A stroke can be 'silent'. That means that it affects such a small area of the brain that it will not be noticed. Generally, a silent stroke is indicated as a 'transient ischemic attack' (TIA). Over time, many TIA's may lead to multi-infarct dementia. Multiple infarcts and TIA's are often the consequence of boxing. Boxing is a violent sport in which athletes accept the risk of brain damage. The most feared consequence of insults to the brain is multi-infarct dementia or dementia pugilistica ('boxing'), now called 'chronic traumatic encephalopathy' (CTE) (Saulle and Greenwald, 2012), the dementia which results from numerous small damages to superficial brain areas (Erlanger et al., 1999).

Frontotemporal Dementia

Frontotemporal dementia (FTD) occurs less often than other forms of dementia, such as Alzheimer's disease or vascular dementia. However, it is a significant cause of dementia in younger people and is most often diagnosed in

people between the ages of 45 and 65. This is considerably younger than the age at which people are mostly diagnosed with the more common types of dementia. Frontotemporal dementia is probably the third most common cause for people in this age group. It affects men and women equally. FTD primarily affects the frontal and temporal lobes of the brain, the areas generally associated with personality, behavior and language (Weder et al., 2007). Portions of these lobes atrophy or shrink (Figure 8) and signs and symptoms vary, depending upon the portion of the brain affected. Some people with frontotemporal dementia undergo dramatic changes in their personality and become socially inappropriate, impulsive or emotionally indifferent, while others lose the ability to use language.

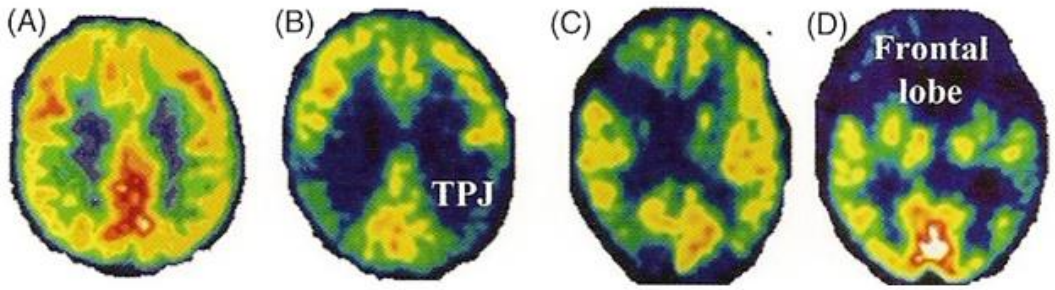

Figure 8. A PET scan can distinguish between different types of dementia. (A) a 55-years old healthy control person, (B) a 60-years old patient with Alzheimer disease, the hypometabolism is most marked in the temporoparietal junction (TPJ), (C) a 50-years old patient with vascular dementia, with a more diffuse hypometabolism, (D) a 69-years old patient with frontotemporal dementia, with most marked hypometabolism in the frontal lobe. [Source: D. Linden, The Biology of Psychological Disorders, Palgrave, 2012].

Approximately 20 to 50 percent of frontotemporal dementia cases appear to be hereditary, meaning that a mutation in a specific gene is known to cause this type of dementia. Currently, mutations in six genes are known to be responsible for frontotemporal dementia. The most common genetic causes are mutations in the tau-gene and the progranulin-gene. Tau is the protein encoded by the MAPT gene. In patients with a mutation of this gene, the tau protein is altered and forms abnormal clumps in the brain. These alterations impair neuronal function, ultimately leading to cell death and disease. Tau clumps are also found in the brains of Alzheimer's patients. Progranulin is a gene that, when mutated, also causes frontotemporal dementia. A mutation results in lowered levels of progranulin protein, and not having enough progranulin protein might cause the death of neurons in frontal and temporal lobes. How mutations in these genes can cause frontotemporal dementia is the focus of much research. The mutated genes provide the molecular handle needed to discover what goes wrong in the brains of frontotemporal dementia patients.

Parkinson's Disease Dementia

Parkinson's disease, previously known as paralysis agitans, is a degenerative disorder of the central

nervous system mainly affecting the motor system (Figure 9). The motor symptoms of Parkinson's disease result from the shrinkage and death of dopamine generating cells in the substantia nigra, a part of the basal ganglia. The basal ganglia are located in the midbrain. The cause of this midbrain cell degeneration is poorly understood, but it is known that alpha-synuclein clumps are likely to begin in the substantia nigra and these clumps are thought to cause degeneration of the nerve cells that produce dopamine (Shulman et al., 2011). The most obvious clinical symptoms are movement related, including shaking and tremor, muscle rigidity, slowness of movements and speech, and difficulties with walking and gait. Later on, behavioral problems such as irritability and anxiety may arise, whereas depression is also a common symptom. Trouble of interpreting visual information with hallucinations, delusions and paranoid ideas are also arising. Other symptoms include concentration problems and sleep disorders, such as nightly sleeplessness, excessive daytime drowsiness and REM-sleep disorder. Parkinson's disease is more common in older people, with most cases occurring after the age of 50 to 60. When it is seen in young adults, it is called young onset Parkinson's disease.

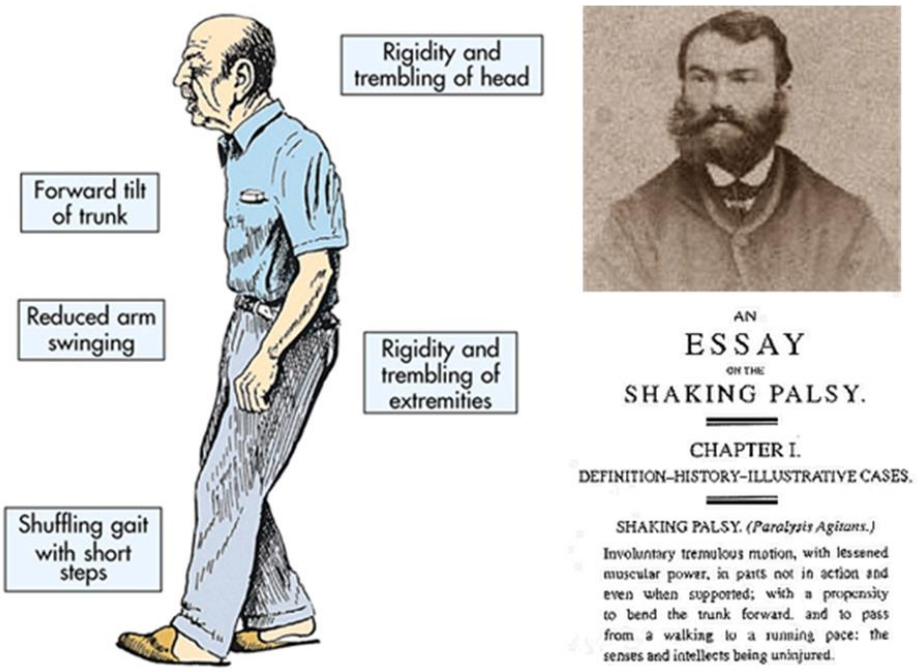

Figure 9. Left: in Parkinson's disease a slowing down of movements in conjunction with rigid muscles, a mask-like face, and trembling of head and extremities may be noticed. A forward tilted posture is also one of the symptoms, in order to prevent falling since the affected person has difficulties in maintaining body balance. Right: James Parkinson (1755 - 1824) an English surgeon, geologist, and political activist, is most famous for his 1817 work, 'An Essay on the Shaking Palsy', in which he was the first to describe 'paralysis agitans', a condition that later was renamed Parkinson's disease.

A person with Parkinson's disease has two to six times the risk of dementia compared to the general population. The prevalence of 'Parkinson's disease

dementia' increases with the duration of the disease. Regardless of age at onset of Parkinson's disease, dementia symptoms tend to appear after about 10 to 15 years, In the advanced stages of the illness an estimated 50 percent of Parkinson patients experience dementia symptoms. Dementia is associated with a reduced quality of life in people with Parkinson's disease and their caregivers, with increased mortality, and with a higher probability of needing nursing care at home. As Parkinson's disease progresses, it often results in a progressive dementia similar to the dementia seen in Alzheimer's.

Lewy Body Dementia

Lewy body dementia is a type of progressive dementia that leads to a decline in thinking, reasoning and malfunctioning because of abnormal microscopic deposits that damage brain cells. Dementia with Lewy bodies which originally was considered as a rare form of dementia, is presently the fourth common cause of dementia after Alzheimer's disease, vascular dementia and frontotemporal dementia. This is due to the fact that symptoms become more and more obvious. The hallmark brain abnormalities linked to this type of dementia are the Lewy bodies (Figure 10) (McKeith, 2002). These are named after the German-born neurologist Friedrich H. Lewy, a colleague of Alois Alzheimer. He discovered these structures while working in Dr. Alois Alzheimer's clinic during the early 1900s. Alpha-synuclein protein, the major component of Lewy bodies, is found widely in the brain, but its normal function is yet not known. Lewy bodies are also found in other brain disorders, including Alzheimer's and Parkinson's disease. Lewy body dementia is closely related to Parkinson's disease dementia. One of the differences is in the location of the Lewy bodies: in Lewy body dementia they are more found in cortical areas, and in Parkinson's dementia in subcortical areas.

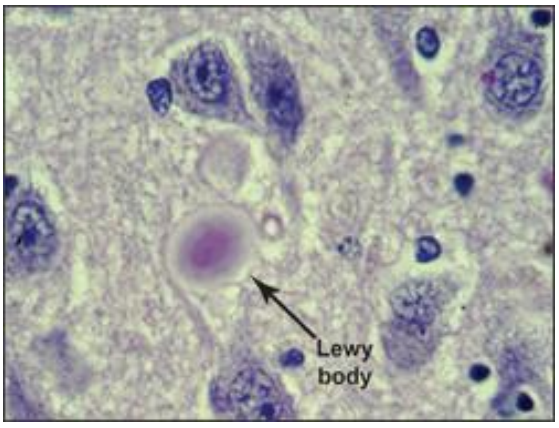

Figure 10. The key brain changes linked to dementia with Lewy bodies are abnormal microscopic deposits composed chiefly of alpha-synuclein, a protein that is found widely in the brain but whose normal function is not yet known. The deposits are called 'Lewy bodies'. [Source: J.M. Ellison, 'National Library of Medicine' (NHI), USA, 2013].

Many people with Lewy body dementia experience movement symptoms reminding Parkinson's disease, such as hunched posture, rigid muscles, a shuffling walk and trouble initiating movements. The memory loss tends to be a more prominent symptom in early Alzheimer's than in early Lewy body dementia, although in an advanced stage memory problems are considerable, in addition to the more typical Lewy body effects on judgment, planning and visual perception. Movement symptoms are more likely to be an important cause of disability in early Lewy body dementia than in Alzheimer's. Also hallucinations, delusions, REM-sleep disorders and misidentifications of familiar people ('Capgras-syndrome') are significantly more frequently occurring in early-stage dementia with Lewy bodies than in Alzheimer's. Also disruption of the autonomic nervous system, causing a

blood pressure drop on standing, dizziness, falls and urinary incontinence, is more common in early dementia with Lewy bodies. The diagnosis of dementia with Lewy bodies is done when dementia symptoms consistent with this type of dementia develop first or when both dementia symptoms and movement symptoms are present approximately at the time of diagnosis. In fact, Lewy body dementia has traits both from Parkinson's and Alzheimer's disease. Medication is done with low doses of levodopa to increase dopamine in the basal ganglia, while the confusions and hallucinations of Lewy body dementia are treated with cholinesterase inhibitors used in Alzheimer's, such as rivastigmine and galantamine.

Huntington's Disease

Huntington's disease is an autosomal dominant neurodegenerative disorder. This implies that each child of an affected parent has fifty percent chance of developing the disease. This is due to an abnormal expansion of the IT-15 gene on the arm of chromosome 4, which gene encodes for the protein huntingtin. Most people develop Huntington's disease between an age of 30 to 50 years old, although it can manifest itself on a much younger or much older age. It is a progressive disorder and death can follow between fifteen and twenty years after onset. Huntington's disease is rare with a worldwide prevalence of five to ten cases per 100.000 persons. The occurrence is highest in West-Europe and lower in the rest of the world. Prevalence is similar for men and women.

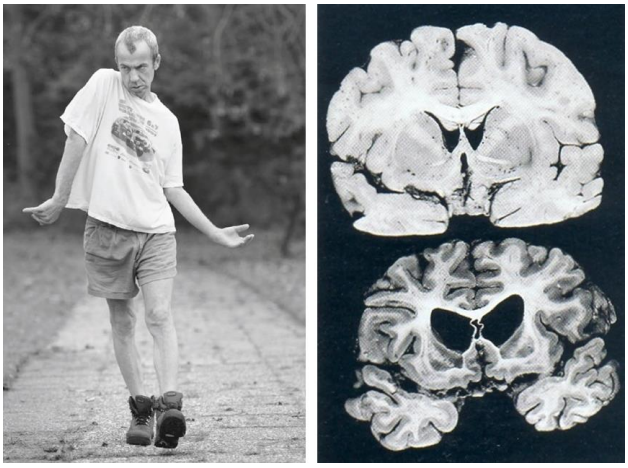

Figure 11. Left: a patient with Huntington's disease. Note the characteristic, chorea–like hand movements. The photo is taken from R. van Hes: 'Dansen aan Zee', ('Dancing at Sea'), Katwijk, NL, 2006. Right: the human brain showing the impact of Huntington's disease. The affected brain is shown at the bottom and a normal brain on top. Brain atrophy is expressed in an expansion of the cerebral ventricles (in black), due to the loss of cerebral neurons. Affection is most extensive in the region of the basal ganglia and cortex. [Source: N.R. Carlson, Physiology of Behavior, Allyn & Bacon, 2010].

Huntington's disease is clinically characterized by a triad of motor, cognitive and psychiatric symptoms (Roos, 2010). Motor features include an impairment of movements, reduced manual skills, slurred speech, difficulties with swallowing, and problems with keeping balance associated with falls (Figure 11). Psychiatric features include mood disorders (particularly depressive episodes), obsessive-compulsive behavior, and social withdrawal. Cognitive features are initially characterized by a loss of speed and flexibility in thinking, but become later more global, expressed in progressive

impairments. Especially affected are executive functions including planning, cognitive flexibility, initiation of appropriate actions, and inhibition of inappropriate movements. As the disease progresses, memory deficits tend to appear. Reported impairments range from working memory to long-term memory deficits. Cognitive problems tend to worsen over time, leading to dementia. In a post-mortem examination of the brain a reduction in brain size is found of up to 20 percent. Neuronal loss is found in the basal ganglia, the globus pallidus, the cerebellum and the cortex (Figure 11). The earliest loss is seen in the striatum of the basal ganglia, where up to 95 percent of, particularly GABAergic, neurons is lost in advanced cases. Huntington's disease can be regarded as having traits both from Alzheimer's and Parkinson's disease, in addition the disorder is characterized by its typical jerky movements.

Huntington's disease is also called Huntington's chorea. The term 'chorea' is derived from the Greek word for 'dance', as the most characteristic jerky, uncontrollable movements of feet and hands are comparable to 'dancing'. They can affect various body parts, and interfere with speech, swallowing, posture and gait. Chorea may worsen with anxiety and voluntary movements, and subsides during sleep. Severe choreiformic movements appear to be wild, violent, and can involve flinging of a body part, inducing injuries. Presently, there is no cure for Huntington's disease. Nevertheless, non-pharmacological approaches to functional difficulties and behavioral dysfunctions in Huntington's disease are important. Dopamine receptor blocking agents can be used if the chorea is seriously disrupting quality of life. Examples of agents used to alleviate chorea include reserpine and neuroleptics such as haloperidol and risperidone. Deep brain stimulation for severe and disabling cases of Huntington's chorea have already been reported.

Normal Pressure Hydrocephalus

The name 'normal pressure hydrocephalus' (NPH) is a typical misnomer since the pressure in the brain is higher than normal. In NPH the increase in intracranial pressure is due to an abnormal accumulation of cerebrospinal fluid in the ventricles of the brain due to a decreased absorption of this fluid. This can cause an enlargement of the vesicles. This ventricular enlargement is putting an increased pressure on the adjacent cortical tissues, causing the typical multiple NPH effects in the patient. Normal pressure hydrocephalus can occur in people of every age, but is most common in the elderly. It might result from a hemorrhage, from a head trauma or from a brain tumor, but people may develop NPH even when none of these factors is present. In these case the cause of the disorder is unknown. The three most typical symptoms of NPH are gait disturbances associated with walking problems, impaired bladder control with urinary incontinence, and a progressive mental slowing and inattentiveness associated with dementia (Figure 12). The patient might also have a general slacking up of his movements. Because these symptoms are similar to those of disorders such as Alzheimer's disease and Parkinson's disease, NPH is often misdiagnosed. The classic symptomatic triad of gait disturbance, urinary incontinence and dementia was first described by Adams and colleagues in 1965.

Treatment for NPH involves the surgical placement of a shunt in the brain to drain the excess of cerebrospinal fluid into the abdomen (Figure 12). This allows the brain ventricles to return to their

normal size. Regular follow-up care by a physician is important in order to identify subtle changes that might indicate problems with the shunt. The shunt treatment can reverse the symptoms and restore normal functioning in approximately 50 percent of cases, or it may do so partially, or it may not succeed at all. The reasons for sometimes not improving the symptoms of NPH with a shunt are yet not known. If NPH is not treated its symptoms get worse over time, although some people may experience a temporary improvement. While the success of treatment with shunts varies from person to person, some patients recover almost completely after treatment and have a good quality of life. Early diagnosis and treatment improves the chance of a good recovery. Without treatment, symptoms generally become more worst and may rarely cause the death of the patient.

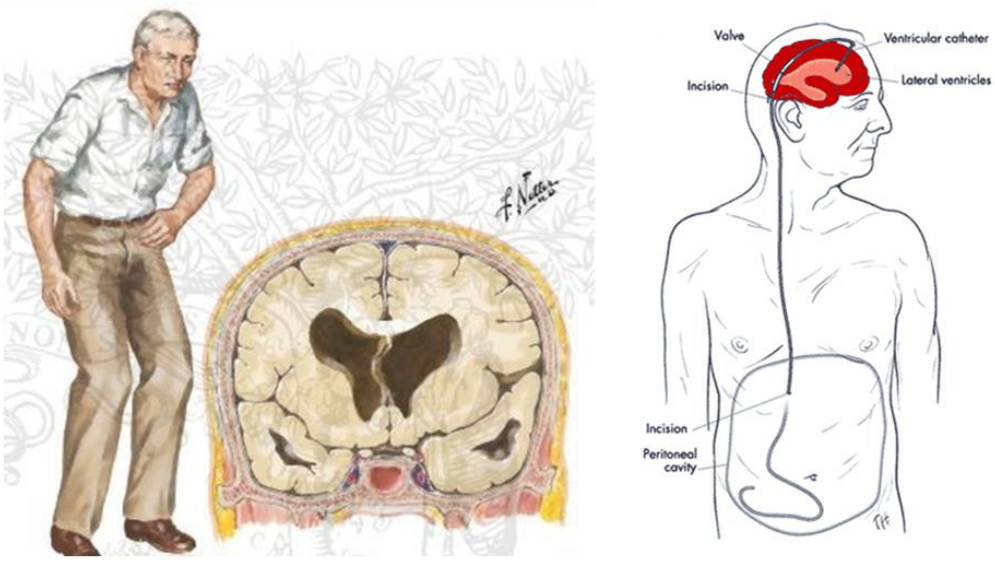

Figure 12. Left: a patient with normal pressure hydrocephalus (NPH), characterized by an abnormal gait, urinary incontinence and dementia. Middle: the enlarged ventricles of the patient's brain. Right: a ventricular catheter is installed in the lateral ventricle of the brain. The superfluous cerebrospinal fluid is drained into the peritoneal cavity of the abdomen. The left drawing is from Frank H. Netter and taken from 'The Ciba Collection of Medical Illustrations' (1986).

Recent population-based studies have estimated the prevalence of NPH to be about 0.5% in those over 65 years old, with an incidence of about 5.5 patients per 100.000 persons per year. Although NPH can occur in both men and women of every age, it is found more often in the elderly, with a common onset between 60 and 70 years of age.

Korsakoff's Syndrome

Korsakoff's syndrome is a chronic memory disorder caused by prolonged and severe deficiency of vitamin B_1, also named thiamine. The syndrome is most commonly induced by alcohol misuse, but other conditions, such as poor nutrition may also lead to this syndrome. The name giver of the syndrome is the Russian

physician Sergei Korsakoff who performed detailed studies towards alcoholic memory impairments (Figure 13). It is yet not known why heavy, prolonged drinking causes severe thiamine deficiency in some alcoholics, though alcoholics often suffer from malnutrition in addition to the fact that alcohol obstructs the uptake of thiamine. Thiamine helps brain cells to produce energy from sugar and when thiamine levels are too low, neurons cannot generate enough energy to function in a proper way. Brain cell atrophy occurs particularly around the mammillary bodies in the hypothalamus, near the hippocampus, and regions of the thalamus and the frontal lobe (Kopelman, 2015). This leads to the clinical symptoms of Korsakoff's syndrome with memory losses, confusions and confabulations.

Figure 13. In 1889, Sergei Korsakoff (1854-1900) a Russian physician who first described the severe memory impairments caused by brain damages and mostly appearing in alcoholics. Later this disorder was given the name 'Korsakoff's syndrome'.

The amnesia that accompanies Korsakoff's syndrome can extend as far back as twenty to thirty years, while old memories are recalled better than more recent ones. Both anterograde and retrograde amnesia can be found in the syndrome (Kessels and Kopelman, 2012). It has been widely accepted that the critical structures that lead to the memory impairments in Korsakoff's syndrome are the mammillary bodies and the thalamic and frontal regions. There is also a gradual degeneration of the patient's mental state, consisting of confusions, hallucinations and confabulations. In particular people with Korsakoff's syndrome often show confabulations, incorrect memories that the patient holds to be true. Korsakoff patients tend to make up stories about past events rather than to admit that they actually do not remember what happened. Patient's stories are generally plausible because they are loosely based on real experiences while the patient self believes in his stories. Confabulations are rather typical for this form of dementia. Symptoms of Korsakoff dementia are essentially the same as the symptoms present in other types of dementia, making this form of dementia difficult to diagnose. Patients with Korsakoff dementia may develop memory problems, language impairments, and an inability to perform complex motor tasks, such as dressing themselves. Patients may also develop apathy, irritability, and resistance. It can occur that people who have Korsakoff-related dementia may have a good verbal intelligence, while their language skills might be rather good preserved. A comparison between Alzheimer's dementia and Korsakoff's dementia shows in general no qualitative, but only

quantitative differences. The degree of the severity of the dementia in Korsakoff might be less serious compared to other forms of dementia, such as Alzheimer's and vascular dementia. Recovery with a vitamin B_1-enriched diet is possible in approximately 20 percent of Korsakoff patients. Most patients, on the other hand spend the rest of their lives in nursing homes or clinical settings.

Epilogue

Dementia is not a single disease but a collective designation for problems that patients experience with their cognitive functions, such as intellect, memory, speaking and language. Alzheimer's disease is the best known under the dementias. All dementias are caused by brain impairments and in particular by degeneration of the brain by a progressive cell loss. The main risk factor for acquiring brain disorders leading to dementia is ageing, although it is not a regular part of this process. Compared to normal ageing abnormal neuronal cell loss causing cognitive impairments is exceptional fast. Since it is impossible to avoid ageing and since the number of older people grow rapidly due to a general age increase, it is inevitable that the number of patients with various types of dementia, in particular with Alzheimer's disease, will show an extensive increase. To keep this rapidly growing problem under a relative control the medical and neuropsychological society must be provided with sensitive screening and diagnostic techniques to identify dementias in an early stage. In the beginning development of the behavioral symptoms of dementia are not manifest implying that brain damage is still relatively small. With valuable clinical practice early indications of beginning dementia can be detected and the braking of a further progress of brain degeneration seems than not impossible. Brain scientists and neuropsychologists have further the challenging task to identify the factors playing a role in the degenerative atrophic process. Knowing the key processes leading to neuronal cell loss and death is a major step forward in the development of a treatment or a final therapy for dementia. Both neurophysiologists and neuropsychologists have so a major responsibility in discovering effective remedial treatments for brain impairments but also for improving the quality of life for individuals with dementia.

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