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Jessica N. Schnetzer

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DEMENTIA:  
TYPES, WHAT THEY ARE AND HOW THEY DIFFER

by  
Jessica Schnetzer

A Thesis Submitted in Partial Fulfillment  
Of the Requirements for the  
University Honor Program

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Department of Medical Biology  
The University of South Dakota  
May 2020

The members of the Honors Thesis Committee appointed  
to examine the thesis of Jessica Schnetzer  
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## ABSTRACT

USD Honors Thesis:  
Dementia: types, what they are and how they differ

Jessica Schnetzer

Director: Ranelle Nissen, PhD, OTR/L

*Dementia: types, what they are and how they differ* centers on the known and unknown complexities of dementia. Dementia is a very complex cognitive disease that consumes the brain, an organ of which we know very little about. Even so, this common disorder is actively being researched and is the topic of special interest of this thesis research.

Described are Alzheimer's disease, Creutzfeldt-Jakob disease, Frontotemporal dementia, Huntington's disease, Korsakoff's syndrome, Lewy body dementia, Parkinson's dementia, and Vascular dementia, focusing on what they are, their specific risks, diagnosis, treatment, and their differing progressions. Guidance of this study provided by thesis director Ranelle Nissen, who studies dementia and is a professor at USD. The remaining two thesis committee members are Mary H. Schmitz, Director of the memory unit and former director of activities at *Grand Living at Lake Lorraine* in Sioux Falls, and Joy Backes, Director of health and wellness, also, at *Grand Living at Lake Lorraine*; all of whom have extensive dementia experience and are reliable resources and mentors during this dementia thesis process.

**KEYWORDS:** dementia, cognitive disease, disorder, Ranelle Nissen, Mary H. Schmitz, Joy Backes, Alzheimer's disease, Creutzfeldt-Jakob disease, Frontotemporal dementia, Huntington's disease, Korsakoff's syndrome, Lewy body dementia, Parkinson's dementia, Vascular dementia

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## CHAPTER ONE

### ALZHEIMER'S DISEASE

#### **What it is and how it differs**

Since 1910, the term 'Alzheimer's disease' has been used to describe this illness, named after Alois Alzheimer (Yang et al., 2016). However, there has been a record of dementia research specific to this disease before the name was assigned. A Swiss researcher named Otto Ludwig Binswanger (1852-1929) did research on neurosyphilis, a causing factor of dementia, along with Dr. Alois Alzheimer (Yang et al., 2016). He described numerous occurrences of vascular dementia in 1894 and in his report, the term 'presenile dementia' was first mentioned (Yang et al., 2016). Later, in 1910, a German doctor by the name of Emil Kraepelin (1856-1926) developed two classifications of dementia, splitting its descriptions into senile dementia and presenile dementia (Yang et al., 2016). He was then the first to title the disease as 'Alzheimer's disease' after Alois Alzheimer, who discovered pathological features of presenile dementia while working as the namesake's student (Yang et al., 2016).

Alzheimer's disease is the most common form of dementia. Alzheimer's disease has two defining factors that separate it from the rest, which are amyloid plaques and neurofibrillary tangles (Ballard et al., 2011). The key component of neurofibrillary tangles is a microtubule-associated protein termed tau (Ballard et al., 2011). The amyloid cascade hypothesis suggests that modifications in tau and resulting neurofibrillary tangle formations are caused by toxic concentrations of A $\beta$ . Several hypotheses have been offered on why this occurs; however, the pathways connecting A $\beta$  and tau are not plainly understood (Ballard et al., 2011).

## **Specific Risks**

Of the 24 million people with dementia, most have been diagnosed with Alzheimer's disease, the most common form of dementia (Ballard et al., 2011). Alzheimer's has such a high occurrence that it even outnumbers stroke, cardiovascular disease, and cancer events in people over 60 years of age (Ballard et al., 2011). Alzheimer's disease has many risk factors, the most common of which are genetics and environmental factors (Ballard et al., 2011). The gene with the highest risk factor of Alzheimer's disease is the APOE gene, which is involved with the transfer of cholesterol and can increase a person's risk of diagnosis by 3-10 times (Ballard et al., 2011). Environmental factors include lifestyle risks (Obesity, smoking, physical activity, cognitive reserve, alcohol) and some medical conditions (Midlife hypertension, stroke, diabetes, midlife hypercholesterolemia) (Ballard et al., 2011). However, because many of the risk factors come from a person's lifestyle, a diagnosis of Alzheimer's disease can be prevented/ prolonged with appropriate lifestyle changes (Ballard et al., 2011).

## **Diagnosis and Treatment**

Up until recent years, the diagnosis of Alzheimer's disease was only definitively possible post mortem (Ballard et al., 2011). With increasing knowledge in neuroimaging technologies and clinical diagnosis, earlier diagnoses have become possible (Ballard et al., 2011). When considering the clinical aspects of diagnosis, the patient's symptoms are assessed, as well as their family history, which plays a great role in diagnosis (Ballard et al., 2011). A neuropsychological assessment evaluates certain aspects of possible cognitive impairment, such as whether social, occupational, or other instrumental

functions have been affected (Ballard et al., 2011). There are specific criteria that can be followed in such assessments: NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association), for example, has over 80% specificity for separating an Alzheimer's case from a non-dementia case (Ballard et al., 2011). However, this criterion has proven less effective when differentiating between a possible Alzheimer's diagnosis and other dementia possibilities (Ballard et al., 2011). Neuroimaging is very important when this comes into play, through which doctors can measure the brain volume of specific structures in the brain (Ballard et al., 2011). The hippocampus, for example, is an important focus when diagnosing Alzheimer's disease, and can help monitor the progression of the disease, as well as concluding an Alzheimer's diagnosis (Ballard et al., 2011). A neuroimaging biomarker assessment is very important in diagnosing a patient, especially when aligned with clinical symptoms (Ballard et al., 2011). There is a wide range of treatments available to lessen the clinical symptoms of Alzheimer's disease; however, there are no available cures or disease-modifying treatments (Ballard et al., 2011). Researchers are working to develop treatments that could potentially slow the progression of the disease through the study of the pathogenesis of brain atrophy in patients (Ballard et al., 2011). Since there are not treatments available to reverse or slow the progression of Alzheimer's disease, early diagnosis is key (Ballard et al., 2011).

### **Progression**

Neuronal dysfunction is caused by "amyloid cascade," which is a hypothesis proposing that deposition of amyloid  $\beta$  ( $A\beta$ ) triggers neuronal dysfunction and death in the brain (Ballard et al., 2011, p. 1019). This leads to the constant progression of

Alzheimer's disease in patients throughout all stages of the disease (Ballard et al., 2011). Alzheimer's disease is extremely common in the dementia field and is trademarked by progressive memory loss. When a patient first develops the disease, he or she will experience very short-term memory loss, which will continue to expand to longer-term memory loss as the disease progresses. Though post-mortem measurements of deterioration of the brain in Alzheimer's patients can often directly coordinate with the patient's degree of memory loss, this is not the case in some patients, which is where more research is to be conducted on whether or not these are misdiagnosed, or if there are other aspects of Alzheimer's disease that have gone unnoticed in previous studies (Ballard et al., 2011).

## CHAPTER TWO

### CREUTZFELDT-JAKOB DISEASE

#### **What it is and how it differs**

Discovered in the 1920s by German neurologists Creutzfeldt and Jakob, Creutzfeldt-Jakob disease (CJD) is a rare form of progressive dementia that's onset is far different from any other form of dementia discussed in this review (Tyler, 2003). CJD is associated with a poorly understood transmissible agent and is an uncommon but habitually fatal degenerative disease of the central nervous system (Centers for Biologics Evaluation Research, 2002). The mechanism of contraction and manifestation of this disease is poorly understood. Research suggests that CJD may be acquired by exogenous exposure to some sort of infectious material, or may perhaps be hereditary, caused by a genetic mutation of the prion protein gene (Centers for Biologics Evaluation Research, 2002). There are two types of this disease: new variant Creutzfeldt-Jakob disease

(nvCJD) and the general CJD (vCJD), which differ in progression and the average age of onset, as well as neuropathologic features (Centers for Biologics Evaluation Research, 2002). These variations have been set apart from other forms of dementia, too, because of their association with bovine spongiform encephalopathy (BSE, also known as “mad cow disease”), which was introduced after the 1980s-1990s epidemic of BSE in the U.K (Biologics Evaluation Research, 2002).

### **Specific Risks**

Clinical symptoms of Creutzfeldt-Jakob’s disease occur due to either genetic or sporadic events. Genetic occurrences result from the aggregation of pathologic isoform (PrP<sup>CJD</sup>) in a common protein called the prion protein (PrP<sup>C</sup>) (Tyler, 2003). Sporadic occurrences result from abnormal proteins found in the cerebrospinal fluid, most commonly the 14-3-3 protein (Tyler, 2003). Cruetzfeldt-Jakob’s disease is much rarer than other diseases with similar symptoms, having a prevalence rate of 1 in every one million (Tyler, 2003). It became popular to the public during the epidemic of BSE, where a largely disproportionate amount of people developed cases of new variant Creutzfeldt-Jakob disease, leading researchers to believe that this condition can also be infectious, as 85% of cases recorded have been listed as sporadic (Tyler, 2003). The compact amount of irregular prion protein present in vCJD lymphoid tissues issued concerns that the spread of vCJD by blood could be a larger threat than for genetically-issued CJD (Centers for Biologics Evaluation Research, 2002). Limited experimental or epidemiological analyses of vCJD transmissibility by blood or plasma have been published, and it is unclear whether human blood can transmit the vCJD agent (Centers for Biologics Evaluation Research, 2002). As a result of this concern, there are new limits on who can

and cannot donate plasma as an extra precaution when dealing with those who could have been exposed (Centers for Biologics Evaluation Research, 2002).

### **Diagnosis and Treatment**

Like many other forms of dementia, neuropathologic testing is the only way to confirm a definitive diagnosis of vCJD, as there are many types of florid plaques possible in diagnosis, which cannot be confirmed clinically (Tyler, 2003). When looking at the basal ganglia and thalamus during a diagnosis, spongiform change should be evident with little distribution in the cerebral cortex of the patient (Tyler, 2003). There may also be a dense accumulation of abnormal prion proteins, which are specifically shown to be common in the cerebrum and cerebellum in a person with vCJD (Tyler, 2003). A final diagnosis is confirmed by the identification of spongiform degeneration, neuronal loss, and astrogliosis of brain tissue (Centers for Biologics Evaluation Research, 2002). Of course, a patient is not diagnosed in most cases until clinical symptoms become apparent. These may include cognitive impairment, pain and paresthesias, dysarthria, and changes in gait (Centers for Biologics Evaluation Research, 2002).

Immunodiagnosis can also be done through antibody analysis, which can recognize both normal and pathologic isoforms of PrP (Centers for Biologics Evaluation Research, 2002). This is done by first providing a pretreatment that causes the antibodies to break down the normal proteins while leaving the pathologic isoforms intact (Centers for Biologics Evaluation Research, 2002). There are simple tonsil biopsies that can be done to diagnose nvCJD, and there is research that suggests the possibility of nasal biopsies being able to diagnose sporadic CJD, as well (Centers for Biologics Evaluation Research, 2002). There is not much successful research published for the treatment of CJD disease; however, medications can alleviate symptoms that develop after the

infection subsides. Scientists deem it possible to interfere with the conversion of PrP<sup>C</sup> to its pathologic state, which could potentially become a therapeutic target for variants of this disease in the future (Centers for Biologics Evaluation Research, 2002).

### **Progression**

Creutzfeldt-Jakob disease progresses much more rapidly than most other cases of dementia, often worsening at a daily pace (Centers for Biologics Evaluation Research, 2002). Common symptoms of early CJD include memory loss, visual hallucinations, varying types of delusions, and intense emotional and mood changes (Centers for Biologics Evaluation Research, 2002). As the disease progresses, a patient may experience “jerking” motor symptoms of the face and limbs, and develop a “startle myoclonus” upon stimulation (Centers for Biologics Evaluation Research, 2002, p. 1). The new-variant type of this disease varies greatly from sporadic cases, most importantly differing in age of onset. The average age of onset of the new-variant type is just 26 years of age, whereas sporadic cases of Creutzfeldt-Jakob disease occur almost four decades later (Centers for Biologics Evaluation Research, 2002). In nvCJD, symptoms of dysphoria, irritability, anxiety, apathy, energy loss, insomnia, and social withdrawal are common in the early to middle stages, and worsen until the mute phase (Centers for Biologics Evaluation Research, 2002). The mute phase is typically seen in the late progression of Creutzfeldt-Jakob disease, which lasts until the patient dies (Centers for Biologics Evaluation Research, 2002).

## CHAPTER THREE

### FRONTOTEMPORAL DEMENTIA

#### **What it is and how it differs**

Arnold Pick, a Czech neurologist, first discovered Frontotemporal dementia (FTD) in 1892. His patient was described to have “progressive deterioration of language associated with left temporal lobe atrophy,” which would later be termed svPPA, also known as semantic variant primary progressive aphasia (Olney et al., 2017, p. 340). Decades later, Frontotemporal dementia research resurfaced upon the publishing of research conducted by Delay, Brion, and Escourolle. This French group of researchers published a seminal paper highlighting the clinical and neuropathologic differences between Alzheimer's and Pick's disease (Olney, 2017). Pick's disease was defined to include frontotemporal atrophy (not including that of the posterior lobes) with histology that showed inflated cells and cortical-subcortical gliosis. Considering clinical aspects of the disease, symptoms included increased changes in behavior, lack of insight, and lack of apraxia and agnosia. These histological and clinical findings can be easily compared to Alzheimer's dementia, as it includes diffuse cerebral atrophy and displays neurofibrillary tangles as well as senile plaques, not to mention the overt presense of agnosia and apraxia. Because of its evident variance, Constantinidis and colleagues divided Pick's disease into three different subtypes much later, in 1974 (Olney, 2017). Interestingly, only one of the three subtypes displayed the “classic” Pick bodies, signifying that Pick bodies are not necessary in concluding a diagnosis of Pick's disease (Olney, 2017). Currently, FTD comprises clinical disorders that include changes in behavior, language, executive control, and motor symptoms (Olney et al., 2017). The three core

Frontotemporal spectrum disorders discussed are behavioral variant FTD (bvFTD), nonfluent/agrammatic variant primary progressive aphasia (nfvPPA), and semantic variant PPA (svPPA) (Olney et al., 2017). FTD is a heterogeneous disorder that involves a range of specific phenotypes in association with neuropathologic substrates of frontotemporal lobar degeneration (FTLD) including, but not limited to, FTLD-tau, FTLD-TDP, and FTLD-FET (Olney et al., 2017).

### **Specific Risks**

Every year, an estimated 1.61 to 4.1 per every 100,000 people in the United States are diagnosed with Frontotemporal dementia leading to the presence of somewhere between 20,000 to 30,000 people with this disease in the country at one time (Olney et al., 2017). Further, Frontotemporal dementia is the second most common dementia in people who are under the age of 65, following Alzheimer's disease (Olney et al., 2017). The typical age range for a Frontotemporal dementia diagnosis is between the ages of 45 and 65, with rare outliers outside this age span (Olney et al., 2017). Overall, gender does not seem to be a risk factor in the likelihood of developing this disease as supported by a multitude of statistics (Olney et al., 2017). The most common form of Frontotemporal dementia is bvFTD, which accounts for a staggering 60% of cases, with the remaining 40% accounting for various language variants of Frontotemporal dementia (Olney et al., 2017). However, this disease is presumably under diagnosed due to its overlapping symptoms with a high number of other psychiatric disorders (Olney et al., 2017). Genetics are also a sizeable risk factor of developing this disease, with 40% of Frontotemporal dementia cases having strong genetic ties (Olney et al., 2017). This includes those having a family history of symptoms associated with Frontotemporal dementia while at least 10% of cases have an autosomal dominant inheritance pattern

(Olney et al., 2017). In fact, FTD-MND is the most heritable clinical syndrome with *C9ORF72*, *MAPT*, and *GRN* being the most common genes associated with Frontotemporal dementia (Olney et al., 2017).

### **Diagnosis and Treatment**

When diagnosing frontotemporal dementia, priorities include assessing a patient's medical and clinical histories in order to pinpoint which area of the brain is affected (Olney et al., 2017). This is to be done as early on as possible, as new clinical symptoms develop with further atrophic progression of the disease (Olney et al., 2017). Various neuroimaging can further support a Frontotemporal dementia diagnosis; however, this is not always done (Olney et al., 2017). A clinical diagnosis for Frontotemporal dementia includes assessment of possible impaired confrontation naming, impaired single word comprehension, impaired object knowledge, or any surface dyslexia or dysgraphia (Olney et al., 2017). There are no approved treatments for FTD, so a prescribed treatment is often recommended based on the patient's symptoms and progression (Olney et al., 2017). Many medications have been tested for this condition, including Alzheimer's medications, acetylcholinesterase inhibitors, and Memantine, which have all proved to be ineffective in treating symptoms (Olney et al., 2017). The most effective drug on the market for FTD has been found to be limited to serotonin uptake inhibitors, such as Trazadone, which can help to lessen a patient's symptoms (Olney et al., 2017). Antipsychotics are pushed for some symptoms of FTD, but should be used with caution, as they come with side effects that vary from person to person and is highly understudied for use in the elderly (Olney et al., 2017). As far as nonpharmaceutical therapies go, exercise has been proven to show improvement for those patients who can safely endure

it, and speech therapy is typically effective in the early stages of the disease (Olney et al., 2017).

### **Progression**

The earliest stages in the progression of Frontotemporal dementia are mild and can vary depending on where deterioration occurs. A patient often experiences changes in behavior, personality, emotion, and executive function such as disinhibition, new compulsions, dietary changes, and symptoms like apathy/lack of empathy are common (Olney et al., 2017). A common first symptom of frontotemporal dementia is difficulty with word-finding, or not being able to associate a word with an idea (Olney et al., 2017). Many of these early symptoms are similar to those seen in psychiatric illness, so in the early stages, a patient is at risk of misdiagnosis (Olney et al., 2017). Symptoms that are associated with dysfunction are caused by deterioration in the paralimbic areas of the brain. These can include the medial frontal, orbital frontal, anterior cingulate, and frontoinsula cortices (Olney et al., 2017). As the disease progresses, symptoms of disinhibition begin to manifest. These can include socially inappropriate behavior, impulsive or careless actions and are linked to right orbital frontal cortex degeneration (Olney et al., 2017). Self-awareness declines later on in Frontotemporal dementia to where a patient is no longer able to recognize his or her disease state (Olney et al., 2017). As the disease progresses, deterioration may favor one part of the brain, making the symptoms unique from patient to patient. Right temporal atrophy is associated with behavioral changes, while left temporal lobe atrophy is associated with language deficiencies (Olney et al., 2017). In the first 5-7 years after diagnosis of right frontotemporal dementia, symptoms of disinhibition increase and food preference may change, leading to weight gain (Olney et al., 2017). On the other hand, left

frontotemporal dementia is much slower to progress, and so a patient may live a dozen years after onset (Olney et al., 2017). In left frontotemporal dementia, the semantic knowledge of the patient is where the most dramatic decline is seen, and severe language impairments (called “primary progressive aphasia”) manifest in the first 2 years of onset (Olney et al., 2017). Many patients with left frontotemporal dementia become non-verbal in the latest stages of the disease (Olney et al., 2017).

## CHAPTER FOUR

### DEMENTIA AND HUNTINGTON’S DISEASE

#### **What it is and how it differs**

In 1872, a 22-year-old American doctor named George Huntington wrote a paper called *On Chorea*, describing a hereditary disorder that would later be known as Huntington’s Chorea, after the paper was published in the Medical and Surgical Reporter of Philadelphia (Phillips et al., 2001). Huntington’s disease (HD) is a progressive neurodegenerative disease that has been found to be caused by a glutamine repeat expansion in mutation huntingtin (mHtt) (Ahmed et al., 2015). This mutation causes profound neurodegeneration, leading to clinical symptoms of dementia with motor abnormalities, passed down as an autosomal dominant disorder (Ahmed et al., 2015). The effects of this disease manifest mainly in the striatum, which results in the dysfunction and death of striatal medium spiny neurons (Ahmed et al., 2015). HD dementia (HDD) is widely compared to Alzheimer’s disease due to a majority of similar symptoms; however, they are not identical and can be easily differentiated during a diagnosis. Those with HDD will likely display symptoms of attention deficit, cognitive slowing, impaired

planning and problem solving, and visuoperceptual and construction deficits (Peavy et al., 2010).

### **Specific Risks**

The biggest risk factor of Huntington's disease (HD) is its dominant genetic transmission (Myers, 2004). In fact, descendants of HD carriers have a 50% chance of developing the disease, with the average onset occurring around age 40 (Myers, 2004). It is inevitable that a child who inherits the gene will eventually develop the disease with time (Myers, 2004). There is a grey area as to whether some carriers will develop Huntington's disease, depending on the carrier's trinucleotide repeat, as HD is a trinucleotide repeat disorder (Myers, 2004). There is an overexpression of CAG repeats in the Huntington's disease gene, and the total number of this repeat present in a carrier determines their likelihood of developing symptoms themselves (Myers, 2004). A typical amount of these repeats in a person without the gene are 26 or less, whereas repeats of 40 or more are associated with clinical disease expression (Myers, 2004). However, some carriers with 36 to 39 repeats have the possibility of developing the disease, but typically any amount of repeats seen between 27 and 39 are usually associated with parental transmission (Myers, 2004). Gender of the carrier plays a role in how the disease is passed on (Myers, 2004). A disproportionate number of cases with onset before the age of 21 had inherited the HD gene from affected fathers, as opposed to maternal transmission, in which case cases develop later in life (Myers, 2004). This is explained by meiotic instability of the repeat in paternal transmission, which has the propensity toward larger repeat expansion, as opposed to possible meiotic instability seen in maternal transmission (Myers, 2004). This larger size of HD repeats seen in paternal transmission

is why a much larger proportion of offspring who express the gene manifests much earlier in life than those of the maternal germline (Myers, 2004).

### **Diagnosis and Treatment**

The diagnosis of HD is initially diagnosed through simple genetic testing, as Huntington's disease is an inherited disease (Myers, 2004). However, early diagnosis of dementia within this disease is extremely important for assessing a patient's progression and developing a treatment plan to alleviate symptoms (Peavy et al., 2010). Testing for HD occurs under three circumstances including a confirmation diagnosis, predictive testing of a person hereditarily at risk, and prenatal testing (Myers, 2004). Predictive testing is often used to decide one's chances of developing certain characteristics of the disease, such as dementia, but this, of course, is not definitive (Myers, 2004). It is essential to look out for any sign of cognitive impairment in Huntington's disease, as an early diagnosis of HDD provides a marker for disease progression, a better understanding of any behavioral changes the patient experiences, and the ability to gain access to psychosocial and financial resources to compensate for functional impairment (Peavy et al., 2010). Treatments for Huntington's are only able to compensate for some symptoms (Myers, 2004). Although Huntington's disease is highly researched, there are currently no treatments available for preventing or delaying the onset of this disease (Myers, 2004).

### **Progression**

The progression of Huntington's disease differs from other forms of dementia because it is a relatively early onset and it is slow progressing. Memory decline happens over time but has been shown to develop relatively later than other forms of dementia (Peavy et al., 2010). Many studies that assess the progression of Huntington's disease

focus on surveying functional impairment such as “deficits in psychomotor speed, attention and executive functions, and visuospatial abilities, as well as motor skills coupled with times visual tracking and demographic variables” (Peavy et al., 2010, p. 1163-1164). A person’s functional ability during the progression of Huntington’s disease varies greatly from person to person, with the most varying symptom being functional ability, followed closely by measures of attention and initiation (Peavy et al., 2010). In order to ensure as much independence as possible in a person with Huntington’s disease, early diagnosis is key, as the disease is slow-progressing and a person with early Huntington’s disease can live independently for years after a diagnosis (Peavy et al., 2010). The first sign of dementia in Huntington’s disease is a change in the patient’s processing speed, which is first affected before a memory deficit onset (Peavy et al., 2010). After the initial onset of Huntington’s disease, the average survival time of a patient with Huntington’s disease is between 17 and 20 years (Myers, 2004).

## CHAPTER FIVE

### KORSAKOFF’S SYNDROME

#### **What it is and how it differs**

The name Korsakoff’s syndrome (KS) comes from Sergei Korsakoff, a Russian neuropsychiatrist who was the first to discuss a comprehensive interpretation of the syndrome in a succession of documents published between the years of 1887 and 1891 (Arts et al., 2017). In these, Korsakoff interpreted findings that the syndrome was typically linked to peripheral nerve inflammation, also known as alcoholic polyneuritis, and recognized that the disease developed from a toxin. And so, Korsakoff termed the syndrome “polyneuritic psychosis or cerebropathia psychica toxaemica” (Arts et al.,

2017, p. 2876). The term was later changed to Korsakoff's syndrome by the German psychiatrist Friedrich Jolly (Arts et al., 2017). It was later discovered by the German neuropsychiatrist Karl Bonhoeffer that KS had a direct relation to another syndrome called Wernicke encephalopathy (WE), which results from thiamine deficiency in the same way that KS does. Bonhoeffer observed that all patients who survived the WE stage advanced to KS as a residual syndrome (Arts et al., 2017). "KS is a largely irreversible residual syndrome, caused by severe thiamine deficiency and occurring after incomplete recovery from a Wernicke encephalopathy, predominantly in the context of alcohol abuse and malnutrition, characterized by an abnormal mental state in which episodic memory is affected out of all proportion to other cognitive functions in an otherwise alert and responsive patient, whose psychological makeup may be further distinguished by executive dysfunction, flattened affect, apathy, lack of illness insight, and possibly by fantastic confabulations in the early stage" (Arts et al., 2017, p. 2877).

### **Specific Risks**

The main risk factor for developing Korsakoff's syndrome (KS) is a thiamine deficiency, which is malnourishment that can arise from many different environmental factors (Arts et al., 2017). Alcoholism is thought to be the main cause of this deficiency and is the most common factor known to lead to KS (Arts et al., 2017). There is no evidence, however, for any other reasoning behind alcoholism leading to KS (Arts et al., 2017). Other factors that can lead to a deficiency in thiamine include hyperemesis gravidarum, starvation, certain gastrointestinal diseases, AIDS, and bariatric surgery recovery (Arts et al., 2017). Korsakoff's syndrome is likely always developed after Wernicke encephalopathy (WE) if the patient lives long enough (Arts et al., 2017). The

only uncertainty that comes with this assumption is that WE is easily overlooked, making a person with KS unaware of the preceding undiagnosed WE (Arts et al., 2017). In a paper published by Arts et al., the writers explain that “severe alcohol abuse certainly contributes to the development of WE: the high-calorie content of alcohol suppresses the feeling of hunger and favors malnutrition, the combustion of alcohol requires extra thiamine pyrophosphate (a co-enzyme in energy-bound processes), alcoholic gastroenteritis impairs the absorption of thiamine, alcoholic liver diseases reduces thiamine storage in this organ, and alcohol may impair the utilization of thiamine” (2017, p. 2880).

### **Diagnosis and Treatment**

Diagnosis of Korsakoff’s syndrome is different from many other dementias as it is not hereditary, and it is the result of WE. WE can be clearly diagnosed with neuroimaging and can help support a later clinical diagnosis of KS disease (Arts et al., 2017). The diagnosis of Karsakoff’s syndrome verifies a chronic state of the condition, rather than the acute state of WE. Symptoms that are looked for in a diagnosis of KS include dietary deficiencies, oculomotor abnormalities, cerebellar dysfunction, altered memory state and/or mild memory impairment (Arts et al., 2017). Although thymine replacement therapy has been proven to be effective for WE, KS is treated differently (Arts et al., 2017). Since KS is a chronic condition, its treatment is more focused on lessening dementia symptoms, improving skills that remain, and subduing symptoms that interfere with the patient’s normal activity (Arts et al., 2017). Though there is current research in medications such as clonidine, fluvoxamine, reboxetine, and rivastigmine for the treatment of Karsakoff’s syndrome, there has been no treatment proven to be effective in delaying the disease (Arts et al., 2017). Any treatments given will be focused solely on

minimizing the patient's symptoms.

### **Progression**

KS is the progression of WE, which develops most often from thiamine deficiency. Once a person is diagnosed with WE, it is fairly simple to treat and recover from with the use of thiamine replacement treatment (Arts et al., 2017). This can happen in a few days to weeks if diagnosed and treated early on (Arts et al., 2017). However, if a patient does not get treatment and have a consistent thiamine deficiency, their disease becomes persistent and incurable (Arts et al., 2017). This is when they are diagnosed with Korsakoff's syndrome. Korsakoff's syndrome cannot be treated and this is the point in progression where a patient begins to experience an unalterable cognitive decline due to permanent damage in the cerebellum (Arts et al., 2017). According to Arts et al., the progression of WE to KS in alcoholics (the most common risk factor group of KS) has been proposed to be as much as 85% of cases, with most of these patients develop "clinically obvious memory impairment" (Arts et al., 2017, p. 2881). In the later stages of KS, it has been recorded that many of the longest living patients end up with residual syndromes of dementia such as Alzheimer's disease. Many have also experienced other non-dementia related forms of brain damage that manifest as a result of long-term alcohol abuse (Arts et al., 2017).

## CHAPTER SIX

### LEWY BODY DEMENTIA

#### **What it is and how it differs**

Dr. Friedrich Lewy discovered Lewy body presence in neurons in 1912 while working as a neuropathologist of Parkinson's disease in the laboratory of Dr. Alois Alzheimer; however, it was not until the 1990s that the cause of these formations could be explained (Sanford, 2018). It was discovered that the misfolding of  $\alpha$ -synuclein protein causes the formation of Lewy bodies in the nervous system and though the role of  $\alpha$ -synuclein is not evident, it is thought to normally function in cell membrane remodeling at neuron terminals (Sanford, 2018). Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia, after Alzheimer's disease (Sanford, 2018). DLB stems from the development of Lewy bodies, which contain aggregations of misfolded  $\alpha$ -synuclein (Sanford, 2018). These are eventually deposited in areas of the nervous system, causing neuronal cell death and leading to clinically ostensible symptoms (Sanford, 2018). Lewy body dementia is an "umbrella" term that encompasses dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD), which have several common symptoms (Sanford, 2018, p. 603). Moreover, DLB and PDD are almost indistinguishable from one another in their final stages (Sanford, 2018). Each disease progression is the consequence of the aggregation of  $\alpha$ -synuclein into Lewy bodies but is clinically differentiated by the location of their Lewy body deposits (Sanford, 2018).

## Specific Risks

The accumulation of overexpressed protein oligomers of  $\alpha$ -synuclein form the Lewy bodies associated with Lewy body dementia (Sanford, 2018). Lewy bodies tend to aggregate in two distinct ways in this disease. Some will deposit predominantly in the cytoplasm of neurons and lead to multiple system atrophy, while others will deposit in the cytoplasm of *both* glial cells and neurons (Sanford, 2018). These formations and accumulations lead to mitochondrial mutilation and disintegration, eventually provoking the cascade of cell death, also referred to as apoptosis (Sanford, 2018). This disease progression is estimated to originate in the enteric nervous system and progress into the central nervous system, particularly through the vagus nerve, and then into the brain stem and higher cortical regions. The propagation of Lewy bodies in Lewy body dementia is considered to follow a comparable pattern to the one suggested for Parkinson's disease (Sanford, 2018). Researchers have not been able to clarify why  $\alpha$ -synuclein has an initial tendency to disrupt neurons in the vagus nerve, olfactory nerve, and brainstem nuclei; however, the accumulation of Lewy bodies in these locations lead to the generic symptoms seen early on in the disease progression. Some examples of these symptoms include anosmia resulting from olfactory nerve cell death and constipation as a result of vagus nerve cell death (Sanford, 2018). One of the earliest indicators of onset is rapid eye movement (REM) sleep behavior disorder (RBD), a symptom that can arise years before a Lewy body dementia diagnosis is made. This symptom is the result of Lewy body buildup in the hypothalamus and reticular activation system (Sanford, 2018).

Following Alzheimer's disease, Lewy body dementia is the second most common neurodegenerative dementia, affecting 1.4 million Americans. Its biggest risk factor is age, as most patients with Lewy body dementia are not diagnosed until around ages 70-

85 years (Sanford, 2018). Gender has proven to be a risk factor for the disease as well as it is estimated that 70% of diagnosed patients are male (Sanford, 2018). Besides age and gender, other risk factors to take into account are possible genetic mutations, even though Lewy body dementia is known to occur sporadically. Yet, there are a few mutual genetic mutations found in diseased patients, which appear in the leucine-rich receptor kinase 2 ( $\alpha$ -synuclein) and glucocerebrosidase A genes (Sanford, 2018).

### **Diagnosis and Treatment**

Dementia with Lewy bodies is commonly underdiagnosed and misdiagnosed (Sanford, 2018). The common clinical diagnosis will assess for any deficits in motor function, changes in behavior, mood disorders, and cognitive impairment (Sanford, 2018). However, many of these symptoms overlap with those of other dementias (Sanford, 2018). The overlap continues into neurological diagnosis, as well, as half of Alzheimer's diagnoses are found to have some degree of  $\alpha$ -synuclein pathology in addition to the anticipated pathological findings (Sanford, 2018). Clinically, it is thought that these overlaps worsen symptoms, but this has not been verified, as there is a discrepancy in the number of actual cases of DLB as clinical diagnoses differ largely from post mortem diagnoses (Sanford, 2018). An autopsy after death is the only way to make a definite diagnosis of DLB, and even then, it is hard to determine a primary diagnosis when overlapping conditions are present (Sanford, 2018).

Treating this disease has proven to be trivial. There are no disease-modifying treatments for DLB, only treatments that help to lessen a patient's symptoms (Sanford, 2018). However, because of the multiple symptoms of this disease, oftentimes multiple medications are needed, which often have negative effects on opposing symptoms (Sanford, 2018). Because one drug may improve a symptom while worsening another, it

is recommended that a patient is introduced to only one medication at a time, making treatment a cumbersome process for the patient (Sanford, 2018). One symptom that is recommended to be treated non-pharmacologically is the presence of visual hallucinations, which is common in patients with DLB (Sanford, 2018). Because of neuroleptic sensitivity of many with DLB, medications are not given for this symptom, except in severe cases (Sanford, 2018).

### **Progression**

Development of Lewy bodies in various nuclei in the reticular activating system of the brainstem can be seen in initial progression stages of Lewy body dementia, manifesting months to even years before the condition is diagnosed (Sanford, 2018). As the disease progresses, a patient may experience varying symptoms including visuospatial deficits, neuroleptic sensitivity, changes in mood, autonomic dysfunction, and recurrent falls (Sanford, 2018). This is when a patient will begin experiencing a lack of independence as these issues complicate normal activities such as walking and driving (Sanford, 2018). Increased cognitive impairment develops, and certain symptoms may get worse with medications, such as Parkinson-like motor deficits (Sanford, 2018). Mood symptoms occur, as well, with the course of this disease and can manifest in many ways including depression, apathy, and anxiety, as well as paranoia, which has been known to occur in those who experience visual hallucinations (Sanford, 2018). Dementia with Lewy bodies is a constantly progressing neurodegenerative disease for which there is no treatment that is able to affect progression, so a patient will continually progress with this disease until death (Sanford, 2018). The decline of DLB is faster than that of Alzheimer's, with patients surviving an average of 4.7 years after initial diagnosis (Sanford, 2018).

## CHAPTER SEVEN

### DEMENTIA AND PARKINSON'S DISEASE

#### **What it is and how it differs**

Parkinson's disease was described in multiple patient documents during the 1700s, but it was not until a man by the name of James Parkinson conducted his medical description of the disease in 1817 that Parkinson's was officially defined (Goetz, 2011). Further research on the disease was conducted in the mid-1800s by Jean-Martin Charcot, who influenced Parkinson's research by comparing the disease with another: multiple sclerosis, along with other disorders that are characterized by tremors (Goetz, 2011). Parkinson's disease (PD) and dementia (PDD) greatly decrease a patient's quality of life and are often labeled as death sentences, as they decrease a person's ability to remain independent (Holden et al., 2016). Though this disease has been thoroughly researched and is increasingly common, the pathogenic pathways of PD remain poorly understood (Yang et al., 2018). PD is, in fact, the second-most common neurodegenerative disease (Yang et al., 2018). Although the pathophysiological signatures are evident in numerous parts of the brain, the characterizing symptoms of PD which include bradykinesia, rigidity, abnormal posture, and resting tremor, actually stem predominantly from progressive loss of DA neurons in the substantia nigra pars compacta (SNc) of the brain (Yang et al., 2018).

#### **Specific Risks**

Parkinson's disease is the number two most common neurodegenerative illness, following Alzheimer's disease (Holden et al., 2016). An estimated 5 million people are living with this disease, a population that is expected to double in the next 20 years

(Holden et al., 2016). Parkinson's disease with dementia, or PDD, worsens the clinical progression of the disease, decreasing patient independence at a rapid rate (Holden et al., 2016). Early progression is slow, though, as those who do develop PDD on average were not diagnosed until 11 years after a PD diagnosis (Holden et al., 2016). For those who live with Parkinson's disease for 20 years or more, the chances of PDD are estimated to increase to as much as 75% (Holden et al., 2016). Although genetic transmission is a huge risk in Parkinson's disease, the biggest risk of PDD is its age of onset (Hanagasi et al., 2017). There is a 12-fold increased risk of developing dementia in late-onset of Parkinson's disease compared to those who first experienced symptoms early in life (Hanagasi et al., 2017).

### **Diagnosis and Treatment**

Those who have been diagnosed with Parkinson's disease are monitored for dementia symptoms through cognitive impairment testing and a thorough investigation of family history. It is unknown where Parkinson's disease dementia originates, making it difficult to treat (Yang et al., 2018).

Certain changes in cellular processes have been tested to gain insight on the possible causes of neuronal depletion: dysregulation of vesicular trafficking, oxidative stress, disruption of the autophagy/lysosome pathway, mitochondrial dysfunction, endoplasmic reticulum stress, and  $Ca^{2+}$  homeostasis (Yang et al., 2018). PD has motor therapies that can help with the disease's symptoms, but PDD is much harder to treat, as physical therapies are not effective in the dementia population (Holden et al., 2016). Treatments for PDD have only marginal therapeutic effects; however, there has been one medication that has been approved to specifically treat Parkinson's disease with dementia (Holden et al., 2016). Rivastigmine, a cholinesterase inhibitor, has been approved by the

FDA for treatment of this condition but is not able to change the progression of the disease, only alleviate its symptoms (Holden et al., 2016). The N-methyl-D-aspartate receptor antagonist Memantine is frequently used in PDD patients, as well, and seems to have similar effects in lessening Parkinson's disease and dementia symptoms (Holden et al., 2016).

### **Progression**

The most common misregulated processes in Parkinson's disease cortical neurons are axonal transport, cell adhesion, and mRNA splicing, all of which manifest very early on in PD progression, before dementia symptoms (Henderson-Smith et al., 2016). Causes of PD/PDD have been associated with differential alternative splicing in the cortex; the spread of  $\alpha$ -synuclein pathology to the cortex is linked specifically with PDD (Henderson-Smith et al., 2016). This is slow progressing and can lead to Parkinson's disease with or without a dementia presence. Age is an important factor in the progression of this disease as the older a patient's Parkinson's disease manifests, the quicker it may progress and the likelihood of dementia presence increases. Stated by Henderson-Smith et al., "RNA-seq clearly reveals the underlying differential alternative splicing in the posterior cingulate cortex during the course of PD and PDD. Alternative splicing of ATXN2, HSPH1, SRRM1, RELA, LRRFIP1, and TRIM9 suggests dysregulation of genes within immune and inflammation responses and transcription and RNA processing" (2016, p. 6). In this paper, Henderson-Smith et al. describe the overexpression of genes CSF3 and SELE, in both Parkinson's disease with dementia and without, occurring prior to pathological changes that occur in the posterior cingulate cortex, suggesting there likely being an early role of immune induction in the progression of Parkinson's disease, as well (Henderson-Smith et al., 2016, p. 6).

## CHAPTER EIGHT

### VASCULAR DEMENTIA

#### **What it is and how it differs**

Vascular dementia (VD) studies can be traced back as far as the 1600s when Thomas Willis described the disease in 1672. However, due to the inability to diagnose such a disease in a living patient, the typical diagnosis for vascular dementia for centuries was conjured up to be nothing but “brain congestion,” due to the “effects of untreated hypertension,” along with other diagnoses such as stroke, anxiety, and cognitive decline (Román, 2003, p. 11). The modern history of vascular dementia was initiated in 1894 when Otto Binswanger and Alois Alzheimer separated vascular dementia from dementia paralytica caused by neurosyphilis, which leads to major discoveries and studies of vascular dementia decades later, in the 1960s, when the seminal neuropathological and clinical analyses of the New Castle school in England introduced the modern era of vascular dementia (Román, 2003). Vascular cognitive impairment distinguishes the diverse nature of the influence of vascular pathology to dementia, as well as other different subtypes (O’Brien & Thomas, 2015). Though well researched, finding the exact contribution of cerebrovascular pathology to cognitive decline and dementia has proven to be exceptionally challenging. While it seems evident that cerebrovascular disease causes pathological damage and alters cognition, the actual cause remains black-boxed (O’Brien & Thomas, 2015). This is, in part, because the cognitive changes of vascular dementia are much more inconsistent than that of other disorders such as Alzheimer's disease, and are exceedingly dependent on the particular neural substrates affected by vascular pathology. Symptoms of VD that are most commonly seen, though, include attention deficits, information processing deficits, and executive function deficits, due to

the interrupting of frontostriatal circuits (O'Brien & Thomas, 2015).

### **Specific Risks**

Vascular events are the second highest cause of dementia; the first is Alzheimer's (O'Brien & Thomas, 2015). The risk of developing dementia due to a vascular event increases greatly with age, and the number of cases has a history to double approximately every 5.3 years (O'Brien & Thomas, 2015). In their paper of vascular dementia research, O'Brien and Thomas explain that "vascular pathology has a heterogeneous nature in which large vessel atherosclerosis and small vessel arteriosclerosis can lead to cortical and subcortical infarcts, subinfarct ischaemic lesions (microinfarcts in grey matter and white matter lesions), and large and small cerebral hemorrhages (microbleeds)" (2015, p. 1675). These events can take place in a variety of areas in the brain and still lead to a vascular dementia diagnosis (O'Brien & Thomas, 2015). Other events leading to vascular disease include heart disease, atrial fibrillation, high cholesterol, high homocysteine concentrations, diabetes, and obesity; however, vascular dementia is most often seen in post-stroke patients (O'Brien & Thomas, 2015). It is estimated that approximately 15-30% of stroke patients will develop dementia within 3 months following the event (O'Brien & Thomas, 2015). The prolonged instance of delayed dementia occurring in those who have had a stroke is estimated to be about 20-25% (O'Brien & Thomas, 2015).

### **Diagnosis and Treatment**

For the diagnosis of vascular dementia, a standard dementia screening test is not enough to pinpoint this specific condition (O'Brien & Thomas, 2015). There are specific screening tests that can more specifically diagnose vascular dementia: for this, the Montreal cognitive assessment scale and the vascular dementia assessment scale are used

for a more accurate diagnosis (O'Brien & Thomas, 2015). To come to a definitive diagnosis of vascular dementia, a CT scan or MRI is needed to correctly compare brain activity with clinical symptoms (O'Brien & Thomas, 2015). The CT scans are able to display infarcts and extensive white matter lesions of the brain, and an MRI examination can precisely show the location and extent of cerebrovascular disease, but a diagnosis can be completed with a simple CT scan when compared with clinical symptoms (O'Brien & Thomas, 2015). There is little explanatory research on the mechanisms of vascular dementia onset and progression, so there are no approved treatments for this specific condition (O'Brien & Thomas, 2015). Though there have been minor cognitive benefits seen with cholinesterase inhibitors and memantine, these medications are not encouraged due to a higher risk than benefit payoff. There are currently clinical trials on possible vascular dementia treatments including calcium channel blockers and other agents that target endothelial function or the renin angiotensin system, but nothing has yet seen approval (O'Brien & Thomas, 2015).

### **Progression**

Studies on the progression of vascular dementia have been most commonly done in post-stroke patients, where brain images of those with and without dementia do not display any notable differences (O'Brien & Thomas, 2015). There have, however, been several studies that have reported: "lacunes, strategic infarcts, substantial burden of white matter lesions" consistent in many vascular dementia cases, which presented one or multiple of these (O'Brien & Thomas, 2015, p. 1673). The presence of white matter lesions are a common indicator of subcortical vascular disease, which presents itself without dementia in its early stages (O'Brien & Thomas, 2015). It is worth pointing out that many of these patients who do experience dementia in this disease more likely than

not, will be experiencing a form of mixed dementia, of which is to say its cause is not vascular, though it may contribute to progression (O'Brien & Thomas, 2015). Vascular dementia arises in the top 10% of the most severe cases of those with a deterioration of vascular origin (O'Brien & Thomas, 2015). As the disease progresses, assessments must be done carefully as white matter lesions can indicate other non-ischaemic causes, but it is safe to draw conclusions of vascular origin in the oldest population (diagnosis at 75 years of age or older) since dementia is commonly more severe in older patients. This late-onset of cerebrovascular disease may not display dementia immediately, but will likely progress quickly, often showing signs of cognitive and functional impairment within three years of onset (O'Brien & Thomas, 2015). Though the pathological progression of vascular dementia is not well defined, the burden of the disease typically will increase with age, similar to other forms of dementia (O'Brien & Thomas, 2015). It is in the best interest of the patient and his or her caregivers to get the earliest diagnosis possible in order to assess and manage the progression of this form of dementia and to preserve the patient's independence as much as possible, mimicking care given to those with an Alzheimer's diagnosis, as the progression of AD is much more commonly assessed (O'Brien & Thomas, 2015).

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