Nutritional Neurosciences

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Nutrition in Brain Aging and Dementia

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Nutritional Neurosciences

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Editors

Nutrition in Brain Aging and Dementia

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Preface

In the book *Nutrition in Brain Aging and Dementia,* we embark on an enlightening exploration into the intricate connections between our dietary choices, the aging process of our minds, and the complex nature of dementia. Within the following pages, we will undertake a journey through the realms of neurology, shedding light on various aspects of dementia, deciphering the inner workings of the brain, and uncovering the factors that may heighten the risk of cognitive challenges.

This book is not a labyrinth of medical terminology; rather, it is crafted as a guided tour aimed at demystifying the symptoms, diagnoses, and treatments associated with dementia. As we navigate through these topics, our shared discovery will highlight the crucial role that nutrition plays in sustaining brain health and preventing the onset of dementia.

We strongly believe that you can picture this book as your trusted guide through the maze of information concerning dietary elements—proteins, micronutrients, and superfoods—and their potential to safeguard our cognitive function. We will also shine a light on the unsung heroes in our diet—vitamins like D and B12, natural antioxidants, and trace minerals—and explore how they can either act as defenders or challengers in the realm of dementia.

Our journey does not conclude there; we take a purposeful detour into the realm of herbal medicine, exploring its potential as a supplementary player in the drama of dementia therapy. Safety and efficacy are our guiding principles as we navigate this less-explored path, adding a rich layer to the narrative.

For those entrenched in the field—doctors, researchers, nutritionists, and healthcare professionals—this book stands as a well-stocked toolbox, offering evidence-based guidance in a field that is rapidly evolving. Consider it your set of strategies to combat the formidable foe that is dementia.

However, this journey is not exclusive to experts. It is an invitation for anyone seeking a deeper understanding of the delicate dance between what's on our plate, the aging of our minds, and the specter of dementia. Through the embrace of a multidisciplinary approach, this book aims to equip you with a comprehensive understanding, serving as a vital resource for those navigating the terrain of brain health.

So, let us embark on this expedition together, unraveling the complexities of diet, brain aging, and dementia with an approach that is both informative and easily comprehensible. Your toolkit for understanding, your roadmap for decision-making, and your companion on this journey await within these pages.

Exploring the intricate realm of dementia, our exploration guides us through pivotal sections. Initially, we investigate the pathophysiology, which involves comprehending the physiological alterations that result in cognitive impairment. Next, we explore both genetic and non-genetic risk variables, elucidating their respective roles in propensity. Progressing further, we will analyze the symptoms and diagnosis, providing insight into effectively traversing this complex terrain. This study is intended for brain researchers, neurologists, and healthcare professionals. Its goal is to provide practical insights that may improve patient outcomes. Moreover, it attracts the attention of experts in the fields of nutrition, pharmacology, and toxicology, therefore enhancing a comprehensive comprehension of the interplay between dementia and the domains of health, nutrition, and neuroscience.

Tbilisi, Georgia — Nasrollah Moradikor
Manchester, UK — Indranath Chatterjee
Kuantan, Pahang, Malaysia — Wael Mohamed

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We thank everyone who helped realize *Nutrition in Brain Aging and Dementia*. Your expertise, unshakable dedication, and genuine passion have greatly improved this book and helped us understand the intricate link between diet, brain aging, and dementia.

We thank the researchers, doctors, and healthcare professionals who generously shared their expertise and talents. This book is based on your innovative research and inspiring devotion to improving patient outcomes.

We thank dementia patients and their families for their insights and inspiration. Your perseverance inspires us to advance dementia research.

We thank our colleagues and mentors for their guidance, support, and encouragement while writing this book. Your expertise and direction helped create and ensure the material's quality. We are grateful to the publishers, editors, and reviewers who helped complete this project. Your dedication to quality and attention to detail helped create the final product.

Finally, we want to thank our families and loved ones for their unwavering support and understanding. Your patience and support have always given me strength and determination.Our comprehensive database should be useful to scholars, clinicians, and healthcare professionals. These sites' content may advance dementia research and worldwide patient care.

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Editors and Contributors

About the Editors

Nasrollah Moradikor, Ph.D. is currently Research Director and Head of Brain Aging and Dementia at the International Center for Neuroscience Research in Georgia. Dr. Nasrollah has demonstrated exceptional leadership skills in promoting applied neuroscience research and establishing fruitful collaborations among scientists worldwide. In 2021, Dr. Nasrollah founded a new community platform named "Neuroscience Network" to support and develop neuroscience in the world. His ability to create a supportive and intellectually stimulating environment has been instrumental in promoting the development of aspiring neuroscientists. He has over 15 years of research and teaching experience and till now he has chaired many national and international events in the area of neuroscience. Nasrollah has been on the scientific advisory board and evaluation committees of several institutions abroad. He has published more than 100 scientific papers, and he currently serves as an editor, editorial board member, and section editor of several reputed journals in the field of neuroscience. His contributions to the scientific community are evident through his publications, as well as more than 15 years of editorial expertise. He is an active professional member of IBRO, FENS, EBBS, ISN, ESN, and MDS.

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Chapter 1
Pathogenesis of Dementia

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Abstract Dementia is a pathological condition characterized by intricate molecular and cellular mechanisms that result in cognitive impairment. Brain damage from a variety of sources, such as injury or disease, results in dementia, which is characterized by symptoms like memory loss and altered thinking. Cognitive dysfunction, memory loss, and personality changes are among the main symptoms. Understanding dementia highlights the role of pathogenic mechanisms by revealing aberrant alterations in the brain. These mechanisms include hypertension, ageing, atherosclerosis, tau protein abnormalities, and amyloid deposition. There are still unanswered questions regarding the molecular and cellular pathogenesis of dementia.

Converging pathogenic mechanisms, including Alzheimer's disease, amyloid deposition, ageing, atherosclerosis, and hypertension, are responsible for vascular cognitive impairment, another factor contributing to dementia. These mechanisms worsen cognitive function by exacerbating cerebrovascular disease.

Keywords Ageing · Dementia · Cognitive function · Pathogenic mechanisms

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1.1 Introduction

As a diverse neurological condition brought on by brain damage from an illness or injury, dementia is defined by a group of related symptoms (Błaszczyk 2023). Its pathophysiology differs among subtypes, contributing layers of complexity to our understanding of this syndrome that is typified by significant cognitive decline interfering with daily functioning (Fan et al. 2020) Alzheimer's disease is a prominent contributor to it. It can arise from specific structural brain diseases and system degenerations (Plum 1986) Dementia has a complex pathophysiology that involves numerous factors and is generally linked to cerebrovascular disease (Chin 2023) The mishandling of tau and amyloid beta (Aβ) proteins can lead to neurocognitive impairment and memory loss, especially in Alzheimer's disease (Luque and Jaffe 2009; Tiwari et al. 2019) Conversely, dementia offers a multifaceted mosaic of aetiology and variations that complicate our comprehension of cognitive deterioration. The complexity of dementia's aetiology is revealed as we learn more about the syndrome, which adds to the complex network of symptoms that characterizes it. For the purposes of therapy phases and prevention, comprehension of the pathological perspective on dementia is crucial (Boche and Nicoll 2020). Because of protein misfolding, which is primarily seen in Alzheimer's disease (AD) with the aggregation of amyloid-β plaques and neurofibrillary tangles, proteinopathy and misfolding are thought to be the cornerstones of dementia pathogenesis (Breijyeh and Karaman 2020). A series of events culminating in cognitive decline are set off by this aberrant protein accumulation, which impairs neuronal function. Outside the domain of proteinopathy, vascular dementia is a prominent subtype that reveals a distinct pathophysiology based on cerebrovascular insufficiency (Jellinger 2008). A holistic view of dementia necessitates a deep comprehension of the complex interactions between vascular factors and cognitive decline (Fig. 1.1). Furthermore, the complexity of dementia encompasses a range of individual differences in neuropsychiatric symptoms, going beyond simple neuropathological changes (Marin 2012). This diversity highlights the need for a comprehensive approach to diagnosis and understanding, taking into account the subtle variations in dementia symptoms (Sweeney et al. 2018). In this thorough investigation, we set out to explore the intricacies of dementia, fusing pathophysiological understanding with a sophisticated comprehension of its various aetiologies.

1.2 Discussion

Dementia is a multifaceted illness that involves several pathological processes and is defined by progressive deficits in thinking, memory, and behaviour (Błaszczyk 2023). Subtypes of dementia—vascular dementia being an exception—have different pathophysiologies associated with major neurocognitive disorders (Emmady et al. 2022; Iemolo et al. 2009) Neurodegenerative disorders have a close

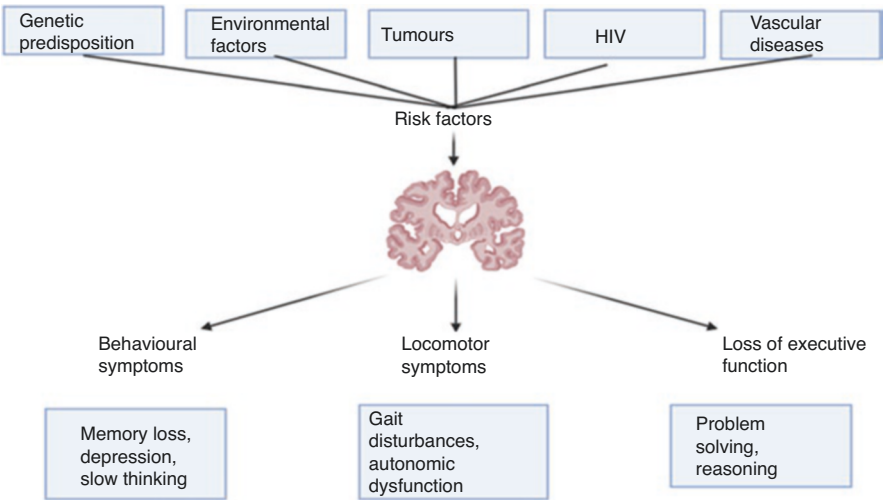

Fig. 1.1 This model describes the intricate interactions between environmental and genetic factors that cause the brain to age and set off the cascade of events that results in dementia. The manifestation of various symptoms is caused by a combination of pathological events that lead to neuroinflammation, disruption of axonal transport, synaptic dysfunction, and ultimately neuronal cell death

connection to prion diseases and dementia (Chen et al. 2022). A protein called prion protein (PrPC), which is normally present on cellular membranes in the bodies of healthy individuals (Sitammagari and Masood 2023) and is primarily prominent in neurons (Brown and Mastrianni 2010), can misfold pathologically to cause prion diseases, also known as human spongiform encephalopathies, which are neurodegenerative disorders. On chromosome 20's short arm, a single exon encodes it (Brown and Mastrianni 2010). Prion diseases are extremely rare, occurring only 1–2 times per million annually (Elziny et al. 2022), but they are fatal due to the neurodegeneration they cause (Tsilioni et al. 2014). Prions diseases can be classified as acquired, sporadic, genetic, or familial, depending on the cause (Sitammagari and Masood 2023; Smid et al. 2017). The genetic manifestations of prion diseases stem from mutations in the prion protein gene (PRNP) (Smid et al. 2017). These mutations increase the possibility of the normal prion protein (PrPC) conforming to the abnormally structured scrapie prion protein (PrPSc) (Elziny et al. 2022). The acquisition of infectivity and pathogenicity in PrPSc is attributed to a loss of alpha-helical structure and a gain in beta-sheet structure (Brown and Mastrianni 2010). Although a large number of PRNP gene mutations have been identified (Ghoshal et al. 2009), their mode of inheritance is autosomal dominant (Zerr and Schmitz 2021). Due to certain and more recent types of familial diseases, genetic prion diseases are estimated to account approximately for 15% of all cases (Smid et al. 2017), may have underestimated their true values (Brown and Mastrianni 2010). Three main presentations are caused by multiple PRNP mutations: GSS (Gerstmann-Schaussler-Scheinker syndrome), fatal familial insomnia, and familial Creutzfeldt Jacob disease

(fCJD). Moreover, similar mutations can result in diverse clinical phenotypes; this unidentified diversity can be attributed to the influence of other genes or the existence of distinct PrPSc subtypes (Brown and Mastrianni 2010). Although the precise role of the protease-sensitive non-pathogenic PrPC is unknown, indications point to its involvement in signalling, neuroprotection, and the establishment, maintenance, and function of synapses (Brown and Mastrianni 2010).

1.3 Dementia and Prions

Prion diseases such as CJD and GSS can have dementia as a clinical manifestation (Brown and Mastrianni 2010; Smid et al. 2017). Although only one of the various types of CJD is exclusively familial, GSS is. But both are caused by variations in the PRNP genes' DNA sequence, such as point mutations or octapeptide repeat insertions (OPRI) (Brown and Mastrianni 2010). The E200K mutation in the PRNP gene (20) is responsible for 70% of familial CJD cases, and the p. Pro102Leu mutation of the same gene is considered to be linked to major cases of GSS. A mutation transforms the protein's structure from a cellular PrPC that is not harmful to a pathogenic isoform called PrPSc (Brown and Mastrianni 2010). PrPSc modifies the structure of pre-existing normal prion proteins in addition to causing neurodegeneration through accumulation in brain tissues (Smid et al. 2017). Additionally, mutations in the PRNP gene cause neuropathological characteristics common to GSS, such as gliosis, amyloid plaques, and neuronal loss. These aspects contribute to a range of clinical manifestations, from cognitive decline to dementia after ataxia (Sitammagari and Masood 2023). Additionally, Smid et al. (2017) discussed certain cases where dementia progressed quickly (Smid et al. 2017). The presentation of CJD results from pathological features such as "spongiform degeneration" or vacuolation that is more pronounced in the grey than in the white matter of the cerebral neocortex, cerebellar cortex, hippocampus, and other brain areas. These symptoms start out as confusion and progress to dementia, along with ataxia and myoclonus (Brown and Mastrianni 2010).

1.4 Dementia and Traumatic Brain Injury

Nevertheless, traumatic brain injury has come to light as a major risk factor for dementia, as supported by a number of studies in this area (Gu et al. 2022). Extensive research has been conducted on the relationship between alterations related to dementia and traumatic brain injuries (TBI), providing insight into the possible long-term effects of TBI. TBI is associated with an increased risk of dementia when compared to people without a history of TBI or people who have experienced trauma other than a traumatic brain injury, according to a study published in the

Lancet Psychiatry (Caye et al. 2018). This study highlights how important it is to work more to comprehend and treat the effects of traumatic brain injury on cognitive function. In addition, a national cohort study looked into the trajectory of dementia risk following traumatic brain injury. It concluded that there is a real risk of dementia in TBI patients, which begs the question of what effects traumatic brain injuries will have in the long run on cognitive function (Nordström and Nordström 2018). Furthermore, a meta-analysis demonstrated that people with traumatic brain injury (TBI) have a higher chance of developing dementia, as evidenced by a pooled odds ratio of 1.81 (Mielke et al. 2022). This emphasizes the significance of considering traumatic brain injury (TBI) as a possible risk factor for dementia and emphasizes the necessity of providing patients with a history of TBI with more comprehensive medical care.

Traumatic brain injuries (TBI) and their possible neurological effects have garnered more attention recently (Iacono et al. 2021), especially when it comes to those connected to the neurodegenerative disease known as chronic traumatic encephalopathy (CTE) (Lee et al. 2019). Researchers have connected TBI to a number of neurodegenerative diseases, including dementia (Iacono et al. 2021). According to Diego Iacono et al.'s study, traumatic brain injury (TBI) can delay the onset of cognitive decline and related disorders by over 3 years for people of all ages, genders, and educational backgrounds (Iacono et al. 2021). Nonetheless, traumatic brain injuries (TBIs) can happen frequently in both civil (like sports participants in football, rugby, soccer, and boxing) and military (like veterans) contexts (Iacono et al. 2021; Ling et al. 2015; Murray et al. 2022). In the former case, TBIs may resemble those from car crashes, falls, sports-related injuries, and more serious military operations (Leung et al. 2022).

Before the last 20 years, dementia pugilistica was believed to exclusively affect boxers, and the condition that connected neuropathology and recurrent head injuries was referred to as "punch drunk syndrome" or dementia pugilistica (Murray et al. 2022). Chronic traumatic encephalopathy (CTE) is the term currently used to refer to dementia pugilistica, and Harrison Martland was the first to describe the long-term motor and neuropsychiatric effects of various types of TBI (McKee et al. 2013). Loss of consciousness (LOC) is a possible side effect of TBI. Still unknown, though, is the relationship between the pathologic characteristics of dementia and a traumatic brain injury (TBI), with or without a loss of consciousness (LOC) (Agrawal et al. 2022). According to a study by Sonal Agrawal et al., there may be a higher chance of late-life neurodegenerative and vascular brain pathologic outcomes associated with dementia with TBI, even in the absence of LOC (Agrawal et al. 2022). Apart from that, a great deal of research has been done to find out how severe a TBI is and how likely it is to lead to dementia. In terms of dementia manifestation, penetrating injuries and intracranial haemorrhages were found to be the most dangerous, followed by mild injuries like concussions and moderated injuries like skull fractures with LOC (Leung et al. 2022). Traumatic brain injury (TBI) can cause bleeding, edema, altered cerebral blood flow, vasospasms, coagulopathy, and disruption of the blood–brain barrier (BBB) in a healthy encephalon (Salehi et al. 2017). Breakdown of the blood–brain barrier is a major contributing factor to

late-onset dementia, according to Abrahamson et al. Within brain micro-vessels, the blood–brain barrier (BBB) is an endothelial membrane covered in perivascular astrocytes and mural vascular cells (Abrahamson and Ikonomovic 2020). In order to maintain a regulated median for neuronal and synaptic activity, its main purpose is to protect neurons from chemicals present in the bloodstream (Sweeney et al. 2018). Increased intracranial pressure or a contusion can agitate tight junction proteins (Yeoh et al. 2013), which results in increased molecular mobility outside of cells, which is frequently restricted by the endothelium barrier (Abrahamson and Ikonomovic 2020). An axonal injury in the fornix, which forms the primary projection routes from the hippocampus that are crucial for memory, was observed in five postmortem cases of APP-immunoreactive and moderate traumatic brain injury (TBI) according to an immunohistochemistry study by Blumbergs et al. (1994). Nevertheless, when APP is disrupted, amyloid-β (Aβ) peptides are generated, which are an essential component in the pathophysiology of Alzheimer's disease (Ling et al. 2015). In addition to neurofibrillary tangles (NFTs) of hyperphosphorylated tau depositions, several autopsy reports revealed widely dispersed Aβ plaques in the majority (Lee et al. 2019). In the meantime, the range of non-tau proteinopathies that manifest in TBI late survivors has not received as much attention as tau pathologies in CTE. Given this, the first consensus criteria for the neuropathological diagnosis of CTE describe the disease solely on the basis of tau distribution and pattern (Bieniek et al. 2015). In addition, a histological analysis of six athletes who passed away within 6 months of receiving a concussion diagnosis showed neurites and focal tau-positive NFTs close to the locations of localized axonal damage and microhaemorrhage (McKee et al. 2013). There is a strong correlation between NFTs and the progression of dementia; typically, the quantity and distribution of NFTs have been shown to correlate with dementia severity and duration (Chen and Mobley 2019). However, altered permeability of the blood–brain barrier (BBB) due to alterations in endothelial cell junctional proteins caused by TBI is another pathogenicity of dementia and chronic neurodegeneration that can be linked to TBI. Chemicals that are normally contained by the endothelium barrier flow more freely throughout cells when tight junction proteins are absent or expressed differently, altering the ratio of plasma to interstitial fluid molecules. Furthermore, neutrophils may interact with transendothelial migration to release inflammatory cytokines and chemokines in addition to inducing contraction of endothelial cells and consequent opening of the barrier (Leick et al. 2014). Furthermore, inflmmation may play a role in the pathophysiology of dementia, as well as inflammatory biomarkers offer fascinating insights into the risk of dementia overall (Dziedzic 2006). These aberrant molecular pathways have the potential to repeatedly alter BBB permeability after a TBI, perpetuating this cascade (Abrahamson and Ikonomovic 2020).

1.5 Dementia and Tumours

A fascinating connection between dementia and tumours has been revealed by recent research, providing insight into their common pathogenesis (Lehrer 2010). The complex terrain of cognitive disorders is influenced by a variety of factors, including traumatic brain injuries and brain tumours, even though neurodegenerative dementias, such as Alzheimer's disease and dementia with Lewy bodies, are common in the elderly (Gale et al. 2018). Most notably, research was done on the fascinating connection between Alzheimer's disease and cancer. The results hinted at common underlying mechanisms and suggested a correlation between the onset of many cancers and the advancement of Alzheimer's disease (Roe et al. 2010). Further research on tumours linked to genes that increase the risk of cancer has provided fascinating new information about possible links between particular cancers and cognitive effects (Binarelli et al. 2023).

Tumours pose a severe risk to public health and are a significant cause of morbidity worldwide (Uwishema et al. 2023). These days, intracranial and central nervous system tumours are becoming more common, especially in the elderly (Uwishema et al. 2023). Because brain tumours have a large impact on surrounding brain tissue, they can cause dementia (Matsuo et al. 2021). In no more than a few years, dementia symptoms can include personality changes (such as akinetic mutism), myoclonus and psychotic symptoms, and an accelerated decline in cognitive, behavioural, and motor function (such as pyramidal and extrapyramidal signs, cerebellar and visual symptoms) (Sanz et al. 2014). In addition to tumours, deferential diagnoses for dementia could also include infectious mechanisms like herpes simplex encephalitis, Lyme disease, subacute sclerosing panencephalitis, toxic-metabolic substances like lithium, neurodegenerative, neoplastic, and autoimmune processes (Sanz et al. 2014). Meningioma, for instance, is a benign brain tumour that has been demonstrated to cause reversible dementia (Matsuo et al. 2021). Since all of the motor cortex, Broca's region, and the main trunk of the anterior and middle cerebral arteries are affected in frontal meningiomas, psychiatric symptoms like mood disorders, psychosis, memory issues, personality changes, anxiety, and anorexia nervosa are often seen (Matsuo et al. 2021). Indeed, the tumour usually affects the hemispheres of the brain and the periventricular zone, but it can also affect deeper brain structures like the thalamus, corpus callosum, and basal ganglia (Deutsch and Mendez 2015; Roth et al. 2012). A closer look reveals sparse amyloid plaques, neuronal loss, gliosis, and typical Lewy bodies in the locus coeruleus, as well as spongiform changes involving both large confluent vacuoles and classic microvacuoles, along with moderate atrophy or demyelination in the affected areas of the nervous system (Vita et al. 2017).

While mass-effect symptoms account for the majority of its neurologic expressions, dementia has also been identified in patients with Primary Central Nervous System Lymphomas (PCNSL). For this reason, this neoplasm should be added to the differential diagnosis of rapid-onset dementias (Degnan and Levy 2014). One kind of non-Hodgkin lymphoma called PCNSL solely affects the central nervous

system (CNS) and does not spread throughout the body (Deutsch and Mendez 2015). Ninety percent of PCNSLs (proliferating large B-cell lymphomas) are DLBCLs, accounting for 3–5% of all brain tumours with an incidence of 5 per million person-years (Achi et al. 2018; Sanz et al. 2014). About this cancer, the disease is characterized by rapidly progressive dementia (RPD), where individual lymphoma cells invade the cerebral white matter without producing a mass effect (Sanz et al. 2014). Numerous genes involved in the regulation of cellular growth have been found to have somatic hypermutations (Montesinos-Rongen et al. 2004). In addition, numerous intracellular pathways have been changed, most notably the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway, which involves an increase in the expression of genes regulated by NF-kB (Sanz et al. 2014). Studies have also shown that p14ARF and p16INK4a are frequently inactivated, which may potentially contribute to the pathophysiology of CNS lymphoma (Nakamura et al. 2001).

Sentinel lesions, or demyelinating lesions, are closely associated with PCNSL. Sentinel lesions are characterized by typical histologic features such as demyelination, widespread macrophage infiltration, histiocytes, Creutzfeldt astrocytes, and lymphocytic infiltrates (T-cells and B-cells) with perivascular distribution (Achi et al. 2018). It is unknown what mechanism leads to the development of PCNSL in conjunction with a demyelinating lesion, which can potentially cross the corpus callosum and result in a "butterfly" lesion (Achi et al. 2018; Degnan and Levy 2014). However, some theories address the noteworthy hypothesis of malignant transformation of an inflammatory process and antibody-mediated demyelination caused by anti-myelin antibodies released by lymphoma cells (Achi et al. 2018). Thus, among all of these pathological, anatomical, and histological alterations, dementia would be expected as a consequence (Brett et al. 2018).

For example, Creutzfeldt-Jakob disease (CJD), the most worrisome and fatal diagnosis within the dementia family, shares clinical features with T-type lymphomatosis cerebri (LC), a subtype of primary central nervous system lymphoma (PCNSL), such as personality changes and myoclonus (Rosenbloom and Atri 2011; Sanz et al. 2014). While lymphomatous dementia is curable, PCNSL can rapidly become fatal if untreated, which is why it is imperative to diagnose lymphomatous dementia as soon as feasible (Deutsch and Mendez 2015).

Greater attention is required due to the critical role that infiltrating and metastatic tumours play in the development of rapidly progressive dementia (RPD) (Deutsch and Mendez 2015). Numerous instances have been documented where metastatic tumours have aided in the development of rapidly progressing dementia. Specifically, miliary cerebral metastasis has been shown to trigger a multifocal cortical involvement that leads to subacute dementia (Degnan and Levy 2014). However, some patients have developed dementia during the course of treating metastatic disease; this condition could be mistaken for a side effect of chemical and radiation therapy (Degnan and Levy 2014).

Malignant tumours have been related to a set of conditions known as paraneoplastic syndromes (PNS); these syndromes are not directly caused by the malignancy itself, but rather by an immunological reaction between the tumour and host

tissues or by the process of secreting particular peptides and hormones that may trigger an immune response (Rowley 2018). The mechanism behind PNS traits is the presence of particular autoantibodies called "onconeural antibodies", which are generated in response to tumours and have been demonstrated to target both tumour cells and nervous system components (Kanaji et al. 2014). The antibodies in question have been associated with acquired neuromytonia due to their ability to bind to membrane channels, nuclear proteins, and intracellular and extracellular antigens. Furthermore, they have been shown to react with voltage-gated potassium channels (VGKC), which are essential to neurophysiology (Rowley 2018). Because paraneoplastic limbic encephalitis, a common feature of PNS, can cause hyperintensities in the caudate, anterior putamen, and medial temporal lobe in addition to anterograde memory impairment, it is recommended that patients suspected of having autoimmune dementia undergo an FDG-PET scan to rule out any underlying malignancy (Degnan and Levy 2014).

1.6 Dementia and HIV

Furthermore, studies on HIV-related neurocognitive impairments have shed light on the aetiology of various subtypes of viral dementia (Cornea et al. 2023). Notably, HIV has been associated with a higher risk of dementia, especially in those at risk of cognitive impairment who have advanced immunosuppression (Sacktor et al. 2009; Valcour et al. 2011). Microglia are thought to be the main source of giant multinucleated cells, a hallmark of HIV-associated dementia. HIV-1 compartmentalization and infected microglia are implicated in neuropathogenesis (Lindl et al. 2010; Rao et al. 2014). Effective treatment strategies are crucial because the incidence of HIV-associated dementia has significantly decreased since the introduction of combination antiretroviral therapy (cART), especially the most severe form known as subcortical dementia (Olivier et al. 2018). The human immunodeficiency virus (HIV) remains a major global health concern (Fonkwo 2008). According to studies, HIV causes a range of symptoms related to neurocognitive impairment and enters the central nervous system (CNS) during the early stages of infection. It then remains there for decades (Almeida and Lautenschlager 2005; Kramer-Hämmerle et al. 2005). Furthermore, it is believed that low levels of HIV CNS infection have a significant histopathological correlation with HAND, HIV-associated neurocognitive disorders, including HAD, HIV-associated dementia (Vartak-Sharma et al. 2014). For instance, it is increasingly recognized that in patients who are still in the pre-symptomatic stage of infection, astrocytes represent a sizable reservoir of viral HIV particles (Thompson et al. 2011). Additionally, it has been reported that HAND is associated with the accumulation of activated and/or infected macrophages/microglia in the central nervous system (CNS), which secrete pro-inflammatory cytokines such as interleukin (IL)-1β and tumour necrosis factor (TNF)-α as well as chemokines, infectious virions, and potentially neurotoxic viral proteins. These HAND-relevant events can result in excitotoxic damage that compromises the

survival and functionality of neurons (Chen and Mobley 2019). Though the brain's microglia and macrophages initiate these neuroinflammatory processes, astrocytes—a crucial element of the blood–brain barrier (BBB)—tightly regulate them (Sabri et al. 2003). These are currently believed to be a component of the innate immune system because they secrete effector proteins such as complement proteins, cytokines, and interferon-related proteins, in addition to changing their cytoskeleton to prevent neuronal damage (Farina et al. 2007). This starts when multiple autocrine and paracrine signalling pathways are exposed to HAND-relevant factors like IL-1β, TNF-α, and/or HIV-1. This causes the production of more cytokines and chemokines, which in turn draws more immune cells to the BBB and contributes to immune activation (Vartak-Sharma et al. 2014).

HIV also enters the central nervous system via a variety of routes. One of the primary mechanisms underlying the blood–brain barrier (BBB) is the transmigration of monocytes, specifically the CD14 + CD16+ subpopulation (Williams et al. 2014). This subset, which makes up only 5–10% of peripheral blood monocytes from healthy individuals, can account for as much as 40% of HIV-positive people (Allen et al. 1991; Pulliam et al. 1997; Thieblemont et al. 1995). To get past an undamaged blood vessel endothelium (BVE), monocytes migrate by both transcellular and pericellular diapedesis (Kamei and Carman 2010). When monocytes come into contact with cell-adhesion molecules, they roll, or exhibit diapedesis. Their response to chemokines is heightened by rolling, which also results in the formation of an integrin–endothelial ligand complex and monocyte migration to the central nervous system (Kamei and Carman 2010). Monocytes help form the viral reservoir within the central nervous system because, unlike CD4 T lymphocytes, they are immune to HIV once they enter the brain (Crowe et al. 1987; Cummins and Badley 2013; Giri et al. 2009; Olivetta and Federico 2006; Reynoso et al. 2012). They release the virus, which makes it possible for it to infect macrophages, microglia, and a small fraction of astrocytes, among other CNS cells (Brack-Werner 1999; Eugenin and Berman 2007). Because they live a long time, differentiated macrophages derived from infected monocytes remain a source of virus (Brack-Werner 1999; Williams et al. 2001). Additionally, it has been proposed that monocytes may also enter the central nervous system through the lymphatic system. Based on research by Louveau et al., this proposal demonstrates de novo the existence of orderly and functional lymphatic vessels connected to the deep cervical lymph nodes in the meninges dural sinuses (Lassmann et al. 1993). According to a recent discovery, there is a new route that allows differentiated macrophages and HIV-positive monocytes to travel from other parts of the body to the brain and back (Louveau et al. 2015). In contrast to the blood–brain barrier, lymphatic vessels consist of a single, basic layer of endothelial cells with multiple discontinuous endothelial junctions, which facilitate easier entry of immune system cells and fluids into the brain (Lamers et al. 2016). While brain tissue is difficult to obtain, CSF is widely accessible and offers information about the central nervous system's metabolic environment (Kuan et al. 2015). Early targeted studies of CSF metabolites identified changes in several neurotoxic metabolites during HIV infection, including those

related to the kynurenine and nitric oxide pathways (quinolinic acid, for example) (Giovannoni et al. 1998; Heyes et al. 1991; Heyes et al. 1992; Wishart et al. 2008).

HIV patients receiving anti-retroviral therapy (ART) have been found to have altered CSF metabolomics in terms of HIV-RNA, CSF neopterin, neurotransmitters/neurpeptides (glutamate, N-acetylaspartate (NAA)), markers of inflammation (chemokines, CCL2, TNF,IL-6) and glial activation (myo-inositol), mitochondrial dysfunction (succinate), and ketone bodies. This implies a potential relationship between glutamate excitotoxicity, astrocyte activation, mitochondrial dysfunction, and metabolic waste accumulation and neurocognitive impairment (Cassol et al. 2014). The overlap of this HAND signature with a CSF metabolite profile associated with ageing in HIV-negative subjects suggested an accelerated ageing pattern (Cassol et al. 2014). This rise in ketone bodies, phenylacetylglutamine, *p*-cresol sulphate, and metabolic wastes was especially noticeable in Alzheimer's disease and other age-related neurodegenerative disorders (Haass and Selkoe 2007; Nedergaard 2013). This can also be linked to the activation of astrocytes, which is increased in HAND (Everall et al. 2009). However, since HAD (St Hillaire et al. 2005) is reported to have increased expression of aquaporin 4 (AQP4), channels where CSF is exchanged with brain interstitial flow to prevent waste accumulation, more research is needed to determine whether damage to the lymphatic system and loss of interstitial flow are factors in the accumulation of metabolic waste and the onset of HAND (Cassol et al. 2014). Furthermore, in studies involving humans, there was a correlation observed between the degree of BBB permeability and CSF WBC counts and neopterin levels. These results imply that a permeable blood–brain barrier in HIV patients (Anesten et al. 2016), which may also be linked to astrocyte activation (Vartak-Sharma et al. 2014), may be the cause of CSF neopterin and WBC infiltration. In addition, HIV-positive individuals may experience neuronal damage as a result of comorbidities, oxidative stress, immunological activation, persistent neuroinflammation, and other factors (Saylor et al. 2016). HAD is linked to HIV-associated compromised gut mucosal barrier, according to another study. The latter results in an increase in the systemic microbial translocation metric, plasma LPS. Low levels of neuroinflammation are a result of both intact blood–brain barriers and low plasma levels of lipopolysaccharide (LPS) in healthy individuals. Increases in systemic inflammation, monocyte activation, and the permeable blood–brain barrier are all caused by elevated plasma LPS in untreated HIV, and these factors ultimately affect neuroinflammation (Jiang et al. 2021).

One of the most frequently discovered HIV-1 proteins in the CSF and serum of HIV-1-positive individuals is HIV-1 Tat, a neurotoxic nonstructural HIV-1 viral protein, when it comes to HIV proteins linked to HAD (Johnson et al. 2013). In the brains of HIV-1-positive individuals, it is believed to be crucial for immune activation and inflammatory processes (Vartak-Sharma et al. 2014). Previous findings indicated that human astrocytes transfected with pTat also displayed HIV-1 Tat-induced cytokine elevation in astrocytes, as evidenced by increased mRNA levels of TNF-α and IL-1β (Borjabad et al. 2010; Xing et al. 2009).Conversely, research on the relationship between ageing and HIV on white matter microstructure has shown that HIV-positive individuals age more quickly (Kuhn et al. 2019). White matter

degradation indicates susceptibility to the combined effects of HIV infection and ageing, as it has been independently linked to both HIV and healthy ageing (Kuhn et al. 2019). In older HIV-positive individuals, white matter loss is common and can lead to cognitive and functional impairment (Bendlin et al. 2010), especially in frontal and subcortical regions of the brain (Brickman et al. 2006; Xuan et al. 2013). According to research by Seider et al., HIV and ageing have combined effects on neurological and cognitive functioning, with older HIV-positive patients showing greater deficits than younger HIV-positive people or older seronegative controls (Seider et al. 2014).

According to some, the effects are cumulative, so while neurological impairment is more prevalent in HIV-positive people, it ages at the same rate in people without the virus (Nir et al. 2014). One well-known long-term study that included a group of HIV-positive people who were generally healthy and did not have dementia showed evidence of accelerated ageing in specific brain regions over a period of 6 months to 8 years (Pfefferbaum et al. 2014). The neocortex, which connects the frontal and temporal poles to the parietal lobe, and the thalamus—specific regions essential for higher-order cognition and the integration of functions—were the affected regions (Pfefferbaum et al. 2014).

Research indicates that individuals living with HIV experience early cognitive decline and white matter damage; however, opinions in the literature differ regarding whether the effects of ageing and HIV are additive, meaning that each causes neurological and cognitive decline on its own, or synergistic, meaning that they combine to produce effects that are greater than additive, possibly as a result of growing shared mechanisms of neurological damage (Cohen et al. 2015). In addition, studies on HIV-related neurocognitive disorders have examined the connection between combination antiretroviral therapy (cART) medications and dementia pathogenesis (Heaton et al. 2010). The extent to which antiretroviral drug toxicity and distribution in the central nervous system (CNS) impact clinical outcomes—including dementia—remains controversial, according to research. Although there may be different mechanisms specifically connecting cART medications to the pathogenesis of dementia, research has focused on these medications' effects on the central nervous system and their possible involvement in neurocognitive disorders, such as dementia (Saylor et al. 2016). HIV, treatment, and neurological complications are intricately intertwined, as evidenced by the correlation between high-efficacy cART regimens and their effects on cognitive outcomes (Saylor et al. 2016).

1.7 Vascular Dementia

Vascular dementia is another pathogenic pathway associated with dementia. One notable and unique kind of dementia is vascular dementia (VaD), which is defined by cognitive decline brought on by reduced blood flow to the brain (Sanders et al. 2023). In contrast to other types of dementia, VaD is strongly linked to cerebrovascular events and vascular factors. A multitude of intricately intertwined

mechanisms, such as cerebral perfusion disruptions, infarctions, and ischemic strokes, play a role in its pathogenesis (Venkat et al. 2015). VaD differs from other neurodegenerative diseases in that these events cause neuronal damage and cognitive impairment (Khan et al. 2016). After Alzheimer's, VaD is the second most common form of dementia worldwide (Chang Wong and Chang Chui 2022). Fundamentally, the condition is often the result of a sequence of cerebrovascular events, such as ischemic strokes and infarctions, which sporadically impair blood flow to specific brain regions, resulting in cerebral hypoperfusion, which in turn causes neuronal damage and consequent cognitive impairment (Bir et al. 2021).

The most prevalent subtypes of vascular brain injury seem to be atherosclerotic and cardioembolic diseases combined (Chang Wong and Chang Chui 2022; Kalaria 2018). This demonstrates the vital and significant role that vascular factors—which include problems with blood vessels and circulation—have in influencing the onset and course of dementia and cognitive decline (Gorelick et al. 2011).

The various mechanisms that comprise the vascular pathogenesis of dementia, such as cerebral hypoperfusion, small vessel disease, and atherosclerosis, all contribute to the intricate interplay of factors that ultimately result in cognitive impairment. The following provides more detail on these subjects:

(a) Atherosclerosis

It is commonly recognized that atherosclerosis is the primary cause of vascular pathology and that it is very important (Bos et al. 2015). Atherosclerosis is a chronic inflammatory disease that is closely associated with vascular dementia (VD) (Huang et al. 2021). It can cause neuronal damage and cognitive decline through a variety of mechanisms, which is why it is important for the onset and progression of AD (Xie et al. 2020). Chronic atherosclerosis affects brain health for the rest of one's life by causing cerebral hypoperfusion, cerebrovascular diseases, and cognitive decline. It may also cause neurodegeneration by reducing oxygen supply to the brain through disturbed cerebral blood flow, which can lead to cognitive decline (Li et al. 2019). Oligemia, or mild chronic hypoperfusion, can cause harmful processes in neurons by interfering with the production of neuronal proteins required for synaptic plasticity, which is an essential mechanism for memory and learning (Nelson et al. 2016). In addition reduced compliance of the carotid artery wall may result in brain hypoperfusion from carotid atherosclerosis. This increases pressure in cerebral blood vessels and triggers adaptive vascular changes that cause localized brain ischemia and may eventually lead to the development of white matter lesions, or WMLs (Devantier et al. 2016). The integrity of the cerebral white matter plays a critical role in determining the effectiveness of cognitive functioning, as stated by Madden et al. (2009) This highlights the significance of vascular components in the decline in cognitive function as well as the possible part that atherosclerosis may play in dementia. Not only does atherosclerosis affect the arteries that supply blood to the brain (the internal carotid and vertebral arteries), but it also plays a major role in the development of dementia, either directly or indirectly, due to the accumulation of plaques, constriction of the arteries, and

stenosis that results from this vascular disease (Shabir et al. 2018) report that a larger volume of calcification is associated not only with worse cognitive function but also with smaller volumes of brain tissue and compromised white matter microstructural integrity. These findings provide insight into possible pathways linking atherosclerosis to deteriorating cognitive function (Bos et al. 2015). Atherosclerosis plays a crucial role in the complex and varied landscapes of cognitive decline in the setting of dementia development, as evidenced by the correlation that has been found between the disease, brain hypoperfusion, the emergence of white matter lesions, and the ensuing impairment of cognitive function. This correlation highlights the important role that vascular factors—including atherosclerosis—play in the development of cognitive impairment and highlights how complex and interdependent these factors are in the onset and progression of dementia.

(b) Small vessel disease (SVD) in the brain

A variety of disorders affecting the cerebral small arteries and microvessels are collectively referred to as cerebral small vessel disease (SVD), which is acknowledged as a major cause of vascular dementia and has been suggested as a potential precursor to Alzheimer's disease (AD) (Kim et al. 2020) (Wardlaw et al. 2013). The hallmarks of cerebral small vessel disease (SVD), the main pathological process in neurological conditions that is important in the development of dementia and stroke, include white matter hyperintensities (WMHs), cerebral microbleeds (CMBs), and lacunes seen on magnetic resonance imaging (Wardlaw et al. 2013) (MRI). Within the context of cerebral small vessel disease (SVD), which is typified by perivascular space expansion, vessel hyalinization, perivascular myelin pallor, and associated astrocytic gliosis, lacunar infarcts—a major substrate for vasomotor disorders (VaD)—are created when age-related changes in smaller brain vessels, such as intracerebral end-arteries and arterioles, disrupt perfusion (Kalaria et al. 2016). Furthermore, disruption of the blood–brain barrier (BBB) and perivascular spaces (PVS), which function together to protect the brain from damage brought on by the accumulation of neurotoxic substances, is a crucial factor in cerebral small vessel disease (SVD) and neurodegenerative diseases linked to cognitive decline (Voorter et al. 2023). A complex genesis for white matter alterations in small vessel disease is formed by the occlusion of deep periventricular-draining veins, which can be identified by disruption of the blood–brain barrier. This leads to fluid and plasma cell leakage, which may exacerbate perivascular inflammation, demyelination, and gliosis (Caruso et al. 2019). Changes in the white matter are indicative of ongoing and developing damage and can be used as a prognostic tool for cognitive decline in the future (Vemuri et al. 2021). Because it is involved in so many interrelated processes, cerebral small vessel disease, which is a spectrum of disorders affecting the brain's small arteries and microvessels, stands out as a crucial component in the complex pathophysiology of dementia.

(c) Stroke

Stroke is thought to be a significant contributor to cognitive impairment and long-term disability. It is a complicated cerebrovascular accident that results