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Abstract

The first aim of this thesis was to evaluate the prevalence of cardiovascular disease (CaVD), hypertension (HT), and type 2 diabetes mellitus (T2DM) in the neurodegenerative disorders Alzheimer's disease (AD) and Lewy body disease (LBD). These conditions are considered modifiable risk factors for vascular dementia (VaD), and recent research has proposed its association with AD. The field is considered unexplored when it comes to LBD, a prevalent form of alpha-synucleinopathy (AS). A second aim was to investigate cardiac disease and the presence of epicardial nerve alpha-synuclein (α-syn) as well as the cause of death in individuals with AS.

In summary, the objective was to investigate and assemble broad clinicopathological data on CaVD, HT, and T2DM in AD and AS as well as to confirm the presence of cardiac α-syn and to determine the cause of death in AS. All studies were based on subjects who had undergone a thorough neuropathological examination of the brain. Pathological and clinical data were assembled through autopsy reports and medical records. A majority of the research in this field has not included neuropathological verification of the neurocognitive disorder (NCD).

In Papers I and **II,** we investigated the prevalence of CaVD, found morphologically at autopsy, as well as clinical HT and T2DM in AD, VaD, mixed AD-VaD, and LBD. We found a low prevalence and no differences regarding CaVD between AD and LBD. This differed statistically from VaD in almost all parameters, which presented with a high prevalence of the studied parameters. The same differences were seen regarding HT and T2DM – a low prevalence in AD and LBD compared to a significantly higher prevalence in VaD.

In Paper III, we investigated the presence of cardiac α-syn in AS patients and a control group with other (non-AS) NCDs. We found α-syn in almost all cases of AS (82%) and within different stages of the disease. No cases within the control group had cardiac nerves positive for α-syn. The samples negative to α-syn in the AS group did not cover the epicardium with stainable nerves. We judged it probable that all AS have α-syn in their cardiac nerves.

In Paper IV, we investigated the immediate cause of death in AS individuals, postive for α-syn in their cardiac nerves, compared with a control group with other (non-AS) NCDs. In addition, we assembled comprehensive data on pathological and clinical CaVD, HT and T2DM. The majority of deaths within the AS group were interpreted as sudden cardiac death (SCD, 51.3%). These were judged to be of cardiac but not vascular-ischemic etiology. The prevalence of SCDs differed statistically from the control group where it was the second most common cause of death (22.6%, $p < 0.001$). No other differences were seen between the groups regarding clinicopathologial CaVD, HT, and T2DM.

We have demonstrated that CaVD, HT, and T2DM have a low prevalence in the neurodegenerative disorders AD and LBD. Our findings oppose the claims of a causal association between these disorders. Furthermore, our results support the association of these risk factors with VaD.

We have additionally indicated that α-syn is present in probably all cases of AS and within all stages of the disease. The high prevalence of SCD in AS indicate that the protein depositions may play a role for impaired cardiac function in these individuals.

Key words dementia, neurocognitive disorder, Alzheimer's disease, Lewy body disease, alpha-synucleinopathies, alpha-synuclein

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“I feel as if I’m losing all my leaves”
Anthony Hopkins in “The Father”

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Papers included in the thesis

I. **Atherosclerosis, Hypertension, and Diabetes in Alzheimer's Disease, Vascular Dementia, and Mixed Dementia: Prevalence and Presentation.** Javanshiri K, Waldö ML, Friberg N, Sjövall F, Wickerström K, Haglund M, Elisabet E. *Journal of Alzheimer's Disease, vol. 65, no. 4, pp. 1247-1258, 2018. DOI: 10.3233/JAD-180644*

II. **Cardiovascular Disease, Diabetes Mellitus, and Hypertension in Lewy Body Disease: A Comparison with Other Dementia Disorders.** Javanshiri K, Haglund M, Englund E. *Journal of Alzheimer's Disease, vol. 71, no. 3, pp. 851-859, 2019. DOI: 10.3233/JAD-190485*

III. **Cardiac Alpha-Synuclein Is Present in Alpha-Synucleinopathies.** Javanshiri K, Drakenberg T, Haglund M, Englund E. *Journal of Parkinson's Disease, vol. 12, no. 4, pp. 1125-1131, 2022. DOI: 10-3233/JPD-223161*

IV. **Sudden Cardiac Death in Synucleinopathies.** Javanshiri K, Drakenberg T, Haglund M, Englund E. Manuscript submitted to the *Journal of Neuropathology & Experimental Neurology,* October 2022, conditionally accepted.

Original publications, not included in the thesis:

I. **Locus Coeruleus Degeneration Differs Between Frontotemporal Lobar Degeneration Subtypes.** Matti N, Javanshiri K, Haglund M, Saenz-Sardá X, Englund E. *Journal of Alzheimer's Disease, vol. 89, no. 2, pp. 463-471, 2022. DOI: 10.3233/JAD-220276.*

Other publications:

II. **Kardiovaskulär sjukdom och diabetes typ II som riskfaktorer för kognitiv sjukdom.** Javanshiri K, Haglund M. *Neurologi i Sverige*, 1, 2020, 2. 52-54 4 s.

III. **Alzheimer's disease not linked to type 2 diabetes or high blood pressure – new study.** Englund E, Javanshiri K, *The Conversation,* 2019.

IV. **Hypertension and Diabetes Mellitus are Features of Vascular Dementia, Not Alzheimer's Disease.** Javanshiri K, Haglund M, Englund E. *Journal of Neurology & Neurophysiology.* 2019 DOI: 10.4172/2155-9562.1000482

Abbreviations

α-syn	Alpha-synuclein
Aβ	Amyloid Beta
AD	Alzheimer's Disease
AGE	Advanced glycation end product
AS	Alpha-synucleinopathies
CaVD	Cardiovascular disease
CeVD	Cerebrovascular disease
CNS	Central nervous system
FTLD	Frontotemporal lobar degeneration
HT	Hypertension
LBD	Lewy body disease
MD	Mixed dementia
MSA	Multiple system atrophy
OH	Orthostatic hypotension
PD	Parkinson's disease
PDD	Parkinson's disease dementia
T2DM	Diabetes Mellitus type II
TH	Tyrosine hydroxylase
VaD	Vascular dementia

Populärvetenskaplig sammanfattning på svenska (General summary in Swedish)

Demens eller kognitiv sjukdom är ett samlingsbegrepp för ett flertal hjärnsjukdomar som påverkar våra kognitiva funktioner negativt, man kan bland annat få försämring av minnet, orienteringsförmågan eller med språket. Kognitiv sjukdom är vanligt, ca 55 miljoner människor lider av det idag, ett antal som förväntas öka i och med att den åldrande populationen ökar över hela världen (WHO). Det som är gemensamt för alla dessa sjukdomar är att av någon anledning sker en förlust av hjärnans celler.

Denna avhandling riktar sig mot tre viktiga problem inom kognitiv sjukdom:

1) Vi saknar idag kliniska verktyg för att med säkerhet kunna ge en korrekt demensdiagnos. Det enda sättet man med 100 % säkerhet kan avgöra vilken specifik kognitiv sjukdom en person lidit av är genom obduktion och efterföljande undersökning av hjärnan. Endast en liten andel av forskningen inom detta fält rör individer som genomgått obduktion med säkerställda diagnoser.

2) Vi vet idag att en hög ålder, familjehistoria och genetiska förhållanden är faktorer som påverkar risken att utveckla en kognitiv sjukdom. Dessa faktorer går naturligt inte att påverka. Under de senaste decennierna har forskningen fokuserat på att hitta riskfaktorer till kognitiv sjukdom som går att förebygga eller behandla. Genom att aktivt försöka påverka dessa skulle man kunna förhindra eller minska risken för att utveckla en kognitiv sjukdom. De vanligaste studerade riskfaktorerna är hjärt- och kärlsjukdom (CaVD), högt blodtryck (HT) och typ 2 diabetes (T2DM). En konsekvens av dessa faktorer är att de samtliga påverkar syreförsörjningen till hjärnan och är starkt associerade med vaskulär demens (VaD), en kognitiv sjukdom som beror på syrebrist till hjärnan till följd av skador på våra blodkärl. Det har däremot på senare tid hävdats att de även bidrar till utvecklingen av Alzheimers sjukdom (AD). AD är den vanligaste kognitiva sjukdomen som traditionellt sett anses bero på inlagring av protein i hjärnan vilket leder till nedbrytning av hjärnans celler. AD tillhör en grupp sjukdomar, neurodegenerativa sjukdomar, där alla kännetecknas av just proteininlagringar som orsak till den kognitiva sjukdomen. Till denna grupp hör även alfa-synukleinopatier (AS), en sjukdom där det skadliga proteinet, alfa-synuklein (α-syn), inte endast förekommer i hjärnan utan även i hjärtat och i flertalet organ. AS består av en grupp sjukdomar där Lewy-kropps-sjukdom (LBD) står för en majoritet av sjukdomsfallen. Man vet idag inte så mycket om CaVD, HT och T2DM och deras koppling till AS.

3) Kognitiv sjukdom är den sjunde vanligaste dödsorsaken i världen och studier visar en högre dödlighet bland de med kognitiv sjukdom jämfört

med den generella befolkningen. Orsaken till denna höga dödlighet är inte kartlagd. Forskning visar att personer med AS har förekomst av det karakteristiska protein, α-syn, i hjärtats nerver och har högre dödlighet jämfört med de andra kognitiva sjukdomar. Mer forskning behövs avseende förekomsten av detta protein i hjärtats nerver och dess eventuella effekt på dödsorsaken hos individer med AS.

I denna avhandling har vi studerat avlidna individer där samtliga har genomgått obduktion och en extensiv hjärnundersökning på patologen i Lund. Vi har därmed säkerställt vilken typ av sjukdom vi studerar i hjärnan. Vidare har vi studerat deras obduktionsrapporter och journaler. Vårt primära mål har varit att undersöka förekomsten av CaVD, HT och T2DM i AD och LBD. Dessutom har vi undersökt förekomsten av α-syn i hjärtats nerver hos individer med AS samt försökt avgöra den direkta dödsorsaken i denna sjukdomsgrupp.

I artiklarna 1 och 2 studerade vi förekomsten av riskfaktorerna CaVD vid obduktion och förekomsten av klinisk HT och T2DM i AD, LBD och VaD. Vi såg att förekomsten av dessa parametrar var låg och jämförbar mellan AD och LBD. Däremot skilde sig förekomsten signifikant från VaD som hade en hög förekomst av samma parametrar. Intressant nog fann vi en markant låg förekomst av T2DM bland AD och LBD, 12 % respektive 8 %, vilket var lägre än i den generella befolkningen i Sverige över 65 år, 15,6 %. Förekomsten av T2DM var 31 % bland gruppen med VaD.

I artikel 3 undersökte vi förekomsten av α-syn i hjärtats nerver bland fall med AS och i olika stadier av sjukdomen. I artikel 4 såg vi att en majoritet av AS individer avlider i en misstänkt plötslig hjärtdöd vilket skilde sig signifikant mot kontrollgruppen som inte hade α-syn i hjärtats nerver eller i hjärnan. Denna hjärtdöd bedömdes inte bero på vanliga anledningar vid hjärt- och kärlsjukdom så som hjärtinfarkt eller typisk hjärt- och kärlsjukdom. Det förekom dessutom inga skillnader mellan grupperna avseende andra dödsorsaker eller förekomst av CaVD vid obduktion. Inte heller fann vi några skillnader när vi studerade journalerna avseende förekomst av CaVD, HT och T2DM. Den enda ytterligare skillnaden mellan grupperna var förekomst av α-syn i hjärtats nerver som fanns i alla fall med AS och inte i något kontrollfall.

Sammanfattningsvis har jag i denna avhandling presenterat fynd som talar för att CaVD, HT och T2DM inte är vanligt förekommande bland de rent neurodegenerativa sjukdomarna AD och LBD. Vi har bekräftat att dessa är vanligt förekommande bland personer med VaD. Vidare har jag presenterat att α-syn förekommer i hjärtats nerver i fall med AS, sannolikt alla, och att dessa individer verkar dö av en plötslig hjärtdöd där det inte går att utesluta att just proteininlagringarna i hjärtats nerver är en bakomliggande orsak.

Min forskning baserar sig på undersökning av avlidna individer där vi säkerställt vår kännedom om kognitiv sjukdomsdiagnos. Våra resultat talar emot att CaVD, HT

och T2DM är riskfaktorer för eller är vanligt förekommande bland AD och LBD. Preventionsåtgärder mot dessa sjukdomar har således sannolikt en liten inverkan på utvecklandet av de rent neurodegenerativa sjukdomarna, även om det har andra hälsofördelar.

AS har förekomst av α-syn i hjärtats nerver. Det är möjligt att dessa inlagringar påverkar hjärtats funktion och leder till död. Detta kan förklara den ökade dödligheten som ses i just denna sjukdomsgrupp. Ytterligare hjärtundersökning av dessa patienter kan således vara motiverat för att hitta störningar i hjärtats funktion samt förebygga en tidig död.

Prologue

My PhD journey began during my last year of medical studies at Lund University. I was a tutor, performing autopsies and teaching younger students about anatomy and pathology. It was then I met the woman who would drastically change my near future – Elisabet Englund, my supervisor. She introduced me to the world of neurocognitive disorders and neuropathology, such as what the problems are concerning neurocognitive disorders, where there are research gaps, and perhaps knowledge that is wrong or is wrongly understood.

I started my research as part of my master's thesis, aiming to unveil more about why we get Alzheimer's disease? Are common public diseases, such as cardiovascular disease, diabetes mellitus type II and hypertension associated with the disease? Additionally, even though my research aim and project plan changed during the course of my Ph.D. studies, I began to reflect early on about neurocognitive disorders and their effects on the people afflicted with these disorders and those around them.

In November 2019, I presented my research at the Researchers' Grand prix, a national competition where one describe one's research in only four minutes for the general public. Here I used a tree as an analogy for neurocognitive disorder:

"*Neurocognitive disorder is an umbrella term for several different disorders. One can see it as a tree, where every branch corresponds to a specific disease."*

The purpose of this analogy was to explain that neurocognitive disorder is not just one disease or refers only to Alzheimer's disease; indeed, it is several disorders. Later, I realised that the analogy has a broader meaning.

In February 2021, I met the girl who would be at the centre of my life for the rest of my days: my daughter Noor. It was also here that the resemblance to a tree was further developed. As she is growing up, I realise that she is learning different abilities that were not there from the beginning. She is developing her cognitive skills.

When someone is affected by a neurocognitive disorder, they exhibit symptoms that impair their cognitive abilities, such as learning, memory, language, complex attention, social cognition, and perceptual motor speed. One can say that they lose abilities that were once part of their everyday life and made them recognisable. For those who are affected by a neurocognitive disorder, abilities that were learned during their first years of life will slowly diminish during their last years of life.

When we are born, we are unaware of the surrounding world, just like a seed that will become a tree. As we grow, and our first branches and leaves sprout, we start to develop certain skills – our cognitive functions. We learn to move, just as a tree moves with the wind. Our attention evolves and we begin to create memories and

remember things, just as a tree remembers the seasons of the year. We learn to communicate, orientate, and interact socially, just as a tree is aware of and interacts with the surrounding organisms. However, once the tree gets older, just like people who develop a neurocognitive disorder, it loses abilities that once had been a natural part of its everyday life. It stops communicating with the outside world as its roots diminish; it does not move as softly with the wind as its branches become stiff and break. In the end, it loses all its leaves; the features that made us recognise it are lost. Neurocognitive disorder is the end point in life for some people, and in many circumstances, it slowly transforms the individual affected to its first-born state, not recognisable to the world.

Old trees have many similarities to people with a neurocognitive disorder. We need to learn from them and develop new ways of addressing these disorders to help future generations flourish to the end of their days.

When Noor was born, I bought a small tree that would follow her through life. In the shadow of her development, this tree will also evolve and grow. Together, they will develop their characters and become recognisable minds. I hope, they will never diminish or return to the state they are currently in but only flourish and enjoy their cognitive abilities. Hopefully, when Noor is older, neurocognitive disorders, and the sad destiny for the ones affected with them, are merely a historical analogy of great medical success. This success will be based on research of these old trees in whose shade no one will ever sit.

Introduction

Dementia is an umbrella term for several disorders with a progressive and chronic decline of our cognitive functions due to organic brain disease. The disorders are characterised by memory impairment, alterations in personality, deterioration in personal care, impaired reasoning ability, and disorientation. Eventually, the damage affects our everyday lives and activities [1, 2]. Dementia is considered the seventh leading cause of death in the world and is expected to increase drastically in prevalence the coming years from 55 million to 78 million, with 10 million new cases diagnosed every year [1]. As it is a disease group that affects not only the patient but also the families and society at large, it is not surprising that the cost for dementia globally is vast and predicted to reach almost 2% of the world's total gross domestic product in 2030 [1, 3]. It is evident that these disorders are a major global challenge and that there is a need for research that can improve the situation concerning dementia.

Terminology

In 2013, the *Diagnostic and Statistical Manual* (DSM-5) incorporated the diagnoses dementia and amnestic disorder under a new entity, "*neurocognitive disorder*" (NCD). As a result, Alzheimer's disease (AD) is currently labelled in the DSM-5 as a "neurocognitive disorder due to Alzheimer's disease". Additionally, a separation has been created between different degrees of cognitive impairment described as "major" or "minor" NCD. The term dementia is still used in the etiological subtypes [4].

The clinical department in which this thesis project was performed is termed Clinical Genetics, Pathology, and Molecular Diagnostics, Region Skane. The University affiliation is the Division of Pathology, Department of Clinical Sciences, Lund. To refer to this department and to simplify the terminology – the term Department of Pathology is used throughout the text.

Alzheimer's Disease

Epidemiology and Clinical Presentation

AD is considered the most common NCD, with a reported prevalence of 40% – 80% [1, 5-8]. Clinically these patients display a progressive decline in their cognitive functions, initially affecting their memory, visuospatial function, language, and attention [9]. The primary risk factors for AD are age – 95 % of patients are above 65 years at diagnosis – and genetic factors. Different mutations can increase the risk for early-onset AD (onset < 65 years) and other genetic variations could either increase or decrease the risk for AD [5]. Cardiovascular disease (CaVD), hypertension (HT), and diabetes mellitus type II (T2DM) have also been suggested as risk factors for AD [10].

Neuropathology

Macroscopically, there is a symmetric cortical atrophy of the parietal and temporal lobes. The frontal and the occipital lobes are generally spared until later in the disease process. Additionally, atrophy is seen in the parahippocampal gyri, amygdalae, and hippocampi, and pallor of the locus coeruleus is frequently observed [5, 11].

Microscopically, there is a global neurodegeneration with loss and disease of the neurons, accentuated in the temporal-limbic and post-central lobes as well as deposition of amyloid in the blood vessels. The accumulation of pathological amyloid and tau protein in the brain are considered hallmarks of the disease and appears as plaques and tangles, see Figure 1. A degeneration of the locus coeruleus is likewise seen regularly [5, 12-14].

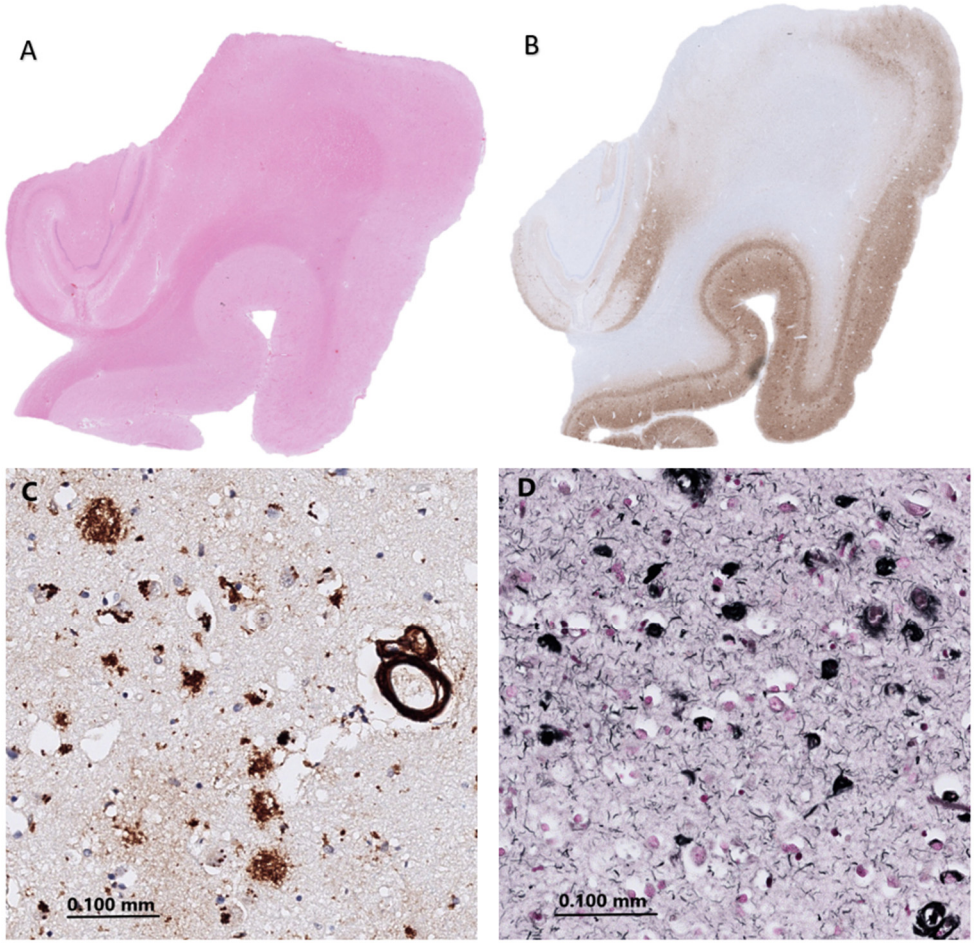

Figure 1. Histopathological features of Alzheimer's Disease
Four microphotographs of the hippocampus in Alzheimer's disease. Overall view in photographs A and B, at 1x magnification. Plaques and cerebral amyloid angiopathy in photograph C, at 27x magnification. Neurofibrillary tangles and neutropil threads in photograph D, at 27x magnification. Immunohstichemical staining with hematoxylin and eosin (A), with AT8 for phosphorylated tau (B), amyloid-β (C), and with Gallyas-Braak silver staining (D).

Alpha-Synucleinopathies

Terminology

Alpha-synucleinopathies (AS) are a group of neurodegenerative disorders that comprise Lewy body disease (LBD) and multiple system atrophy (MSA) [15]. LBD connotes Parkinson's disease (PD), Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) [16]. Although DLB and PDD share many clinical, neurochemical, and morphological features [17], differences exist and they are described as two different entities in the DSM-5 as "*neurocognitive disorder with Lewy bodies*" and "*neurocognitive disorder due to Parkinson's disease"* [4]. Hereinafter, we use the terms DLB and PDD.

Epidemiology and Clinical Presentation

DLB is considered the second most prevalent neurodegenerative disease after AD [18] and is believed to account for 7.5% of all clinical dementia cases [19]. However, autopsy studies indicate that DLB is highly underdiagnosed with a reported prevalence of 20%–25% [20-22]. PD is considered the most prevalent AS with an overall prevalence in the population of 0.3% of whom up to 31% are expected to develop PDD [23-25]. PDD is estimated to represent 3.6 % of all dementia cases [25]. MSA is a rare sporadic disease with an approximated incidence of 0.6–3 per 100 000 individuals and increasing in occurrence with age [26].

Autonomic dysfunction is frequently observed in all AS with symptoms of constipation, urinary incontinence, orthostatic hypotension (OH), reduced heart rate variability, and dysphagia [27]. DLB and PDD exhibit similar clinical phenotypes, both having cognitive impairment and parkinsonism but differing in the temporal onset of cognitive and motor symptoms [28]. In DLB, the cognitive impairment precedes the motor symptoms [29], whereas PDD is defined as a cognitive disease arising in established PD [30]. The cognitive impairment is characterised by fluctuations in cognition, visual hallucinations, memory impairment, and affected visuospatial ability [28]. The only confirmed risk factors for LBD are genetic variations and age. Environmental factors involving toxins, smoking, body mass index, and dietary factors have been proposed but not confirmed [15].

MSA is usually divided into two phenotypes or admixtures of these with the onset of either atypical parkinsonism (MSA-P) or progressive ataxia (MSA-C) [31]. Cognitive impairment is common in MSA but is clinically significant, on average, after seven years [32]. The disease is sporadic, and with the exception of identified genetic mutations, only environmental toxins have been proposed but not verified as risk factors for the disease [33].

Neuropathology

On gross examination, LBD often presents with depigmentation of the substantia nigra and locus coeruleus. Medial temporal atrophy is prevalent in some cases of LBD but if it occurs, it is often not accompanied by notable cortical atrophy and not as extensive as can be seen in AD. MSA is characterised by cerebellar, pontine, and putaminal atrophy [15].

Microscopically, all AS are associated with misfolded and abnormal aggregates of alpha-synuclein (α-syn) in neurons and/or surrounding glial cells. LBD displays formations of cytoplasmic α-syn inclusions, Lewy bodies, and neuritic α-syn aggregates, Lewy neurites [5, 34], see Figure 2. For a histopathological diagnosis of PD, a neuronal loss and presence of Lewy bodies in the substantia nigra are required [35]. LBD is divided into three stages based on the regional extent of pathology to LBD cortical, LBD limbic, and LBD brainstem [36]. Recently, studies revealed that LBD pathology is not only limited to the brain and the central nervous system (CNS) but also is widespread in nerves of other organs, such as the heart [37-40]. This has raised the discussion of whether the pathological aggregations initially occur outside the brain, in the body first, with a caudo-rostral spread, and/or if, in some cases, the brain is the primary site affected [38, 41-43].

MSA exhibits glial inclusions of α-syn and lacks the presence of Lewy neurites [5, 15]. The olivopontocerebellar system is the main site affected in MSA-C, whereas the striatonigral system is primarily affected in MSA-P [33].

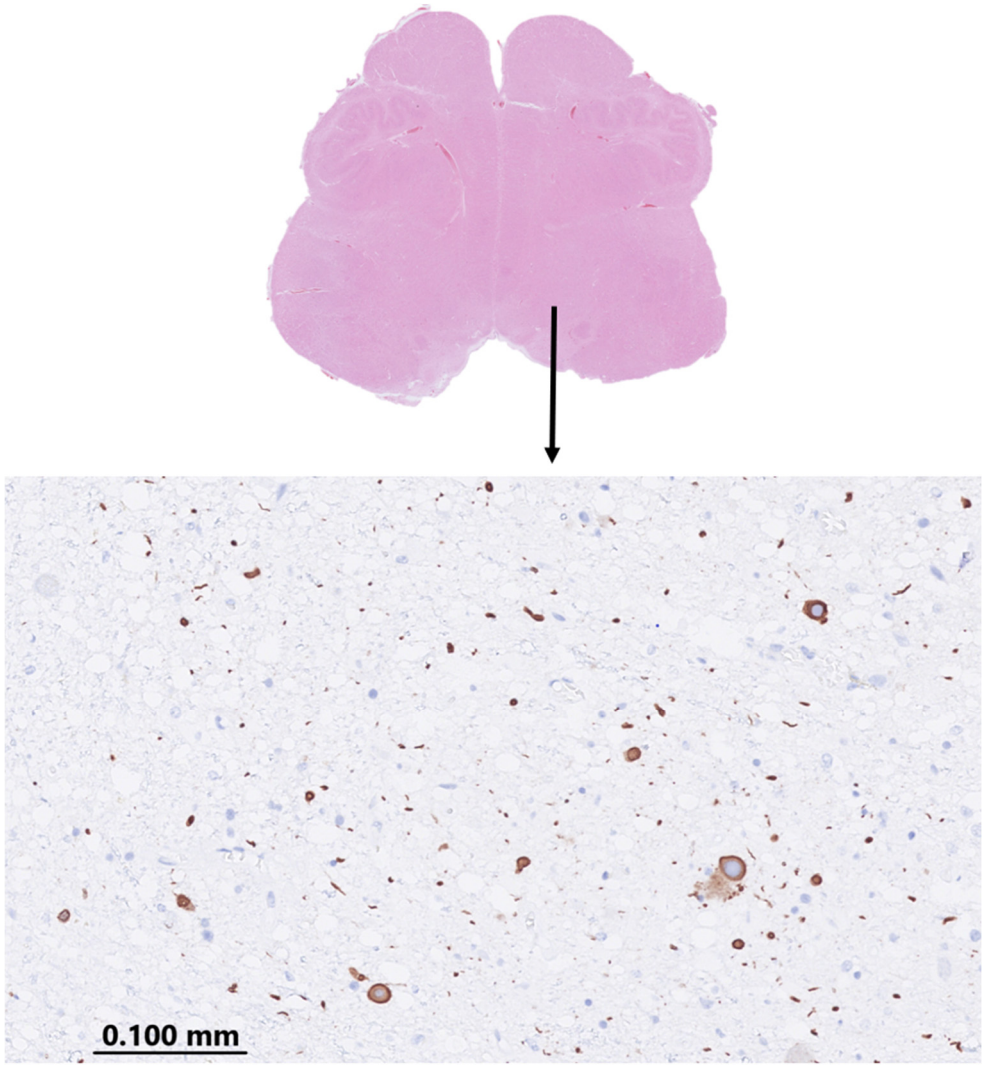

Figure 2. Histopathological features of Lewy Body Disease
Two microphotographs from the medulla oblongata. Upper picture with overall view, immunohistochemical staining with hematoxylin and eosin, at 1x magnification. Lower picture with α-synuclein immunohistohemistry at 20x magnification, demonstrating Lewy bodies and Lewy neurites.

Vascular Dementia

Terminology

Vascular dementia (VaD) is a syndrome of cognitive impairment due to ischemic or haemorrhagic etiologies [44]. Vascular cognitive impairment (VCI) defines disorders with impairment in any cognitive domain because of impaired brain perfusion or with vascular origin [45, 46]. Vascular cognitive disorder (VCD) includes both VaD and VCI, and serves as a global category for disorders with cognitive impairment of vascular origin [47]. In DSM-5, the term *"major vascular neurocognitive disorder"* has been introduced which replaces VaD and restricts VCI to cases without cognitive impairment or not fulfilling a dementia diagnosis [4]. In this thesis, the term VaD is used for the subjects studied and represents individuals with a clinically suspected or validated NCD due to haemorrhagic or ischemic lesions observed on neuropathological examination, i.e., no primary neurodegenerative disease.

Epidemiology and Clinical Presentation

VaD is regarded as the second most frequent NCD. The prevalence varies among studies from 0.3% to 58% because of diagnostic challenges and a lack of consensus criteria [48, 49]. It is defined as a disorder in which cerebrovascular disease (CeVD) is responsible for the cognitive symptoms as a result of affected oxygen supply to the neurons [5]. Thus, diseases that contribute to CeVD or an impaired oxygen supply to the brain – such as CaVD, HT, DM, and atherosclerosis – are considered risk factors for VaD [49]. Clinically, the symptoms vary depending on the location of the vascular damage, including both cognitive and motor symptoms, and can develop abruptly or slowly and progressively [50].

Neuropathology

Macroscopically, VaD displays few exposing signs. Apart from apparent infarcts, central atrophy with widening of the ventricles as well as a particular attenuated white matter in the frontal lobes, with or without infarcts, can be seen [51].

Microscopically, the disease exhibits various pathological traits that connote vascular-ischemic pathology. Some of these are arteriosclerotic or hypertensive vasculopathy, focal infarcts; see Figure 3, ischemic white matter rarefaction or regionally and numerically reduced and pyknotic neurons [51, 52].

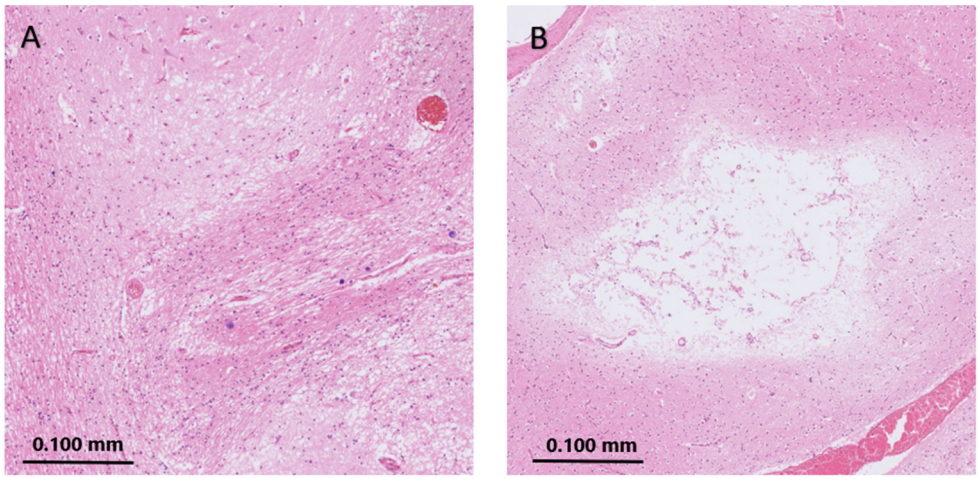

Figure 3. Histopathological Examples of Vascular-Ischemic Pathology
Microphotograph from the hippocampus demonstrating microinfarct (A), at 5x magnification, and from the basal ganglia demonstrating a lacunar infarct (B), at 5x magnification. Immunohistochemical staining with hematoxylin and eosin.

Mixed AD-VaD Dementia

Epidemiology and Clinical Presentation

Mixed dementia (MD) typically refers to a disease with cognitive impairment due to the coexistence of a neurodegenerative disease and VaD. The mixture of AD and VaD is believed to be the most common type of MD [53, 54]. In this thesis, we have focused on individuals with the coexistence of AD and VaD pathology; thus, hereinafter the term MD refers to the combination of these disorders. As MD is a disease with a combination of different pathologies, there is an overlap in both clinical and neuropathological phenotypes, which creates diagnostic difficulties. Therefore, it is not surprising that the reported prevalence varies from 1.7% to 35 %, where some argue that it is the most prevalent NCD [53, 55]. Because of its pathological genesis, MD shares both clinical symptoms and risk factors with AD and VaD, although the cognitive impairment is estimated to be generally more severe than in AD [53].

Neuropathology

Neuropathologically, the disease exhibits a combined pathology of AD (amyloid plaques, neurofibrillary tangles, and neuronal loss) and VaD (vascular-ischemic lesions). The diagnosis necessitates that the different pathologies are judged

severely enough. In the case of AD, a Braak stage III or more is considered to give rise to cognitive impairment [53, 56, 57]. Regarding the vascular-ischemic pathology, several lesions are usually required, except when a large infarct in supply-territories of major cerebral arteries is apparent, to be considered as sufficient to cause cognitive symptoms. Some of these lesions are strategical lacunes or multiple microinfarcts in the basal ganglia, hippocampus, thalamus, and the basal forebrain, multiple microinfarcts in cortical border zones, hippocampal sclerosis, or white matter lesions [58].

Challenges with Neurocognitive Disorders

Today, there are several challenges concerning NCDs:

1) The first and most significant challenge is that no curative or disease-modifying treatment currently exists for any of these disorders. The present treatments are aimed towards the symptoms [59]. Recently, BioArctic reported positive results for its Phase 3 clinical trial of Lecanemab on its primary endpoint to slow disease progression in AD [60]. Although these results might be ground-breaking, this does not solve the overall challenge, and we still lack effective treatment against NCDs.

2) The second challenge is that we continue to need diagnostic tools that can accurately diagnose the specific NCD. The diagnosis is based on criteria from neuropathological examination of the brain, and although clinical criteria, biomarkers, and imaging modalities have evolved and improved, they are still not considered to be as sensitive as examination on autopsy [36, 49, 61, 62]. This is confirmed by studies revealing that many of the clinical diagnoses are not entirely correct, mostly due to an inaccuracy among the clinical criteria used and mixed pathologies [49, 63-65]. This might not be a clinical problem today, as treatments for NCDs are focused on the symptoms; however, better diagnoses will be necessary in the future as treatments targeting the underlying pathology may become available. Additionally, this is a limitation when it comes to epidemiological or clinical research, which in many cases, has studied and will study the wrong disease. This stresses the importance of autopsy-verified research and the development of new criteria, biomarkers, and imaging techniques.

3) A third challenge is to find treatable and preventable risk factors that could either prevent or reduce the risk of developing AD. The established risk factors for AD are age, genetic factors, and family history [66], and these are naturally unmodifiable. It has been proposed that CaVD, HT, and T2DM, which are modifiable and robustly associated with VaD [49], may contribute to the development of AD, and by treating and inhibiting these

disorders we might prevent or reduce the risk for AD [10]. The association between these factors and AS has not been explored sufficiently.

4) A fourth challenge is to increase the life length of people suffering from an NCD. It is the seventh leading cause of death [1], and there is, in general, an increased mortality among these disorders compared to the general population [67], although the underlying mechanisms remain unknown. More knowledge is needed regarding the cause of death and what might lead to the death in patients with NCDs. Of special interest is AS, a disease group in which α-syn is suggested to be widespread in nerves outside the CNS, including the heart [37, 38].

This thesis primarily targets the third and fourth challenges concerning NCDs. It was our experience that most research regarding this field is performed without neuropathological confirmation of the NCD. Thus, we investigated individuals who had undergone a thorough neuropathological examination of the entire brain, resulting in a clear insight into the existing neuropathology. The NCDs studied in this thesis were AD, AS, VaD, and mixed AD–VaD dementia. Other common NCDs, such as frontotemporal dementia or frontotemporal lobar degeneration (FTLD), were not specifically investigated in this thesis.

Illustration representing the challenges adressed in this thesis. The tree symbolizes neurocognitive disorders: a group of brain disorders where every branch corresponds to a different disease. The Brain: neuropathologically confirmed disease in the study subjects. The Heart: the modifiable risk factors, exploring the presence of alpha-synuclein in the heart and the cause of death in alpha-synucleinopathies.

Cardiovascular Disease and Risk Factors in Neurocognitive Disorders

Large population-based cohort studies have presented several risk factors for cognitive decline and NCDs [10, 66]. However, there is a complexity in studying risk factors for these disorders, since the etiology is multifactorial, and the prevalence of mixed pathologies is presumably high. Firstly, epidemiological or observational studies, which in many cases have laid the foundation for these associations, are based on a clinical diagnosis with the limitations of missing mixed pathologies or studying the wrong disease. Such research also lacks causality, and the findings are generally observational; thus, the reason for the associations is mostly speculative. Secondly, it is unknown whether the risk factors exert their effect on their own or in combination with other factors, and the complexity increases as these emerge at different timepoints during life [68] [69]. Additionally, there is the possibility that the NCD might influence the risk factor by reverse causation. As an example, hypotension is reported as an independent risk factor for NCD [70], but AD is known to induce degeneration in brain regions affecting the autonomic system, potentially causing systemic hypotension [71].

During recent decades, an effort has been made to identify modifiable risk factors for these disorders, largely as a result of not having a disease-modifying or curative treatment and with the intention to reduce the risk and to prevent NCDs, mostly AD. It is important to clarify that reducing risk does not automatically result in preventing a disease. Even if we treated and managed the modifiable risk factors, individuals may be less likely to develop the disease or develop it later than if the preventive actions had not been taken.

The most common modifiable risk factors claimed are HT, T2DM, obesity, and smoking with HT and T2DM considered to be the most robust ones [66, 72]. They contribute to cognitive impairment through vascular damage and decreased cerebral blood flow (CBF) [73]. The vascular damage is mainly caused by general atherosclerosis, including coronary and cerebrovascular atherosclerosis. This increases the event of embolic strokes/micro infarcts or haemorrhages/micro bleeds with the consequence of neuronal damage and cognitive impairment. Subsequently, these factors also promote CaVD, CeVD, and death by increasing the incidence of myocardial infarctions and strokes [74]. Their proposed association with cognitive impairment is further supported by the decline in dementia incidence in Western populations, which is believed to be the result of improved cardiovascular health to some degree [66]. Additionally, it has been estimated that nearly 40% of all the NCDs could be prevented by targeting these risk factors [75].

The CBF decreases with increasing age [76]. The modifiable risk factors could through atherosclerosis worsen this decline [77], resulting in hypoperfusion to the brain and an imbalance in neuronal supply and demand [78]. Over time, this will

comprise astroglia or neuronal metabolism and cause an ischemic-hypoxic state resulting in cognitive impairment [79].

The modifiable risk factors that affect the vascular system are established risk factors for VaD [49]. However, evidence points to these factors similarly contributing to the development of and increasing the risk for AD [10]. The vascular hypothesis of AD, proposed by de la Torre and Mussivand in 1993 using animal models, proposes that the hallmark pathology of AD starts as a downstream effect of chronic hypoperfusion to the brain [78]. According to this hypothesis, hypoxia promotes one of the cleavage pathways of amyloid beta (Aβ), as an attempt to protect the brain against the ischemic-hypoxic state, but with the consequence of an increase in Aβ load and the development of AD.

The complex interplay of all of the modifiable risk factors is that they increase the risk of one another as well as independently increase the risk for atherosclerosis. Therefore, AD could be claimed to be the downstream effect of atherosclerosis promoted by these modifiable risk factors, which would lead to cognitive impairment through embolic strokes/micro infarcts, haemorrhages/micro bleeds, or neurodegenerative changes through a decrease in CBF and a resulting hypoxic state [73].

Atherosclerotic CaVD has also been proposed to be a risk factor for AD [10]. An association has been reported in clinical studies, where indicators of peripheral arterial disease (carotid wall thickness and ankle-brachial index) were associated with an increased risk of AD [10]. Additionally, autopsy studies have indicated that microvascular lesions were as closely associated with dementia as the number of Alzheimer lesions, and that women with brain infarcts on autopsy had an 11-fold higher prevalence of AD compared to those without infarcts [80, 81]. As the modifiable risk factors also give rise to CaVD [74], it remains unclear whether they synergistically increase the risk for AD, whether CaVD independently increases the risk for AD, or whether CaVD and AD simply share risk factors. Another theory proposes that Aβ deposition increases as a phenomenon of aging, and that the specific peptide associated with the vascular damage and the main pathological entity in cerebral amyloid angiopathy (Aβ-40) also gives rise to CaVD [82].

Our experience is that many of the findings above are based on studies lacking neuropathological confirmation of the NCDs. Additionally, given the discussion above, one of the aims of this thesis was to investigate the prevalence and presentation of CaVD, HT, and T2DM in a cohort with neuropathologically confirmed AD, VaD, MD, and LBD.

Cardiovascular Disease and Risk Factors in Lewy Body Disease

One might assume that LBD shares the same risk factors as AD, since they are both considered neurodegenerative disorders with protein depositions being the hallmark

pathology, and since LBD is often accompanied by AD pathology [5]. However, studies on CaVD and vascular risk factors in LBD are rare. One clinical study found a lower association of HT and T2DM in LBD compared to AD, whereas an autopsy study found a similar association of vascular risk factors between DLB and AD [83, 84]. Ghebremedhin et al. [85] demonstrated an inverse correlation between Lewy body pathology and the severity of CeVD (small vessel disease, atherosclerosis, infarcts) and history of stroke. Given the similarities and the common coexistence of LBD and AD pathology in the brain [5], and the relatively few studies on the associations among CaVD, the modifiable risk factors, and LBD, this thesis aimed to investigate their prevalence in this disorder. The results will increase the knowledge regarding the associations among CaVD, HT, and T2DM in LBD and, together with the prevalence in AD, in a majority of the neurodegenerative disorders.

Hypertension in Neurocognitive Disorders

HT is believed to cause NCD and AD through atherosclerosis leading to embolic stroke, microinfarcts, white matter lesions and micro- and macro bleeds or the vascular hypothesis [86]. Still, findings of research concerning the association between HT and NCD have varied greatly. The East Boston study [87], a clinical study that lacked confirmation of the neurocognitive diagnoses, found no effect on cognition when comparing individuals with a systolic blood pressure <130 and individuals with a systolic blood pressure >160. Other clinical studies reveal that mid-life HT is associated with all NCDs, including AD [70, 75, 88, 89]. Furthermore, these studies have revealed a reduced risk for cognitive impairment and AD in individuals receiving antihypertensive treatment [90-93]. As HT is a risk factor for CaVD [74], and anti-hypertensive treatment reduces the risk for CavD [94, 95], it remains to be explored whether these disorders synergistically increase the risk for NCD or whether they contribute independently.

A decline in blood pressure in late-life is also considered a risk [70], although this could be an effect of reverse causation as many of the NCDs have pathological alterations in brain regions controlling blood pressure [71]. This is supported by findings of brain atrophy in individuals with mid-life HT, a common attribute for brains with neuropathology consistent with an NCD [96].

Generally, HT is regarded as a treatable and important risk factor for all types of NCDs, although a large portion of the evidence comes from studies lacking neuropathological assessment where both the existence of mixed pathologies and misdiagnoses may be a limitation.

Diabetes Mellitus Type II in Neurocognitive Disorders

T2DM is one of the more strongly associated modifiable risk factors for NCD and AD. Large observational studies have seen that T2DM is observationally linked with a higher risk for AD [97, 98], although the underlying pathogenesis is unknown. T2DM – which is heavily connected to obesity and low physical activity, two additional modifiable risk factors for NCDs and AD – increases the risk for atherosclerosis and CaVD and, thus, could contribute to AD both through the vascular hypothesis or through direct consequences of atherosclerosis [73]. Just as for HT, it is unclear whether T2DM is a risk due to its contribution to CaVD or independently. However, there are several other proposed explanations for its association with cognitive impairment and AD. Some theories, such as insulin resistance and advanced glycation end products (AGEs), are more closely linked to specific T2DM pathology [99].

The theory of insulin resistance is based on findings that cerebral glucose utilisation and energy metabolism represent early changes that precede cognitive impairment [99]. This hypothesis has given birth to the term "type 3 diabetes" (T3DM), where impaired insulin signalling is believed to play an important role in AD pathogenesis [100]. T3DM is conceptually characterised by chronic insulin resistance and insulin deficiency that is mainly confined to the brain [99]. Studies report that tau gene expression and phosphorylation are regulated through insulin and insulin-like growth factor signalling cascades, and animal models have presented that impaired insulin signalling could promote the degeneration seen in AD [99, 101, 102]. Additionally, loss of insulin-bearing neurons has been demonstrated to increase in line with progressive AD changes [103].

AGEs are glycated proteins or lipids and are considered, along with their receptor (RAGE), to cause most of the complications seen in diabetes, such as retinopathy, nephropathy, and neuropathy [104]. AGEs are believed to play an important role in the pathogenesis of AD through the accumulation of Aβ, neuronal degeneration, and the formation of tangles [105]. Excessive accumulation of AGEs have been observed in hyperglycaemia, oxidative stress, and inflammatory stress seen in AD [106]. Furthermore, the activation of RAGE, where Aβ could serve as a ligand, causes an inflammatory response and upregulation of the receptor [106].

Interestingly, AGEs are believed to play a role in PD as well [107]. Glycated α-syn has been detected in the brain tissue of PD patients, and observations of a co-localisation of AGEs and α-syn in Lewy bodies in the substantia nigra have been made. Glycated α-syn is believed to be less easily degraded and, thus, more prone to accumulation [107]. Studies reveal an increased risk for PD among those with T2DM, where the duration of T2DM seems to play a role [108, 109]. To support the claim, treatment with specific anti-diabetic drugs in patients with T2DM has, in some studies, demonstrated a decreased incidence of PD, although some studies

revealed no decrease. Studies are currently ongoing that seek to evaluate the effect of anti-diabetic drugs on PD [107].

T2DM is considered a robust risk factor for all NCDs although the underlying pathogenesis is unknown, and most of the association is established on research conducted without confirmation of the NCD. Furthermore, research concerning its role in DLB is limited. Thus, a primary aim for this thesis was to study the prevalence of T2DM in the different neurodegenerative disorders.

Cause of Death in Neurocognitive Disorders

Dementia is considered the seventh leading cause of death globally, and its burden is expected to increase with a growing aging population [1]. As it is a common disease, usually occurring late in life, it might not be unexpected that it serves as one of the leading causes of death. However, a substantial number of studies have noted a higher risk for mortality in NCDs [67], but the underlying mechanisms remain unclear. It is important to understand the cause of death in these patients in order to evaluate ways of preventing death and prolonging life, to understand the value of terminal care, and to gather information regarding the prognosis of these disorders.

According to the International Classification of Diseases (ICD), the underlying cause of death is defined as the condition that gave rise to all other conditions leading to the death of the individual [110]. However, when someone with an NCD dies, the NCD is not commonly listed on the death certificate as an underlying cause of death [111, 112]. Reports indicate that conditions such as pulmonary embolism and bronchopneumonia are common immediate causes of death in patients with NCDs compared to cognitively healthy individuals, implying that the NCD may have been the underlying cause of death [113, 114]. At the same time, pulmonary embolism and bronchopneumonia has been seen to be underreported on death certificates as well [114]. This highlights the complexity of studying these conditions in a clinical setting or through registers alongside the complicating inability to verify the specific neurocognitive diagnosis. This warrants research in cases where the cause of death and the neuropathological diagnosis are confirmed through autopsy.

Individuals with an NCD are estimated to have at least twice as high a mortality risk than those who are considered cognitively healthy [115]. In AD, the expected life duration after diagnosis is seven to 10 years when patients are diagnosed in their 60s and early 70s [116]. Individuals with VaD have been seen to have both a poorer and a better prognosis than AD, whereas DLB has been reported to have a higher mortality risk than AD [117-119]. LBD, in general, is considered to have a mortality risk three times higher than that of the general population [120]. Considering AS as

a group, Savica et al. [121] concluded in a population-based study that MSA with parkinsonism had the highest mortality risk compared to the control group, followed by DLB and then PD/PDD. A recent large systematic review and meta-analysis found no differences in mortality rates between VaD and LBD. It also concluded that although AD is considered the most prevalent NCD and is well-studied regarding mortality risk and cause of death, it had the lowest mortality risk and longest life expectancy compared to the other disorders studied – VaD, LBD, and FTLD. LBD and each individual subgroup, PDD and DLB, had the highest mortality rates [122].

According to ICD, the immediate cause of death is defined as the determining injury, complication, or disease directly causing death [110]. Studies have demonstrated that respiratory diseases – bronchopneumonia and asphyxia, in particular – are more common in patients with NCDs and AD than in the general population. Circulatory system disease, ischemic heart disease, CeVD, and pulmonary embolism are less profound in AD and are highly prevalent in VaD [113, 123]. An autopsy study presented that LBD had a remarkably high prevalence of circulatory diseases as the immediate cause of death [123]. Although this prevalence was not greater than that for the general population – 59.5 % and 74 %, respectively – it was numerically greater than AD, 49.5%, and in line with all dementing disorders studied, 59.0%. Describing the results further, one could see that most of the circulatory diseases consisted of circulatory failure, 21.9%, which was in great contrast to AD, 9.5%; VaD, 6.9%; FTLD, 5.0%; and the general population, 12.5%. The authors concluded that the diagnosis circulatory failure represented conditions resulting in cardiac arrest or failure, such as arrhythmia or heart failure, and possibly mixed pathological conditions not easily detected through autopsy [123].

At the Department of Pathology in Lund, Sweden, several individuals with AS have succumbed to an unnatural cardiac death that was not obviously due to vascular-ischemic causes. Together with the evidence above that AS seem to have a higher mortality risk than most of the other NCDs as well as autopsy findings of circulatory failure being a prominent immediate cause of death among these people [122-124], we sought to investigate this further in this thesis. Moreover, the recent evidence of α-syn deposits in the cardiac nerves of AS [37] adds further interest in investigating the effects of these cardiac depositions and their involvement in the cause of death in these individuals.

Cardiac Alpha-Synuclein

In the CNS, misfolded aggregates of α-syn in surrounding glial cells and neurons are believed to damage mitochondria with subsequent apoptosis [125]. The spread of the pathology is considered to be from one anatomical location to adjacent regions [126]. Braak et al. proposed a caudo-rostral spread in PD where lesions initially occur in the vagal, glossopharyngeal, and olfactory nerves and then ascend

from the brainstem to cortical areas [41]. Additionally, the origin of the pathological alternations in MSA is yet not established [5]. The caudo-rostral spread in LBD has been further developed due to evidence of nerve engagement in the heart and multiple organs [37, 38]. A transcellular spread has been suggested where lesions initially occur in the enteric nervous system and then ascend and finally reach the cerebral cortex [127-129].

Cardiac α-syn in the epicardial nerves has been reported in pre-symptomatic and early-stage PD patients and in most individuals with LBD [40, 130, 131]. In PD, it is also believed to correlate with the duration and severity of the disease [132]. These aggregates have been associated with cardiac sympathetic denervation [37], which may not be unexpected given their effect in the CNS [125]. Intriguingly, cardiac innervation in MSA is reported to be better preserved and the prevalence of these aggregates less frequent [37, 133].

The clinical relevance of cardiac α-syn remains unclear. Cardiac sympathetic denervation is believed to play a role in OH and autonomic dysfunction of the cardiovascular system, probably in combination with arterial baroreflex failure and extra-cardiac noradrenergic denervation seen in AS [134]. This is further strengthened by reduced heart rate variability, which may be a potential marker for autonomic dysfunction and has been observed in DLB and reported as a risk factor for PD [27, 135, 136]. Interestingly, sudden deaths have been reported in PD, and an association between sudden death and reduced heart rate variability has been observed in epilepsy [137, 138]. Furthermore, cardiac α-syn has been suggested to cause a prolongation of the QT interval corrected for heart rate (QTc) [139], which is known to increase the risk for terminal arrhythmias and sudden deaths [140, 141].

In summary, cardiac α-syn may be the underlying mechanism for cardiovascular dysfunction and terminal arrhythmias in AS patients. This might explain why these individuals are reported to have a higher mortality rate and poorer prognosis than those with other NCDs [122]. Most of the studies that have investigated the presence of cardiac α-syn and cause of death in AS do not provide neuropathological confirmation of the NCD and consists of small cohorts. Furthermore, a majority of studies in this field have focused on sympathetic denervation and not the presence of α-syn. Because of this and the discussion above, we felt compelled to investigate the occurrence of cardiac α-syn as well as the immediate cause of death in neuropathologically confirmed individuals with AS, together with an extensive assembly of clinical and pathological data on CaVD and risk factors.

Aims

The primary aim of this thesis was to investigate the prevalence of the modifiable risk factors CaVD, HT and T2DM in AD and the assumed contribution of T2DM in AD, studying the effects of hyperglycaemia and AGEs on AD pathology. Additionally, LBD was intended to be included, allowing the acquisition of knowledge regarding these risk factors in a disease group that is understudied and that shares similar pathogenesis with AD. However, due to methodological challenges, we were unable to find a suitable way to prospectively investigate hyperglycaemia and to analyse AGEs. Thus, the project plan changed after **Paper II.** We had already investigated the prevalence of CaVD, HT, and T2DM in AD and LBD, and these risk factors are known contributors to death through myocardial infarction and stroke [74]. With this as a foundation – and given the experience within the department that several AS individuals have suffered unnatural cardiac deaths, that previous research had suggested the presence of cardiac α-syn within AS, and that α-syn is a possible mechanism behind lethal arrhythmias and sudden deaths – we found it natural to steer our aim towards investigating the prevalence of cardiac α-syn and its possible role in the cause of death in AS.

General Aim

The general aim of this thesis was to investigate the prevalence of CaVD, HT, and T2DM in AD and LBD. In addition, the aim was to explore the presence of α-syn in the cardiac nerves as well as to investigate its potential role in the immediate cause of death in AS.

Specific Aims

I. To investigate the prevalence of CaVD, HT, and T2DM in AD, VaD, and MD.

II. To investigate the prevalence of CaVD, HT, and T2DM in LBD compared to AD, VaD, and MD.

III. To investigate and explore the prevalence of cardiac α-syn in AS.

IV. To investigate the cause of death and the prevalence of CaVD and risk factors in AS positive for cardiac α-syn.

Material and Methods

General Study Settings

The studied individuals in this thesis were referred to autopsy at the Department of Pathology in Lund, either for neuropathological examination or to obtain the cause of death. Upon referral to autopsy, most cases had a suspected or confirmed NCD. A comprehensive neuropathological examination was a prerequisite for inclusion, which consisted of an examination of the entire brain with sampling from whole-brain coronal sections and entire lobar regions [6]. A detailed description of the neuropathological assessment of each diagnosis is explained in the methods section of every paper. Table 1 presents the various cohorts studied in this thesis.

Table 1. Neuropathological Diagnosis of the Various Cohorts studied Studied in This Thesis
Subjects included in the four papers, presented in (N) numbers. AD, Alzheimer's disease; VaD, vascular dementia; MD, mixed dementia; LBD, Lewy body disease; AS, alpha-synucleinopathies. *Including cases with dementia with Lewy bodies, Parkinson's disease dementia, and dementia with Lewy bodies with a significant presence of Alzheimer's disease pathology (Braak ≥ III). **Including cases with Lewy body disease and multiple system atrophy. ***Including cases with Alzheimer's disease, vascular dementia, frontotemporal lobe dementia, or admixtures of these.

Neuropathological Diagnosis	Paper I	Paper II	Paper III	Paper IV
Total	**268**	329	100	131
AD	**81**	81		
VaD	**106**	106		
MD	**81**	81		
LBD*		**61**		
AS**			**68**	**78**
Control***			**32**	**53**

The neuropathological diagnoses and pathological macro- and microscopical findings of CaVD, cause of death, and cardiac α-syn were assembled through autopsy reports and clinical data on CaVD, and risk factors were retrieved from electronic health records, medical archives, and the Swedish National Diabetes Register (NDR), Gothenburg, Sweden. Table 2 presents the various pathological and clinical parameters studied in each paper.

Table 2. Pathological and Clinical Parameters Studied in This Thesis in the Various Papers.

Autopsy Parameters	Paper I	Paper II	Paper III	Paper IV
Myocardial infarction	X	X		X
Myocardial hypertrophy*	X	X		X
Coronary and aortic sclerosis	X	X		X
Nephrosclerosis	X	X		X
Cardiac alpha-synuclein			X	X
Cardiac fibrosis				X
Heart valve disease				X
Cardiac dilatation				X
Immediate cause of death				X
Clinical parameters	**Paper I**	**Paper II**	**Paper III**	**Paper IV**
Hypertension	X	X		X
Type 2 diabetes mellitus	X	X		X
Congestive heart failure				X
Arrhythmia				X
Prolonged QTc				X
Coronary artery disease/angina pectoris				X
History of myocardial infarction				X
History of stroke and/or transient ischemic attack				X
Orthostatic hypotension				X
Underlying cause of death				X

Autopsy Referrals as a Cohort

None of the papers included a control group with neurocognitively healthy subjects. The main reason for this is that a mere referral to autopsy, to determine the cause of death could be considered to be a selection bias. The referred individuals often die unexpectedly and tend to exhibit acute diseases as their cause of death, such as myocardial infarction, stroke, vascular events, and pulmonary embolism. Accordingly, they are probably not representative of the general population. This was also supported by Degerskär et al., who used national death certificates to identify a discrepancy in the cause of death in neurocognitively healthy individuals reported on autopsy with the overall population [123]. Consequently, the cases referred to autopsy present with a higher degree of atherosclerosis and prevalence of cerebro- and cardiovascular disease as well as greater risk factors than what might appear in the general population. Conversely, individuals with a clinically suspected or confirmed NCD are more frequently referred to autopsy to determine the specific NCD and not the cause of death. Therefore, these cases might be more representative of a wider population of people with NCDs. Hence, a comparison between a neurocognitively healthy group of subjects referred to autopsy with the NCDs studied, would perhaps have led to wrong conclusions. Therefore, we chose to compare the disease groups studied with each other, where the brain pathology was considered the main difference among the groups.

Paper I

This was a retrospective study including cases with AD, VaD, and MD referred to autopsy between 1992 and 2017; all other NCDs or admixtures of these were excluded. A total of 268 cases were included, comprising 81 cases of AD, 106 cases of VaD, and 81 cases of MD; see Table 1.

Pathological data studied in this paper included atherosclerosis in the coronary arteries and the aorta, the presence of myocardial infarction (both acute and subacute myocardial infarctions as well as older lesions), the presence of myocardial hypertrophy (both through measurement of the ventricular walls and based on the heart weight), and nephrosclerosis.

From the medical records and the NDR, information regarding the diagnoses of HT and T2DM were noted, but only the presence of diagnoses was accounted for and not treatment nor disease duration. Cases with anti-hypertensive treatment were assumed to have had HT.

Paper II

This was a retrospective study including cases with a significant LBD pathology, referred to autopsy from 2001-2018. The study enrolled a total of 61 cases with

LBD, 52 cases of DLB, three with PDD and six cases with DLB with a significant presence of AD pathology (Braak ≥ III), see Table 1.

The parameters studied from the autopsy reports, the medical records, archives and the NDR were the same as in **Paper 1**, see Table 2.

Paper III

This study analysed cases neuropathologically diagnosed with AS regarding the presence of α-syn in the cardiac nerves. A group with other NCDs without any signs of α-syn pathology in the brainstem or above served as controls. Cases were included retrospectively from 2010 to 2019 and prospectively from 2020 to May 2021 regarding cardiac tissue sampling. Exclusion criteria in this study, in addition to a limited neuropathological examination, were the lack of archival cardiac tissue or samples void of epicardial nerves in the retrospectively analysed cases. A detailed description of the assessment of cardiac α-syn is available in the methods section of the paper.

The AS were considered as a group, thus encompassing LBD, MSA, and cases with α-syn pathology in the brainstem; brainstem LBD, and with other predominant neuropathology; AD; VaD; FTLD; or admixtures of these.

A total of 68 subjects with AS were studied, including 64 cases with LBD and four cases with MSA. Among these, concomitant pathology was found in 25 cases with AD pathology being most common. The control group (*n = 32*) consisted of cases with AD, VaD, FTLD or admixtures of these.

Paper IV

In this study we analysed cases with AS, LBD, and MSA positive for cardiac α-syn regarding the cause of death and the prevalence of pathological cardiac findings on autopsy and clinical CaVD, HT, and T2DM. Cases were analysed retrospectively from 2010 to 2019 and prospectively regarding cardiac tissue sampling from 2020 to August 2022. The pathological parameters studied were the underlying and immediate cause of death, cardiac hypertrophy, cardiac fibrosis, cardiac valve pathology, nephrosclerosis, and coronary and aortic atherosclerosis. A detailed description of the investigation of the cause of death is presented in the methods section of the paper. The clinical parameters included were history of myocardial infarction, history of angina pectoris/coronary artery disease, congestive heart failure, arrhythmia, history of cerebrovascular insult or transient ischemic attack, QTc, HT, T2DM, and OH. In addition, cases with clinically reported congestive heart failure, arrhythmia, coronary artery disease/angina pectoris, or previous myocardial infarction were considered positive for the variable “clinical heart

disease". Other non-AS NCDs without α-syn pathology in the cardiac nerves nor the brainstem or above served as controls

A total of 78 cases with AS positive for α-syn in the cardiac nerves were included, 74 with LBD and four with MSA. Concurrent pathology, other than AS disease, was present in 29 cases where most individuals had an AD pathology. The control subjects consisted of 53 cases with AD, VaD, FTLD or admixtures of these.

All studied parameters were compared pairwise and not as a group. A sub analysis was performed in which three groups were compared: a group with brainstem LBD, a group with more severe disease degree of AS; limbic, cortical and MSA, and the control group. This was done as an attempt to determine whether prodromal stages of cognitive disease, such as brainstem LBD, would reveal any differences to more severe stages of AS and the control group.

Results

Paper I

Regarding the parameters from autopsy – myocardial infarction, both acute and subacute myocardial infarctions as well as older lesions, myocardial hypertrophy, nephrosclerosis and pathological heart weight – VaD displayed the highest prevalence with a significant difference compared to AD in all parameters, which presented with a low prevalence. MD presented the second highest prevalence of all studied parameters but differed statistically only to VaD regarding myocardial infarctions ($p < .001$). No statistical analysis was performed on the degree of atherosclerosis in the coronary arteries and the aorta. However, there was a clear numerical difference between VaD and AD where VaD was judged to have the most severe degree of atherosclerosis. MD had the second most severe degree of atherosclerosis among the groups.

Regarding the clinical parameters, HT and T2DM, both were the most prevalent within the VaD group, 74% and 34%, respectively; compared to MD, 44% and 19%; and AD, 37% and12 %. The differences were significant between VaD and AD in both HT and T2DM ($p < .001$ and $p = .014$) but only regarding HT between VaD and MD ($p < .001$). MD did not differ significantly compared to AD in any of the clinical parameters. Key characteristics and results from **Paper I** are presented in Table 3.

Comments: As displayed above, all studied parameters differed significantly, both pathologically and clinically, between AD and VaD. With this discovered low prevalence of CaVD, HT, and T2DM in AD, the results indicate that the association or the effect of the modifiable risk factors in promoting AD are questionable. Furthermore, MD differed significantly with VaD only in the prevalence of myocardial infarctions and HT and in none of the parameters compared to AD. This is remarkable, as the pathological definition of MD includes an evident amount of concurrent VaD and AD pathology.

No statistical analysis was performed on the degree of atherosclerosis as these were based on subjective judgements on autopsy by various pathologists, converted into a scale. An analysis of these results would have led to a risk of inaccurate conclusions.

Due to the retrospective nature of this study, with cases ranging back to 1992, we were unable to obtain information regarding the parameters studied in all cases because of autopsy reports lacking information or medical records not available in the medical archives.

Paper II

In this study, cases with LBD were compared to the groups in **Paper I** regarding the same clinicopathological parameters; see Table 2. LBD presented with a likewise low prevalence of pathological and clinical findings as AD, with no statistical differences between the groups. Compared to MD, only nephrosclerosis revealed a significant difference (p = .008) and compared to VaD, all parameters except pathological heart weight (p = .04, not significant after Bonferroni correction) differed statistically. No statistical analysis was made regarding atherosclerosis; however numerically, there was a similar degree of atherosclerosis between LBD and AD and more cases of LBD with none-to-mild atherosclerosis both in the coronary arteries and the aorta compared to MD and VaD.

Regarding HT and T2DM, the LBD group demonstrated a low prevalence of each disease, 37% and 8%, respectively, differing significantly only with VaD (p < .001 and p = .002, respectively). Key characteristics and results from **Paper II** are presented in Table 3.

Comments: As seen in **Paper I,** LBD portrayed a nearly identical prevalence of CaVD on autopsy, HT, and T2DM as AD. The results clearly indicate a low prevalence of the studied risk factors in LBD and, together with **Paper I,** imply that these modifiable risk factors are not highly prevalent in the neurodegenerative disorders.

An attempt was made to adjust the scale for atherosclerosis in this paper into two groups – none-to-mild and moderate-to-severe – compared to three groups in **Paper I** – mild, moderate, and severe. However, no statistical analysis was performed to avoid false conclusions.

There was more obtainable data in the LBD group from the clinical records regarding HT and T2DM, compared to the other groups studied in **Paper I,** as the earlier cases were from 2001 and not 1992. However, there was less obtainable autopsy data, probably because more LBD cases are referred to autopsy for neuropathological examination only and not to obtain the cause of death with a consequent full body autopsy.

Table 3. Characteristics and key Rsults of the Studied Parameters in Paper I and II.
Prevalence of obtainable data among the various neuropathological diagnoses. AD, Alzheimer's disease; VaD, vascular dementia, LBD; Lewy body disease. [a]Chi-square between each compared group adjusted with Bonferroni correction.

Characteristic & Parameters	Paper I Prevalence		Paper II Prevalence	Paper I *P*-Value	Paper II *P*-Value[a]	
Neuropathological diagnosis (n)	AD, 81	VaD, 106	LBD, 61	AD/VaD	LBD/VaD	LBD/AD
Age at death (interquartile range)	80 (72-88)	81 (76-86)	79 (75-83)			
Sex, n (%) women	50 (62)	49 (46)	24 (39)			
Myocardial hypertrophy, n (%)	20 (25)	53 (52)	14 (26)	<.001	.002	.860
Signs of infarction, n (%)	22 (28)	77 (75)	17 (33)	<.001	< .001	.540
Nephrosclerosis, n (%)	25 (45)	66 (68)	16 (31)	.006	< .001	.360
Type 2 diabetes mellitus, n (%)	6 (12)	21 (31)	5 (8)	.014	0.002	.540
Hypertension, n (%)	21 (37)	60 (74)	21 (36)	< .001	< .001	.890

Paper III

The prevalence of cardiac α-syn in the AS group was 82% (n = 56) compared to zero cases in the control group (p < .001). Cardiac α-syn was found in all stages of LBD: cortical, limbic, and brainstem. For examples of the epicardial nerve engagement, see Figure 4.

Comments: Twelve AS cases were negative for cardiac α-syn and a majority of these had cortical LBD (n = 9*).* They were all from the retrospectively assembled cases where the sampling from the heart was primarily done to determine the cause of death, in other words, to localise a myocardial infarction. All cases assembled prospectively were positive for cardiac α-syn where the sampling was done from the epicardium and with the present study in mind. This implies that all AS cases, regardless of stage, probably have α-syn in their cardiac nerves.

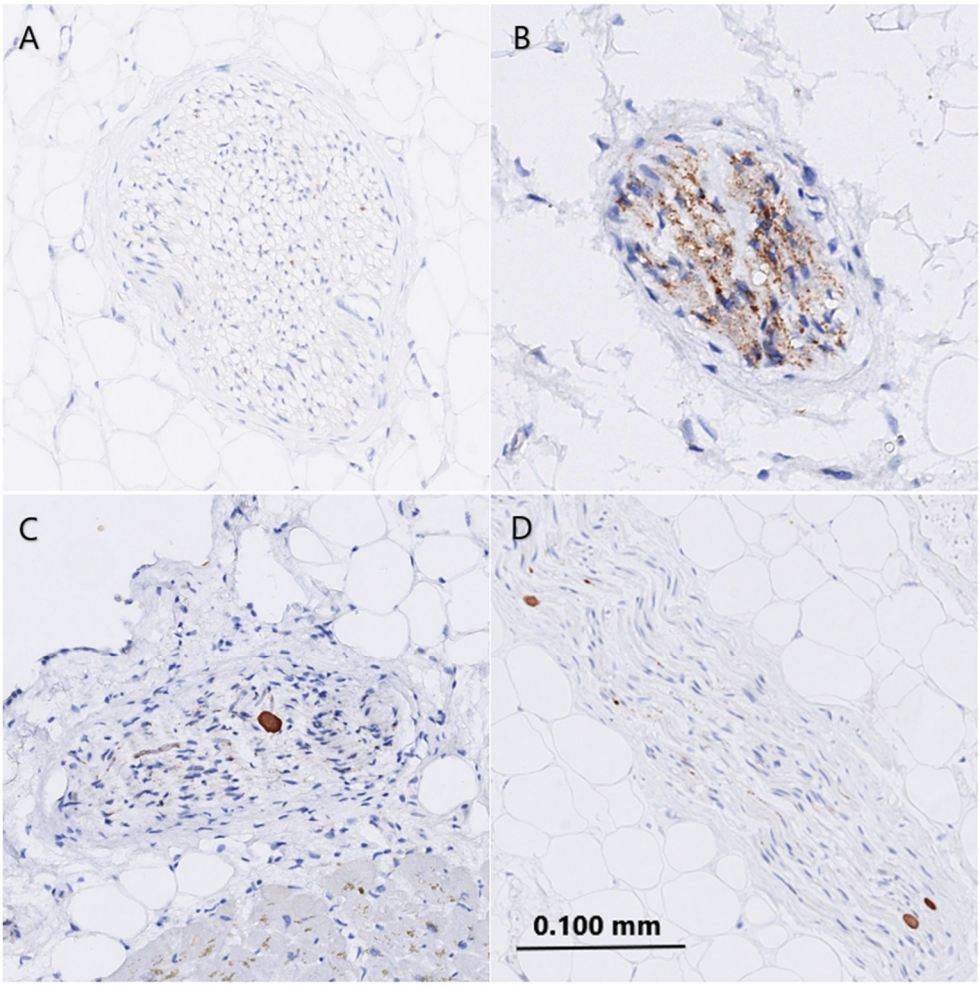

Figure 4. Demonstrating Epicardial Nerves with α-synuclein Immunohistochemistry.
Four microphotographs with α-synuclein immunohistochemistry, at 27x magnification. Negative epicardial nerve (A), postive epicardial nerve with granular depositions of α-synuclein (B), and distinct positive epicardial nerves with Lewy bodies (C + D). Longitudinal section in A-C and transversal section in D.

Paper IV

The most prevalent cause of death in the AS group was SCD (n = 40, 51.3%), and it was the second most common cause of death in the control group (n = 12, 22.6%; $p < .001$) after acute myocardial infarction. The SCDs were judged to be due to cardiac causes but not to vascular-ischemic causes. In a sub-analysis, the occurrence of SCD differed between MSA, limbic LBD and cortical LBD to the control group ($p < .001$*)* but not to the individuals with brainstem LBD ($p = .059$*)*. No differences were seen when subjects with brainstem LBD were compared to the controls ($p = .179$*)*. No other differences were seen in the immediate cause of death between the groups, and no cases within the control group were positive for α-syn in the cardiac nerves. However, positivity was seen in all stages of LBD and in cases with MSA, albeit only a few cases (n = 4*)*. There were no other differences regarding the pathological parameters studied.

The prevalence of OH differed significantly between the groups and was reported in 34 cases, 43.6%, in the AS group and six cases, 11.3%, in the control group ($p < .001$). A difference was also seen regarding OH when individuals with brainstem LBD were analysed as a separate group from the remainder of the AS group, MSA, limbic LBD, and cortical LBD ($p = .007$) but not from control group ($p = .269$). Otherwise, no differences were seen with regard to any other clinical parameters studied.

Comments: The only difference seen between the AS group and the control group, in addition to the positivity for cardiac α-syn and OH, was the prevalence of SCD as the immediate cause of death. Thus, cardiac α-syn may induce lethal alterations in cardiac function leading to sudden death in AS patients. Additionally, we once again found cardiac α-syn in all stages of LBD and in a larger cohort than in **Paper III.** This further strengthens the hypothesis that all AS, regardless of stage, have α-syn pathology in their cardiac nerves.

Conclusions: Studies I—IV

CaVD, HT, and T2DM demonstrated a low prevalence in AD and LBD with a clear difference compared to VaD, and in some respects, a similar or lower prevalence than the general population. This contradicts reports of the association between these modifiable risk factors and neurodegenerative disorders and also lends support to their association with VaD. The prevalence of these risk factors was similarly low in AD and LBD, which indicates that the typical protein pathology, that is considered a hallmark for these disorders, is not promoted by CaVD, HT, and T2DM.

Cardiac α-synuclein is present in all cases of AS and in various stages of the disease, even cognitively healthy, brainstem LBD. These depositions might cause lethal alterations in cardiac function, that are not vascular-ischemic, and they could be an explanation for the high mortality and sudden deaths witnessed in people with AS.

Discussion and Future Perspectives

Cardiovascular Disease and Risk Factors in Lewy Body Disease and Alzheimer's Disease

We found a similar and low prevalence of CaVD on autopsy in AD and LBD cases with a significant difference to VaD, which presented with a high prevalence. Looking at atherosclerosis of the coronary arteries and the aorta, we found that in the VaD group, 93% of the cases presented with moderate to severe atherosclerosis in the aorta and 83% in the coronary arteries, compared to 60% and 52%, respectively, in the LBD group, and 59% and 40%, respectively, in the AD group. The differences were corroborated by the presence of myocardial infarction, which could be interpreted as a general marker for atherosclerosis, where 75% of the cases in the VaD group had signs of infarction compared to 33% and 28% in the LBD and AD group, respectively. Although we did not perform any statistical analysis of the severity of atherosclerosis, the numerical differences are clear.

These results clearly confirm the expected high prevalence of CaVD in VaD [49], however, its association with the neurodegenerative disorders might be more complex and possibly mistaken. Our findings are in line with what has already been reported by Ghebremedhin et al. [85], who presented an inverse correlation between the severity of atherosclerosis and Lewy body pathology, and studies reporting no or limited association between vascular risk factors, presumably giving rise to CaVD, and cognitive decline in AD [142]. In general, the risk factors in LBD are unexplored and, to our knowledge, **Paper II** is the first comprehensive study reporting substantial data on CaVD and confirmed diagnosis of LBD. AD is commonly associated with these risk factors in studies that have not verified the neuropathological diagnosis, with the possibility of misdiagnosis and failure to detect significant vascular pathology.

Papers I and **II** did not evaluate any direct causality, nevertheless, the low prevalence of CaVD seen in the neurodegenerative disorders does not lend support to alleged claims of an association among CaVD, LBD, and AD. Furthermore, none of the parameters studied differed statistically between LBD and AD, two disorders often accompanied in the brain and with similar pathogenesis [5] that is vastly different from that of the pathology seen in VaD. This indicates that CaVD and the

other parameters examined do not contribute to the typical protein pathology seen in these neurodegenerative disorders.

A possibility still remains for an association between these disorders and CaVD. To answer this, clinical follow-up studies are needed to investigate the association in cohorts with neuropathologically confirmed diagnoses void of wrong diagnosis and mixed pathologies that are interpreted as AD. One might also argue that, if the prevalence of CaVD is low in these disorders, and if we strive to inhibit these disorders with the intent to specifically prevent LBD and AD, what are the effects on a societal level, and should this effort be given the tremendous resources it currently receives? There is no doubt, however, that these risk factors should be addressed to prevent VaD.

Another interesting finding is the prevalence of CaVD in MD. These subjects presented with a nominal higher prevalence in all studied parameters compared to LBD and AD but a lower nominal prevalence than VaD. No prominent differences were observed between MD and AD, and when compared to LBD and VaD, only nephrosclerosis and signs of infarction differed significantly. It is surprising that the level of CaVD was not similar between the MD and the VaD groups as the amount of cerebrovascular pathology was considered equal in these groups, and the only difference was a more severe AD pathology, Braak $\geq$ III, in the individuals with MD compared to the individuals with VaD, Braak $\leq$ II. Could AD pathology in some way have an inhibitory or protective effect on CaVD? This might not be unreasonable as AD pathology is estimated to begin 10 to 20 years prior to clinical symptoms [143, 144], and the vascular risk factors in mid-life are believed to contribute to the disease and are associated with CaVD [69, 74, 75]. It additionally raises the possibility that CaVD and AD share risk factors and are not directly associated with each other.

Hypertension in Lewy Body Disease and Alzheimer's Disease

In **Papers I** and **II,** we found a similar prevalence of HT in LBD and AD – 36% and 37%, respectively – compared to a significant difference of 74% in VaD. The results were further supported by the same pattern of prevalence seen in nephrosclerosis, increased heart weight, and myocardial hypertrophy; all of these are pathological alterations that are highly associated with HT [145-148]. Among the AS cases in **Paper IV,** 58% presented with HT but only 45% had nephrosclerosis, suggesting a relatively mild degree of HT [149]. Furthermore, it was estimated in 2008 that more than 50% of the Swedish population older than 65 years had HT [150], which is a higher incidence than was observed in the LBD and AD groups but lower than that in the VaD group.

The higher rate of HT among the AS individuals in **Paper IV**, compared to the LBD group in **Paper II,** is most likely explained by the number of cases with a significant VaD pathology (n = 14, 18%).

Our results clearly indicate a low prevalence of HT in the neurodegenerative disorders and confirm the expected high prevalence in VaD; therefore, they contradict the association between HT, LBD, and AD, even though a direct causality was not investigated.

HT was considered when the diagnosis was reported in the medical journals or when anti-hypertensive treatment was noted. Given the retrospective nature of our studies, we could not determine the number of cases in which HT had been reconsidered later in life due to hypotension, which is commonly seen in NCDs [68]. Neither did we investigate the prevalence of mid-life HT or any timepoint of the diagnosis. Therefore, our reporting of HT should be considered as the occurrence of HT during life in each group. Additionally, it strongly indicates that the prevalence is low in LBD and AD, and the contribution of HT to neurodegenerative pathology is uncertain, particularly given the prevalence seen in a similar age group in the general Swedish population.

The association seen in clinical studies could presumably be the result of vascular disease and mixed pathologies. Studies that have investigated this association, mostly in AD, as LBD is considered unexplored, are well-constructed and have clearly demonstrated an association among HT, NCDs in general, and AD [70, 88, 89]. What they all lack is a neuropathological confirmation of the dementing diagnosis, which is necessary for future research within this field.

T2DM in Lewy Body Disease and Alzheimer's Disease

T2DM is considered one of the more robustly associated modifiable risk factors for AD [73]. The prevalence of T2DM in LBD and AD was 8% and 12%, respectively, while the prevalence of T2DM in VaD was 31%. Furthermore, the prevalence of T2DM in **Paper IV** was 14,1% in the AS group, which consisted mostly of individuals with LBD, although concurrent pathology of AD, VaD, and FTLD was apparent in 37,2% of the cases, whereas 18% had significant VaD pathology. Interestingly, the prevalence of T2DM in Sweden in 2013 was reported to be 15,6% among individuals over 65 years [151], which is higher than our reported prevalence figures in LBD and AD and half as high as the prevalence in the VaD group. These results are supported by a recent large register-based follow-up study by Celis-Morales et al. that investigated the incidence of AD, VaD, and non-vascular NCDs in people with T2DM as well as the association of glycemic control and risk for NCDs [152]. They found a higher risk of VaD and non-vascular NCDs in individuals with T2DM and a lower risk of AD. Moreover, poor glycaemic control,

measured as glycated haemoglobin, was not associated with an increased risk of AD but with the other NCDs studied.

An argument for the low prevalence of T2DM witnessed among AD and LBD cases could be earlier deaths seen in individuals with T2DM [152], which would reduce their probability of developing AD. However, this argument was not supported in our cohorts, as the ages among the various NCD cases studied were similar.

We could not evaluate the prevalence and possible association of T2DM in PD, as no PD cases were included in our studies. In **Paper II,** only three cases, 5%, had PDD. The reason for this is most likely because individuals with PD and PDD are less likely to be referred to autopsy and neuropathological examination, as the diagnosis is often considered to be determined clinically. DLB cases are more often seen with referrals to determine the specific neuropathological diagnosis. Nevertheless, 31% of PD patients are expected to develop PDD and duration of PD is considered to be a risk for PDD [15, 22-25]. Together with the clear pathological similarities between PDD and DLB [59], one could assume that the prevalence and influence of T2DM on LBD pathology in general would be similar, unless there is a different underlying mechanism of how T2DM could promote the motor symptoms and cognitive decline, independently, in LBD.

Additionally, we were unable to study the potential causal links, hyperglycaemia and AGEs, between T2DM and the neurodegenerative disorders. However, given the low prevalence seen, causality could be questioned. T2DM is a common disease, and if there is a strong causal link between the disorders, one could expect a higher prevalence. Thus, it raises the question of whether treatment and preventive actions for T2DM have any effects on a societal level in lowering the risks for AD and LBD. Future research should aim to study the suggested association between these disorders in subjects with a neuropathologically confirmed diagnosis and to adjust for CaVD to determine whether T2DM independently increases the risk.

Cardiac Alpha-Synuclein and Death in Alpha-Synucleinopathies

Cardiac Alpha-Synuclein

We found cardiac α-syn in 82% of the AS cases in **Paper III** and in all selected cases in **Paper IV.** All prospectively analysed cases, where the samples were taken from the epicardium, were positive for α-syn. The cases judged negative or excluded from both papers were all assembled retrospectively, without the current studies in mind; they were sampled with the intention of detecting a myocardial infarction or confirming the cause of death. These cases lacked stainable nerves and/or archived

heart tissue and, thus, were excluded. The negative cases presented mostly with a neuropathology consistent with cortical LBD. As cardiac sympathetic denervation is a known feature of AS [153], one could argue that the negative cases were the ones most severely affected. However, this was not our experience, as the epicardial nerve engagement was judged to be equal in the AS group regardless of disease stage and clinical symptoms. Furthermore, we found cardiac α-syn in all stages of LBD: brainstem, limbic, and cortical.

These results, which were presented in a larger cohort than previous studies with a similar methodology [37, 40], clearly indicate that cardiac α-syn is present in all cases and all stages of LBD. The findings support the caudo-rostral spread of protein pathology suggested in LBD [41, 127-129], as cardiac aggregates were found in cases with only minimal α-syn pathology in the brainstem. Both sympathetic denervation and the presence of these depositions have been reported to be less profound in MSA [37, 133]. We found cardiac α-syn in all MSA cases, but due to the small sample size ($n = 4$), no further conclusion could be drawn.

Cause of Death in Alpha-Synucleinopathies

The majority of deaths in the AS group, in **Paper IV,** were judged to be SCDs due to cardiac reasons and not to vascular-ischemic causes**.** The prevalence of SCD was the only cause of death or pathological and clinical cardiac parameter studied in which there were significant differences between the groups ($p < .001$). Thus, no other pathological parameters denoting vascular-ischemic disease or other cardiac condition differed between the groups. In a subgroup analysis, cases with a more severe α-syn pathology in the brain, MSA, limbic LBD, and cortical LBD were analysed. Interestingly, the event of SCD differed statistically when these cases were compared with the control group ($p < .001$) but not when compared with cases with brainstem LBD ($p = .059$), and no significant differences were seen when individuals with LBD brainstem only were compared to the control group ($p = .179$).

The results clearly indicate that α-syn may promote pathological alterations in the heart that lead to SCD, which might be reasonable given the negative effects of α-syn seen in the CNS [33, 36]. These alterations do not appear to be easily noted through standard autopsy routines and do not seem to represent typical clinical heart disease (ischemia, myocardial hypertrophy/dilatation, coronary disease), as no differences were seen regarding these parameters between the groups. Furthermore, the findings indicate that there might be a dose-dependent association of the burden of cardiac α-syn and SCDs, as there were significant differences in the prevalence of SCD between individuals with MSA, limbic LBD, and cortical LBD and the controls but not between the controls and the individuals with brainstem LBD only. However, since no differences were noted between subjects with more severe α-syn pathology in the brain and the cases with brainstem LBD, although this might be due to cohort size, the cardiac burden of α-syn could still be considerable in

brainstem LBD and could perhaps promote SCD. In general, the previously reported high prevalence of circulatory failure [123] as well as the high mortality and poor prognosis in LBD and AS [122, 124] could be a result of cardiac α-syn promoting SCD.

A potential consequence of cardiac α-syn pathology and explanation for SCD could be terminal arrhythmias. Although we did not find any differences regarding QTc and the prevalence of arrhythmias, there were still a considerable number of cases in the AS group with sick sinus syndrome, congestive heart failure, and history of stroke. These conditions might be explained by atherosclerosis and HT [154] but could also represent arrhythmias. We chose to dichotomise the QTc values into normal and prolonged values, as several of the AS subjects had concomitant VaD pathology with a probable high rate of atherosclerotic CaVD and possible ischemia, which is known to affect QTc [155, 156]. Future studies should aim to analyse the QTc intervals in "pure" AS cases, and to investigate the mean differences with healthy controls and other NCDs. Additionally, it is of interest to evaluate differences during the disease course and whether alterations occur before the onset of clinical cognitive symptoms.

OH was the only clinical parameter studied in **Paper IV** that differed significantly between the groups ($p < .001$) and when LBD brainstem was compared as a separate group to the rest of the AS group, MSA, limbic LBD, and cortical LBD ($p = .007$) but not with the control group ($p = .269$). A potential explanation for OH in AS is cardiac sympathetic denervation, which is associated with cardiac α-syn, and has been observed in LBD. The sympathetic denervation is believed to contribute to autonomic dysfunction of the cardiovascular system including OH [134]. Furthermore, Serrano et al. reported that AD patients with concomitant LBD pathology that failed to meet DLB clinicopathological criteria did not have reduced tyrosine hydroxylase (TH) fibre density, representing sympathetic denervation [157], compared to cognitively healthy controls [158], which is consistent with our findings in the individuals with LBD brainstem only. On the other hand, the TH fibre density was reduced in cases with PD and cases with concomitant significant AD/DLB pathology. Additionally, the study presented a negative corelation between reduced TH fibre density and reduced neurofilament immunoreactive nerve fibre densities with cardiac and brain α-syn pathology. This implies that our findings of differences in the prevalence of OH within the AS group might represent various severity degrees of cardiac α-syn burden in different stages of LBD, leading to sympathetic denervation and OH. Moreover, one might expect that a relatively low degree of cardiac α-syn aggregates does not affect the sympathetic nervous system, although further research regarding this is needed.

As the study cohort in both **Papers III** and **IV** consisted of retrospectively assembled cases without the studies in mind, the cardiac sampling was heterogenous. Thus, we could not evaluate whether the quantity of cardiac α-syn or the intensity of the staining correlated to various stages of LBD or the various

parameters studied; SCD, cardiac pathology, or clinical heart disease. There is a demand for future research to investigate this and additional pathophysiological effects of cardiac α-syn on cardiac function and its role in the cause of death in AS. A way to explore this would be through an extensive outlining of the allocation of these aggregations in the heart, to evaluate whether specific regions are more affected than others. Ghebremedhin et al. [159] reported a global impact in the heart regarding sympathetic denervation, including the atrium and conduction system, albeit few subjects were included. Other studies have focused mostly on aggregations or denervation in the left ventricular wall [37, 158]; thus, the distribution could be considered unexplored. In addition, most studies have focused on sympathetic denervation, expecting this to be a result of α-syn pathology. However, there is still the possibility that α-syn exerts other effects on the cardiovascular system that remain unknown. This warrants future research to explore the dispersal of α-syn in the heart and other potential effects of these aggregates, except sympathetic denervation.

Another aspect of interest for future research is the evaluation of biomarkers and imaging modalities. 123I-metaiodobenzylguanidine myocardial scintigraphy (MIBG) has been suggested as a tool to differentiate DLB from AD and to detect probable autonomic dysfunction, and it is considered indicative for sympathetic cardiac denervation [36, 160]. Additionally, reduced cardiac 123I-MIBG uptake has been reported to be a risk for cardiac mortality in people with T2DM [161]. It remains to be determined whether different severity degrees of sympathetic denervation correlate to clinical heart disease as well as when this occurs during the disease course. A challenge to answer this through 123I-MIBG is that the cardiac uptake is affected by various medications and other disorders such as T2DM, arterial HT, ischemic heart disease, and heart failure [160]. Furthermore, it is not yet established how well reduced MIBG uptake correlates with α-syn depositions and whether it could be used to estimate the burden of these aggregates in the heart. Among the subjects in **Papers III** and **IV**, this diagnostic procedure had been performed in only a few cases, and, therefore, we could not evaluate if different outcomes correlated with SCD, pathological cardiac findings, or clinical heart disease.

Mixed Pathologies and the Diagnosis of Neurocognitive Disorders

Considering that several of the clinical diagnosis of the NCDs are not entirely correct and, in many cases, are due to mixed pathologies [49, 63-65], we chose to base our research solely on neuropathologically confirmed cohorts. The diagnostic challenges are several. From a clinical point of view, clinicopathological studies

have demonstrated that the most common major NCDs – AD, VaD, MD, LBD, and FTLD – are difficult to diagnose accurately [63-65]. As a consequence, this could affect the final diagnosis, treatment, and care of these patients. At the same time, the neuropathological criteria used also differ in their accuracy to correctly determine the NCD. An autopsy study that investigated eight neuropathological staging systems for PD/PDD and DLB [162], including Braak PD and the 2005 Consortium on DLB [29, 41], found a discrepancy between the tests regarding the number of unclassifiable cases and the staging of Lewy body pathology. The 2005 Consortium on DLB has also been indicated to have a low clinical sensitivity [163]. A similar study was performed regarding AD, in which three common neuropathological scales for staging – all of which focus on a different pathology – were examined [164]. The topographical distribution of neurofibrillary tangles are assessed by Braak and Braak [12, 13] and the quantity of neocortical neuritic plaques by the Consortium to Establish a Registry for Alzheimer's Disease [165]. The National Institute on Aging and the Reagan Institute have proposed a combination of these [14]. The study concluded that the choice of these three scales affects the final diagnosis and that the correlation among the various measurements was suboptimal [164]. Regarding VaD, the diagnosis is more complex. The prevalence of the disease varies greatly in both clinical and neuropathological settings [57]. This is probably explained by the low sensitivity and the varying specificity among current clinical criteria [49] and that there are no consensus criteria for the neuropathological diagnosis. Moreover, regional differences probably affect the reported prevalence figures due to different management of CaVD and risk factors [57].

In both clinical and neuropathological settings, it is complicated to correctly diagnose mixed pathologies and to determine whether one or several NCDs is responsible for the symptoms. Lewy body pathology often coexists with AD pathology, and AD is believed to affect the clinical severity and prognosis of DLB [166]. Furthermore, a DLB diagnosis is often missed in these individuals [19]. However, the Consortium on DLB 2017 [36] has presented guidelines on when mixed Lewy-related pathologies and AD are expected to fulfil clinical criteria for clinically probable DLB. Thus, in this mixed entity, there are clear guidelines to support the neuropathological assessment and determination of the dominating pathology.

However, it is still unclear how admixtures of VaD should be interpreted. Firstly, it is our experience that some parts of the research community question the existence or high prevalence of "pure VaD", without the admixture of neurodegenerative pathology. In addition, the prevalence of mixed AD/VaD is also regarded as uncertain. Still, clinico-pathological correlative studies have reported a prevalence of pure VaD ranging from 2.4% to 23.7% and mixed AD/VaD from 4.1% to 21.6% [8, 167]. The prevalence of pure VaD seems to decline among the oldest, > 90 years, whereas the prevalence of mixed AD/VaD increases [48, 57], which indicates a

continuous rise in neurodegenerative disease with age. The various prevalence figures reported for mixed AD/VaD are probably due mostly to the lack of consensus criteria for diagnosing VaD, and, thus, determining when the VaD pathology should be considered sufficient to cause clinical cognitive symptoms [57]. Additionally, it remains unclear whether the vascular lesions lower the threshold for cognitive impairment in AD and whether they independently or synergistically provoke cognitive impairment. The answer to this is further complicated, as a large number of patients with cognitive decline and with significant cerebrovascular lesions have exhibited more severe AD pathology [168]. Some argue that there are different cerebrovascular lesions in AD and VD than in MD. In AD and VaD the lesions more frequently involve subcortical regions or are multiple microinfarcts, whereas in MD, large/hemispherical infarcts and multiple microinfarcts are more common [58].

In **Papers I** and **II**, we defined MD as individuals having a significant cerebrovascular component and AD pathology, Braak stage of III or more, because this severity degree of AD pathology is associated with cognitive impairment [5]. Presumably, an individual with AD pathology of Braak stage III and a large/hemispherical infarct or critically located small lesions will have cognitive symptoms as a result of both pathologies. However, studies suggest that vascular lesions in more advanced AD stages, Braak stage V–VI, have minor importance [58], and cognitive decline has been suggested to be weighted on pathological lesions in the following order: neurofibrillary tangles > Lewy bodies > Aβ plaques > macroscopic infarcts [169].

Less is known about the impact of vascular pathology in LBD, and more research is needed. DLB has been reported to have a lower occurrence of vascular lesions than in PD and AD as well as cognitively healthy individuals. Furthermore, the cognitive impairment is suggested to be independent from the vascular lesions and is mainly due to Lewy body and Alzheimer pathology [170, 171]. Additionally, the severity degree of Lewy body pathology has been reported to be inversely correlated with cerebrovascular disease [85].

In summary, it is clear that improved clinical criteria for NCDs and more research regarding the impact of mixed pathologies on cognitive decline are needed. A key step in achieving this is to establish consensus criteria for the neuropathological diagnosis of VaD, which is an existing entity and is presumably on the rise throughout the world as the life expectancy increases globally. Moreover, this stresses the importance of studies with a neuropathological confirmation of NCD but also exposes the challenges of determining the role of VaD in cognitive decline in individuals with concomitant AD and/or Lewy body pathology.

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About the author

Keivan Javanshiri graduated from the School of Medicine at Lund University in 2019 and he is currently specializing in Oncology at Skanes University Hospital. He has a special interest in presenting his research and educating others in popular scientific communication and presentation technique. This thesis is written at the Division of Pathology, Department of Clinical Sciences, Lund.

In this thesis, the prevalence of cardiovascular disease, hypertension, and diabetes mellitus type 2 in Lewy body disease and Alzheimer's disease are investigated and discussed. Additionally, Keivan explores the prevalence of cardiac alpha-synuclein and its role in the cause of death in alpha-synucleinopathies.

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