Neurodegeneration

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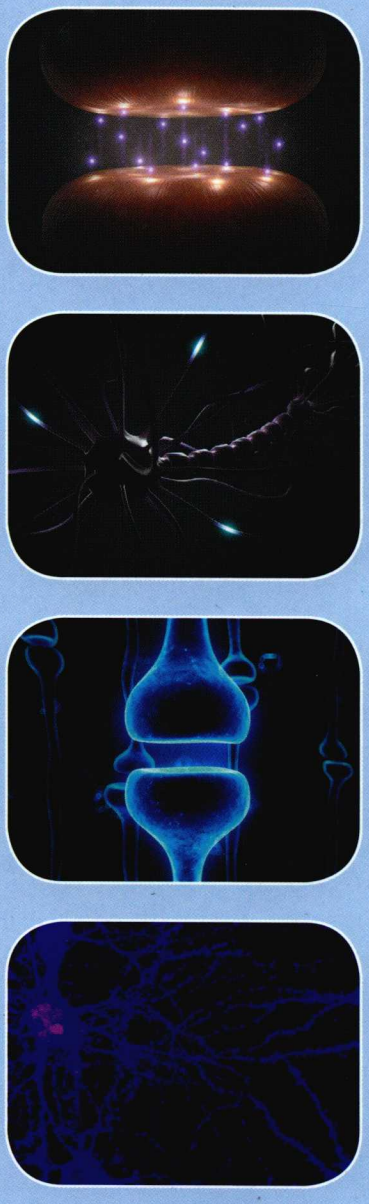

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Registered Office(s)
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

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Library of Congress Cataloging-in-Publication Data

Names: Schapira, Anthony H. V. (Anthony Henry Vernon), editor. | Wszolek, Zbigniew K., editor. | Dawson, Ted Murray editor. | Wood, N. W. (Nicholas W.), editor.
Title: Neurodegeneration / edited by Anthony Schapira, Zbigniew Wszolek, Ted Dawson, Nicholas Wood.
Other titles: Neurodegeneration (Schapira)
Description: Oxford, UK; Hoboken, NJ: John Wiley & Sons Ltd, 2017. | Includes bibliographical references and index.
Identifiers: LCCN 2016041714 (print) | LCCN 2016043003 (ebook) | ISBN 9780470672686 (cloth : alk. paper) | ISBN 9781118661925 (Adobe PDF) | ISBN 9781118661918 (ePub)
Subjects: | MESH: Neurodegenerative Diseases--physiopathology
Classification: LCC RC355 (print) | LCC RC355 (ebook) | NLM WL 358.5 | DDC 616.8—dc23
LC record available at https://lccn.loc.gov/2016041714

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Set in 9/11pt Minion Pro by Aptara Inc., New Delhi, India
Printed and bound in Singapore by Markono Print Media Pte Ltd

10 9 8 7 6 5 4 3 2 1

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Preface

The study of the function and dysfunction of the human brain and nervous system now constitutes the major focus of the biological sciences. Neurological disorders are often chronic and disabling, associated with a significant reduction in quality of life for patient and caregivers, increased morbidity and dependency, reduced life expectancy and a substantial financial burden on families and state. This pattern is seen with a broad range of neurological diseases, but is exemplified by the neurodegenerative disorders.

The enlarging global population coupled with a rise in life expectancy across the globe has highlighted the imperative of discovering therapies that can prevent the onset, slow or stop the progression of neurodegenerative diseases. While this ambition has been a priority since the first description of disorders such as Alzheimer (AD) or Parkinson (PD) disease, it is only with a clearer understanding of their potential causes that this has become a realistic focus. The advent and application of the molecular neurosciences and neurogenetics to the neurodegenerative diseases have provided the ability to identify often multiple aetiologies and pathogenetic pathways for neuronal dysfunction and death. Huntington disease (HD) is an example where the discovery of the huntingtin triplet repeat and the relationship of its size to clinical features provided invaluable insight into the pathology, selective neurodegeneration and biochemical defects found in HD. However it is only recently that this knowledge has begun to translate into potential treatments. A similar pattern is seen in AD, where the discoveries of amyloid mutations as a cause of familial AD led to the amyloid hypothesis for aetiology and pathogenesis. Again, it is only recently that therapies focussed on the amyloid pathway have come to clinical trial, although with rather uncertain benefits to date. PD has provided a rather more coherent story for the cause and progress of the disease. Studies prior to the application of modern genetics identified mitochondrial dysfunction, protein aggregation and oxidative stress as important features of PD pathogenesis. Subsequently, mutations were discovered in genes encoding proteins participating in these pathways, emphasising the importance of their role in PD. Further genetic and cell biological studies have combined to emphasise the role of lysosomal function and inflammation not only in PD but also in other neurodegenerations. Novel therapies based on these pathways are now emerging for PD and some are in early clinical trial.

HD, AD and PD are but examples of an enormous spectrum of neurodegenerative diseases affecting the central and peripheral nervous systems. It is notable that discoveries in some, e.g. the triplet repeat in HD, provide insight into others, e.g. triplet repeats in the spinocerebellar ataxias. Likewise the identification of mitochondrial dysfunction in PD was followed by evidence for bioenergetics defects in HD and AD. Protein accumulation, misfolding and aggregation, and more recently propagation have become a focus of attention in the neurodegenerative diseases, and a common theme across many of them.

In this text, we have sought to provide the reader with a modern view of the spectrum of neurodegenerative diseases. We have included not only the archetypal neurodegenerations such as AD, PD and HD, but also those disorders that have more recently been identified as distinct at the clinical, pathological and aetiological levels such as multiple system atrophy, progressive supranuclear palsy etc. We have sought to cover the degenerations of spinal cord and peripheral nervous systems, as well as site specific degenerations such as the optic nerve. Axonal loss in multiple sclerosis has been a focus of attention and some now consider that this disease justifies inclusion in the spectrum of neurodegeneration.

Writing and publishing a modern text book has its challenges, as well as its infinite pleasure upon completion. We have sought to be inclusive in providing the reader with an understanding of the range of neurodegenerative diseases, their causes, pathology, clinical expression and possible treatments. The edition is comprehensive, but not intended to be all inclusive. Any omissions are our responsibility and not those of the authors. We thank them for their enthusiasm, diligence and forbearance! We thank the publishers for their help and support in seeing this project through to completion.

Anthony HV Schapira
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Dedication

Christian W. Wider, MD was an Associate Physician at the Department of Neurology and Head of the Neurogenetic Diseases Unit of the Centre hospitalier universitaire vaudois (CHUV) in Lausanne, Switzerland. He completed his three-year Movement Disorders fellowship at the Mayo Clinic Florida in 2009.

Despite his short life he was able to contribute significantly to the research field of clinical genetics of neurodegenerative disorders and dystonia. He was an excellent diagnostician and was loved by his patients.

Dr. Wider died tragically in July 2016. He will be greatly missed by his family, friends, colleagues, and patients.

CHAPTER 1

Pathology of Brain Aging

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Introduction

The goal of this chapter is to describe the prevalent pathologic changes that are found in the brains of aged individuals. When comparing older persons' brains with younger persons' brains, it is challenging to distinguish the sequelae of particular diseases from the biological processes linked to "brain aging". What is clear is that there are specific pathological manifestations observed in the brains of elderly individuals and the presence of a subset of those pathologies correlates strongly with the severity of cognitive impairment. Brain aging-linked diseases include neurodegenerative conditions such as Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson disease dementia (PDD), frontotemporal lobar dementia (FTLD), hippocampal sclerosis of aging (HS-Aging), and others [1–3]. Also strongly implicated in aging-linked cognitive impairment is the heterogeneous group of conditions that manifest as cerebrovascular disease (CVD) pathology. Here we discuss some of the evolving concepts related to the brain changes that are seen in individuals of advanced age, with panels of photomicrographs to depict their appearance from a pathologist's perspective, and a consideration of the linkages between neuropathologic and genetic data. We emphasize that there is increasing awareness of the importance of CVD and HS-Aging pathologies as drivers of cognitive impairment in the "oldest-old".

The need for better understanding of the aging process and human brain pathologies: clinical and epidemiological aspects

Aging is a fundamental property of terrestrial life. Although not considered a disease per se, advanced aging-linked changes can be detrimental to biological fitness. In all cells and organisms that have been observed, there are phenomena characteristic of the mature epoch of life, and multiple mechanisms have been described to explain those phenomena [4, 5]. Senescence near the end of life has been attributed to mitochondrial dysfunction, telomerase activity, free radicals, oxidative stress, and other factors [4, 6–9]. In addition, genes have been described that either stimulate deleterious aging processes or that delay normal aging effects in some organisms (e.g., sirtuins).

Despite the insights that have been gained as described above, the concepts of aging and in particular brain aging are not well defined currently. Two things are certain: (1) aged individuals are going to constitute an ever-greater proportion of the overall population of developed countries in the upcoming decades [3], a demographic fact with far-reaching implications; and (2) advanced human age is accompanied by characteristic medical conditions that affect the central nervous system (CNS) and other tissues [10]. A defining feature of aging is that it is universally linked to the physical time dimension. Median life expectancy in developed countries is approximately 76 years for men and 81years for women [11]. Here we focus on those individuals that live longer than average, without addressing the problematic question of "when does 'aging' begin?"

The epidemiology of diseases that affect 95-year-olds is not identical to that of 75-year-olds [12]. In extreme old age, human organs develop a combination of vascular pathologies accompanied by weaker regenerative capacity. The background of generalized infirmity, specific high-morbidity diseases, polypharmacy, metabolic and mood disorders, and sleep pattern changes represents a formidable challenge to determining if a specific factor correlates with a specific disease, or contributes to impaired cognitive functioning through other mechanisms [12–15].

This chapter describes some of the prevalent brain pathologies observed in aged persons' brains. These observations help frame a discussion of their relationship with the aging process and with specific brain diseases. A better understanding of these issues will help us to define, diagnose, and treat the distinct conditions linked to cognitive impairment in the elderly as we move past the incorrect perception that "dementia" is linked overwhelmingly to Alzheimer's disease.

Brain pathologies in aging

Neurodegenerative diseases such as AD and DLB are covered in detail in Chapters 9 and 11. We will briefly describe these diseases, focusing on their pathological substrates and definitions. Pathology can provide insights about disease mechanisms when the molecular pathways are modeled in other experimental systems. However, pathological assessments themselves are cross-sectional (generally seen at autopsy) and often relate to the visual manifestation of histochemical or immunohistochemical staining. Here we use photomicrographs to demonstrate the appearances of the various pathological entities linked to brain aging. Our discussion will include two largely under-appreciated brain diseases (HS-Aging and CVD) that are linked to advanced age and which can be correlated with cognitive impairments.

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Nonspecific and non-diagnostic pathologies in aging brain

Relative to pristine brains from younger individuals, there are specific alterations that are observed consistently in the aged human brain, some of which are seen in increased abundance in individuals who died with impaired cognition. Our main emphases are on those brain changes that are indicative of a particular disease process and thus are pathologically diagnostic (for example, plaques and tangles in AD). However, there has been substantial focus on less disease-specific brain changes such as synapse loss, myelinopathy, neuroinflammation, glial activation, and the oxidation of proteins, lipids, and nucleic acids [16–19] which are discussed in other chapters of this volume. Some subtypes of those changes may in the future be proven to be specific to "brain aging" or to specific diseases, but more work needs to be performed in those areas. For example, although synaptic pathology is widely considered to be important in AD, and for credible reasons [20, 21], we note that all neurodegenerative diseases that culminate in dementia – without exception – are associated with synapse loss. Thus, loss of synapses is not disease-specific, much less diagnostic of AD. Until a particular, novel synaptic mechanism is universally accepted for AD, the specificity of synapse loss to AD remains unproven. Nor has the direct link between "brain aging" and synapse loss been exactly defined [3]. Further, some brain changes such as Hirano bodies, granulovacuolar degeneration, and cerebral amyloid angiopathy (CAA) are linked with AD [22] but their specificity and correlative impact on cognitive loss have not been firmly established.

An important step forward for neuropathologists is the most recent (2012) revision of the National Institute on Aging–Alzheimer's Association (NIA-AA)_recommendations for the neuropathologic approach to AD diagnoses [1, 23]. These recent consensus guidelines have advanced the field in at least three ways: (1) they removed the necessity of documented ante mortem cognitive impairment so that AD (like any other disease) can be diagnosed using the pathological "gold standard" alone; (2) they provided greater guidance for the diagnoses of non-AD comorbid pathologies such as HS-Aging, DLB, and CVD pathologies; and (3) they provided guidance to pathologists for anatomical regions to sample and stains to employ in the assessment of neurodegenerative diseases.

AD neuropathologic changes: neurofibrillary tangles

Neurofibrillary pathology comprises aberrant, partly insoluble, protease-resistant, hyperphosphorylated tau aggregates – some with paired helical filament appearance by electron microscopy [24] – inside various cellular compartments or extracellular after death of the parent cell. Neurofibrillary tangle (NFT) is the term that describes neurofibrillary pathology found in cell bodies (Figure 1.1A, B). NFTs are not specific for AD [25–27]; indeed, they are found in almost every class of brain disease and are observed universally (yet topographically and quantitatively restricted) in normal aging subjects [28]. NFTs are also found in the brains of individuals who suffered from frontotemporal degeneration with tauopathy (FTD-MAPT), myotonic dystrophy, prion diseases, metabolic diseases, some brain tumors, chronic traumatic encephalopathy, viral encephalitis, and other brain diseases [29–32]. This suggests that NFTs are, at least under some conditions, a secondary response to injury. Yet tau gene (MAPT) mutations can produce clinical dementia with NFTs, which establishes that under some conditions NFTs may be directly linked to the primary or at least proximal neurodegenerative changes [25, 27, 32]. There is no condition with *widespread neocortical NFTs* that lacks cognitive impairment [33, 34].

AD neuropathologic changes: Aβ plaques

In contrast to NFTs, Aβ amyloid plaques (AβPs) are extracellular [35, 36], often roughly spherical structures containing Aβ peptide and other material (Figure 1.1C–F). AβPs may be detected in histological preparations using Congo red, silver stains, and thioflavin-like molecules. Diffuse (or "primitive") AβPs can be visualized using silver stains and anti-Aβ immunostains. AβPs are found in a high proportion of all elderly persons but are not universal [37–39]. A particularly important subtype of AβPs is "neuritic plaques" (NPs), which have also been referred to as "senile plaques", and which are more likely to be associated with cognitive impairment than diffuse AβPs [40–42]. NPs are AβPs that are surrounded by degenerating axons and dendrites that often contain hyperphosphorylated tau aggregates. It is important to note that in elderly individuals, widespread neocortical NFTs are virtually nonexistent without the presence of widespread AβPs, except in the minority of cases with clear-cut tauopathy (e.g., FTD-MAPT). This observation and others (see below) have led researchers to hypothesize that AβP development is "upstream" of neocortical NFTs in AD pathogenesis [43]. Although the clinical–pathological data are complex, it should be stressed that the extant literature does indeed indicate the existence of a specific disease that is characterized by the presence of AβPs and NFTs [34].

Notes on AD pathology in persons past 90 years of age

For a description of the neuropathological hallmarks of AD and how their distributions have been observed in aging, see Table 1.1. Accurate clinical–pathological correlation requires that both components – clinical workup and pathological analyses – are performed optimally; there are potential obstacles to both of these in extremely old individuals for whom clinical assessments are challenging and autopsy rates are generally low. According to many different studies, dementia prevalence in the populations of developed countries is approximately 2% at age 65 and then doubles every five years thereafter [44–46]. Dementia incidence appears to level off after age 90 [46–50] although clinical dementia prevalence probably does keep increasing [51, 52]. In contrast to the increased prevalence of dementia with advanced age (a clinical observation), the appearance of neuritic AβPs and NFTs by pathology seems to level off in older cognitively impaired individuals according to multiple autopsy series [53–56], with the caveat that not all studies agree (discussed in [57, 58]). Further, as previously discussed, there is a greater "background" of hippocampal and brainstem NFTs in chronologically old individuals' brains. These phenomena have been interpreted to indicate a "dissociation" between AD neuropathologic change and cognitive status in extreme old age. However, even in extreme old age, the presence of many neocortical NFTs (Braak neurofibrillary stage VI) correlates with ante mortem cognitive decline [59–61]. Thus, no "dissociation" exists between the AD neuropathologic change and cognitive impairment. The question relates to cognitively impaired individuals of advanced age whose brains lack substantial AD pathology at autopsy. The answer to this question may lie in understanding the many powerful non-AD pathologies that occur beyond the eighth decade of life.

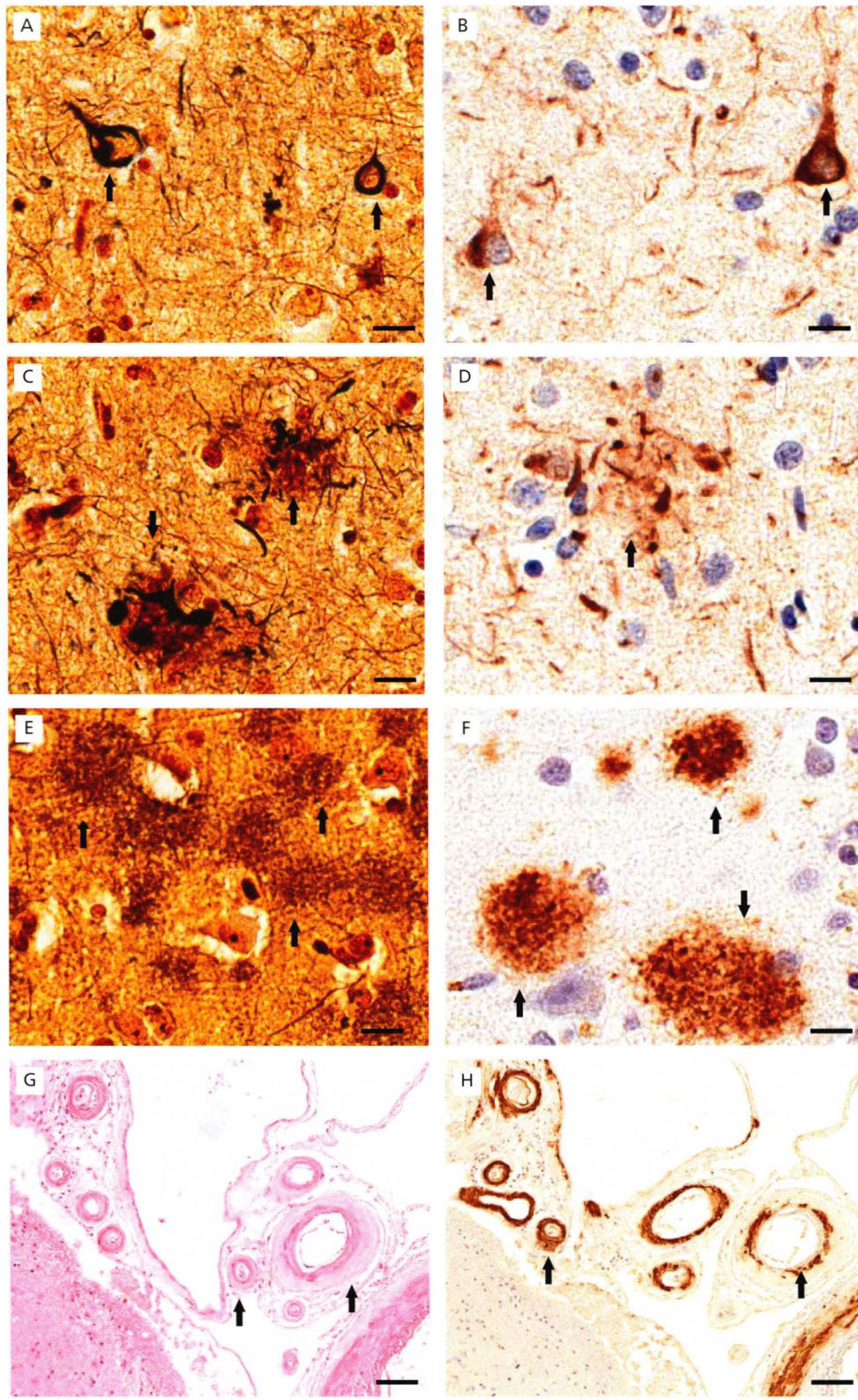

Figure 1.1 Alzheimer's disease (AD). (A) and (B) show the densely staining intracellular neurofibrillary tangles (arrows). Neuritic plaques (B, C, arrows) have a central nidus of amyloid with radiating tau-laden neuritic processes. Diffuse plaques, on the other hand, have only amyloid collections (E, F). Often seen accompanying AD type changes is cerebral amyloid angiopathy, which gives a thickened hyaline appearance to the vessels (G) and stains with amyloid (H). [Scale bar: 10 μm (A–F); 50 μm (G, H). Stains: A, C, E: modified Bielschowsky; B, D: PHF-1 tau immunohistochemistry; F, H: β-AP immunohistochemistry; G: H&E.]

Table 1.1 Subtypes and locations of Alzheimer's disease (AD) neuropathologic changes in aging and in different stages of AD.

Human brain condition	Locus coeruleus NFTs	Hippocampal NFTs	Neocortical NFTs	Hippocampal Aβ plaques	Neocortical Aβ plaques
Mid-life without AD or with extremely early AD	+	–	–	–	–
Advanced aging without AD	+/++	+	–	–	–/+
Presumed preclinical AD	++	++	–	–/+	+/++
Presumed early AD	+++	++/+++	+/++	+	++/+++
Late AD without comorbid pathologies	+++	+++	+++	++/+++	+++

Indicator of pathological severity: –, no disease-specific pathology; –/+, scattered or inconsistent pathology; +, low level of pathology; ++, moderate level of pathology; +++, high level of pathology. NFTs, neurofibrillary tangles.

Dementia with Lewy bodies (DLB)

DLB presently can only be diagnosed with certainty at autopsy and there is no known cure; this disease is discussed in greater detail in Chapter 9. The pathology of DLB by definition [62, 63] includes abundant aberrant deposits of α-synuclein (α-SN immunoreactive Lewy bodies and Lewy neurites; see Figure 1.2). Neuropathological data are especially important for cases with mixed pathology, such as AD with concomitant DLB, where precise clinical diagnostic criteria are lacking. Remarkably, some individuals with amyloid precursor protein (APP) gene mutations have early-onset cognitive symptoms with AD+DLB pathology [64, 65]. It is also important to note that "pure" DLB (extensive neocortical Lewy body pathology in individuals lacking AD pathology) is relatively rare and is far more often seen in males than in females, but has a definite cognitive impact [60, 66–69].

HS-aging and pathological TDP-43 inclusions

Hippocampal sclerosis (HS) refers to neuronal cell loss and astrocytosis in subiculum and cornu ammonis (CA) subfields of the hippocampal formation unrelated to AD pathology (Figure 1.3). In contrast to the disease also referred to as "hippocampal sclerosis" that affects younger adults [70], HS in older individuals is associated with significant ante mortem cognitive dysfunction [71, 72] but not necessarily with epilepsy. There is no universally-applied specific nosology for these cases and we use the term "HS-Aging" to refer to the disease with HS pathology in aging individuals [2].

Despite recent progress from many research centers, the specific clinical and pathological features related to HS-Aging have not been definitively characterized. The disease was described decades ago [73, 74], yet researchers and clinicians only recently recognized the high prevalence of HS pathology in aged populations [72, 75–77]. HS-Aging and AD have overlapping clinical and radiographic features related to hippocampal dysfunction and atrophy, so improved clinical identification of HS-Aging patients would enable more specific management of both HS-Aging and AD patients.

In addition to being linked to advanced age, HS-Aging pathology is also associated strongly with aberrant TDP-43 immunohistochemistry [78–80]. In the largest autopsy series of HS-Aging to date, we found that approximately 90% of HS patients had aberrant TDP-43 immunohistochemical staining (Figure 1.3C), in comparison to approximately 10% in older controls irrespective of the presence of other pathologies. TDP-43 is an RNA-binding protein, normally

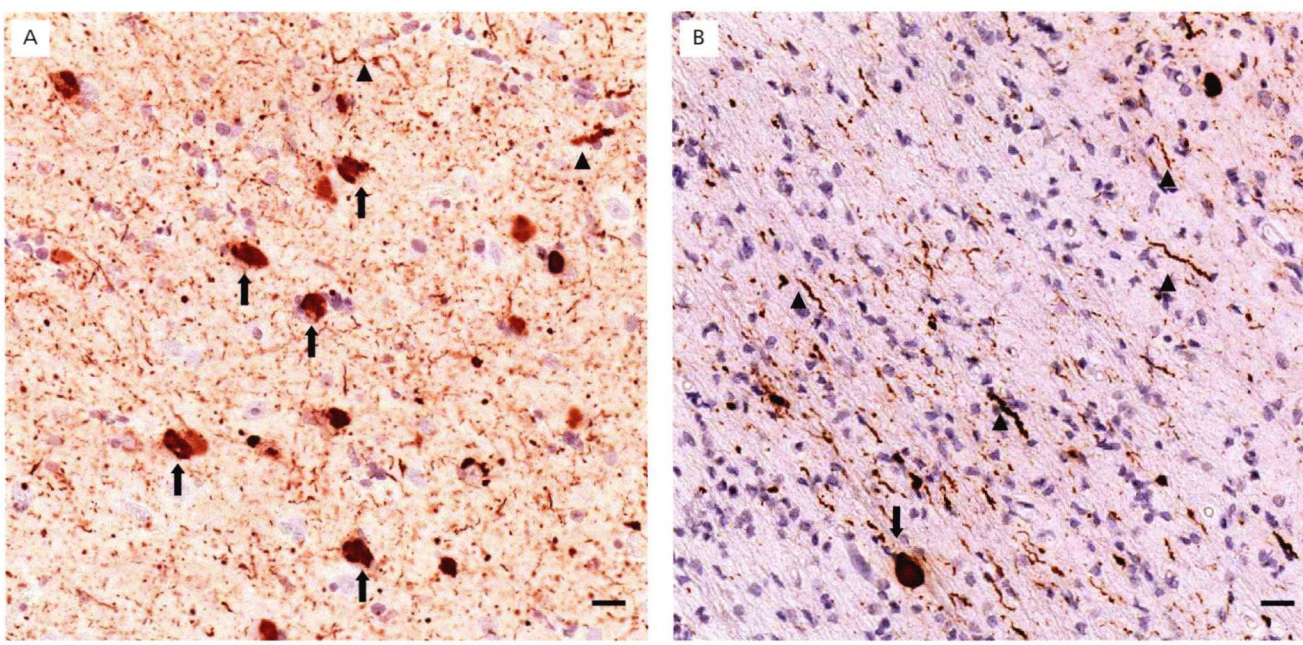

Figure 1.2 α-synucleinopathy in Lewy body disease. The amygdala (A) and olfactory bulb (B), showing both Lewy bodies (arrows) and Lewy neurites (arrowheads). These anatomical locations often harbor some of the earliest α-synucleinopathic changes seen in the brain. [Scale bar: 10 μm; α-synuclein IHC.]

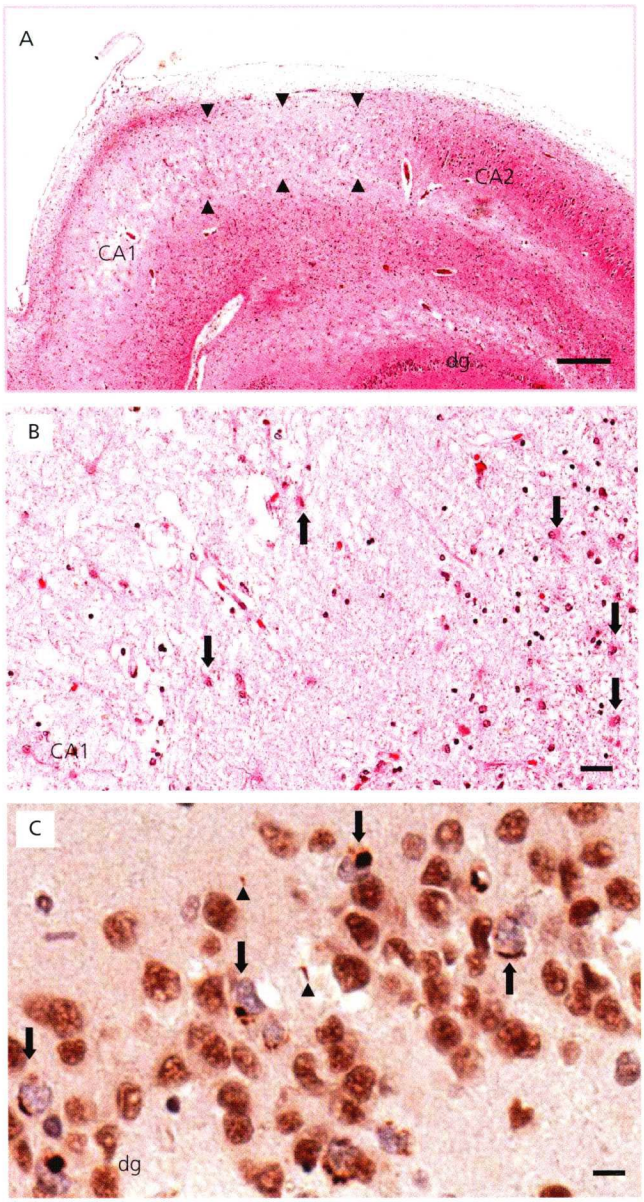

Figure 1.3 Hippocampal sclerosis. (A) A relatively intact CA2 region leading into a markedly sclerotic CA1 region (arrowheads). Examination at higher power (B) shows marked loss of the pyramidal neurons with abundant reactive astrocytes (arrows) and rarefaction of the neuropil. A TDP-43 immunostain (C) shows abnormal dense cytoplasmic localization (arrows) with occasional neuropil threads (arrowheads) in the dentate gyrus (dg). [Scale bar: 0.5 mm (A), 20 μm (B), 10 μm (C).]

localized mainly to the cell nucleus, that is linked pathogenetically with amyotrophic lateral sclerosis (ALS; see Chapter 14) and FTD (see Chapter 12), in addition to HS-Aging. The interface between HS-Aging and TDP-43-positive FTD has not been well defined [81–83]; clearly, HS-Aging cases do not fit neatly into the existing FTD classification [32]. It remains to be seen whether the TDP-43 abnormalities are causally linked with HS-Aging pathology. We did not find a link between HS-Aging and CVD pathology [2]. A speculative hypothesis, dovetailing on the recently described association between TDP-43 pathology and chronic trauma-induced encephalopathy [84, 85], and the fact that HS-like pathology is observed in some blunt trauma cases [86], is that aberrant TDP-43 with HS pathology in advanced age may reflect physical wear-and-tear.

Whereas the pathological data may be biologically informative, there is a practical need for improved clinical detection of HS-Aging to enable better management of both HS-Aging and AD patients. We found that the neuropsychological profiles of individuals with incipient HS-Aging differed systematically – even in the earliest stages of cognitive decline – relative to individuals who would eventually die with advanced AD pathology [2].

Cerebrovascular disease (CVD) pathology

Although not necessarily considered a "neurodegenerative disease", CVD comprises the most prevalent non-AD pathology in advanced aged brains and is directly relevant to any clinicopathologic study related to dementia among the elderly [3, 61]. The difficulties introduced by this prevalent, multifaceted, and clinically unpredictable disease category in aged individuals have been discussed previously [75, 87–95]; in individuals beyond the age of 90 years, some degree of CVD pathology is practically universal [61, 96–98]. We note the lack of an ideal rubric for CVD clinical–pathological correlation, although the recent NIA-AA criteria attempted to systematize neuropathologic assessment of this complex form of brain injury [23]. Despite its high prevalence and profound impact, researchers tend to under-appreciate the importance of CVD pathology [99–101].

The pathologic findings attributed to CVD are very broad, ranging from lobar hemorrhage/infarction down to mild alterations in small vessel morphology (Figures 1.4, 1.5). Large caliber vessel involvement typically consists of atherosclerosis of the cerebral vessels at various branchpoints around the circle of Willis. While the morphologic changes resemble those of systemic atherosclerotic lesions, severity is usually much less than that seen in the systemic circulation, often falling within the mild category [102]. Blockage of these vessels, by either local disease or emboli from elsewhere, leads to ischemia and, without restoration of blood flow, infarction. Systemic metabolic, toxic, or anoxic insults can also induce pathologies that resemble histomorphologic changes due to disrupted blood flow.

Arguably the most prevalent, and least quantifiable, subtype of CVD pathologies is the small vessel changes noted in the subcortical white matter, deep gray nuclei, and brainstem (Figure 1.5). Thickening of the smaller arterioles and capillaries, due to arteriolosclerosis or lipohyalinosis, is often present. Disruption of the smaller perforating vessels in the subcortical gray matter and brainstem (a process exacerbated by hypertension) can induce lacunar-type infarcts [103]. The Virchow–Robin spaces, normally small slit-like structures hugging the perimeter of the blood vessels, can vary dramatically in size. Pigment-laden macrophages are often seen in the expanded perivascular spaces. The surrounding white matter can take on a ragged, moth-eaten appearance. Corpora amylacea litter the perivascular and subpial parenchyma. These changes, seen both microscopically and to some extent via imaging modalities (where they are known as leukoaraiosis), are found more commonly with increasing age. To date, however, their relative abundance, size, or location cannot be correlated consistently with clinical symptomatology [104, 105].

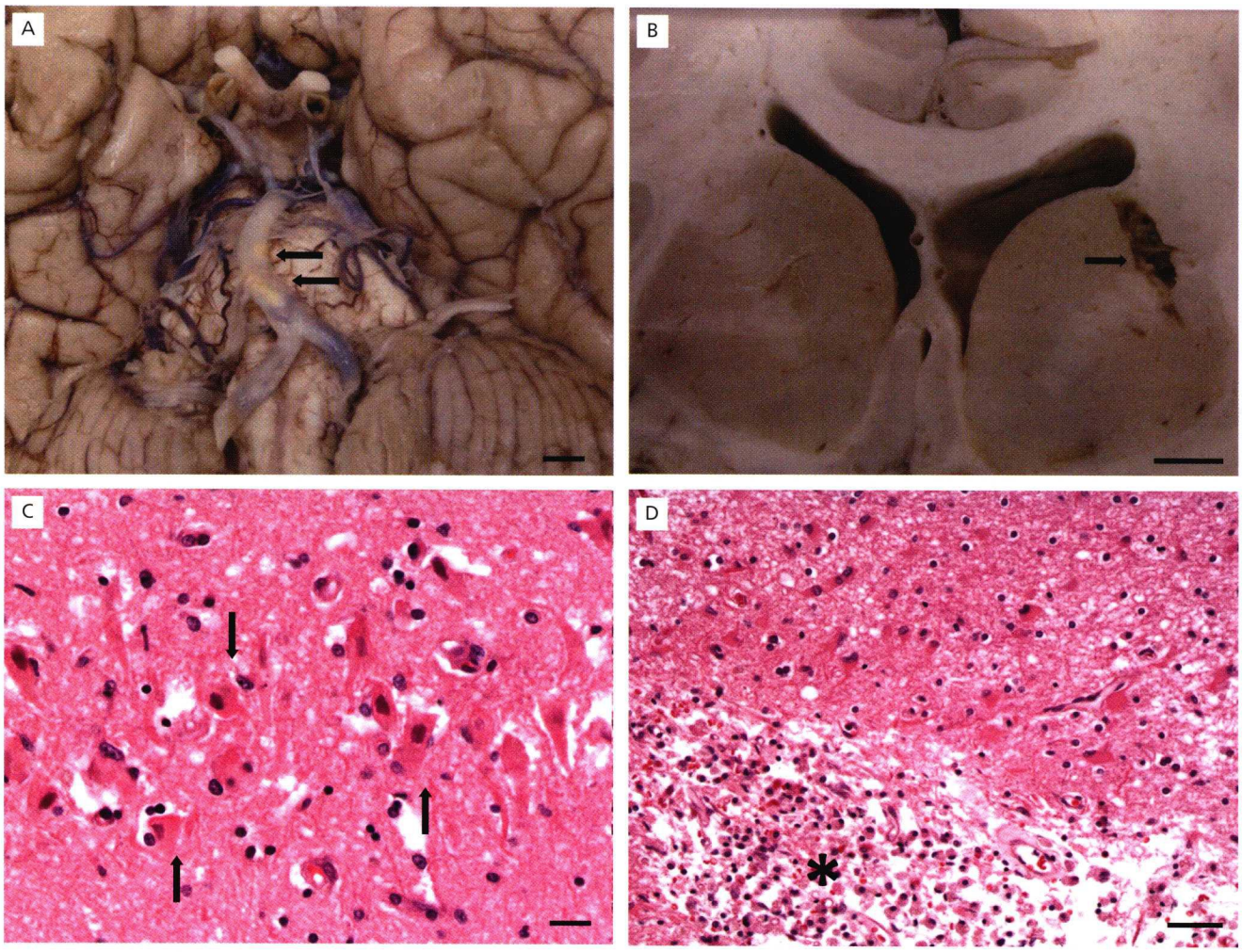

Figure 1.4 Cerebrovascular disease. Atherosclerotic changes may be noted grossly within the basilar artery (arrow) and elsewhere (A). Infarcts that occurred well before death are frequently observed in older patients, particularly within the basal ganglia (B). Microscopically, infarcts can range in appearance from acutely ischemic neurons (C, arrows) in an acute setting, to a macrophage-laden (*) cavity with surrounding gliosis in more chronic lesions (D). [Scale bars: A, B: 1 cm; C, D: 20 μm.]

Genetics and the environment: risk factors and potential therapeutic targets

Human genetics are critically relevant to any discussion of aging and neurodegenerative disease pathology, providing key insights into each. Approximately 70% of a given individual's risk for developing AD pathology is conferred through his or her genetic repertoire [106–108]. Thus genetics is one important place to seek clues as to whether the "aging" phenotype links specifically to AD pathology or to any other prevalent aging-linked brain pathology.

A subset of human genetic aberrations causes well-characterized phenotypes with specific features of advanced human aging in chronologically younger individuals. These diseases are called "progerias" [109, 110]. It has been suggested that progerias provide insights into the pathways that are involved in human aging [111, 112]. Clinical signs and symptoms that may exist even in pre-teens include cognitive impairment, wrinkled skin, atherosclerosis, brittle bones, cataracts, and many other changes, although there is not a single progeria that can be said to definitely cause "accelerated aging".

There is no firm indication that individuals with progerias have any increase in a specific pathology (AD, DLB, HS-Aging, or FTD) linked with brain aging [3]. One non-demented individual with Werner syndrome and apolipoprotein E (APOE) ε4 genotype was reported to have incipient AD-type pathology upon death at age 55 [113]. Otherwise, the link between Werner syndrome (or any other progeria) and AD pathology has been queried and not found to exist [114–116] although some of the progerias do in fact involve cognitive impairment. Mutations of the lamin gene (LMNA) cause a severe autosomal dominant progeria syndrome, muscular dystrophy, and Charcot–Marie–Tooth disease, but not AD [112]. In contrast, gene defects in presenilin-1 (PSEN1) produce early-onset autosomal dominant AD and a wide range of associated neurologic deficits but not a progeria syndrome (see below). Nor is there any firm association between AD and other known aging genes including the sirtuins (for example SIRT1 or SIRT3) although these have been exhaustively analyzed for AD-linked polymorphisms [117]. The dissociation between premature aging-linked genetic aberrations and AD pathology cannot by itself negate the hypothesis that AD is caused by aging mechanisms but it is a pertinent clue because

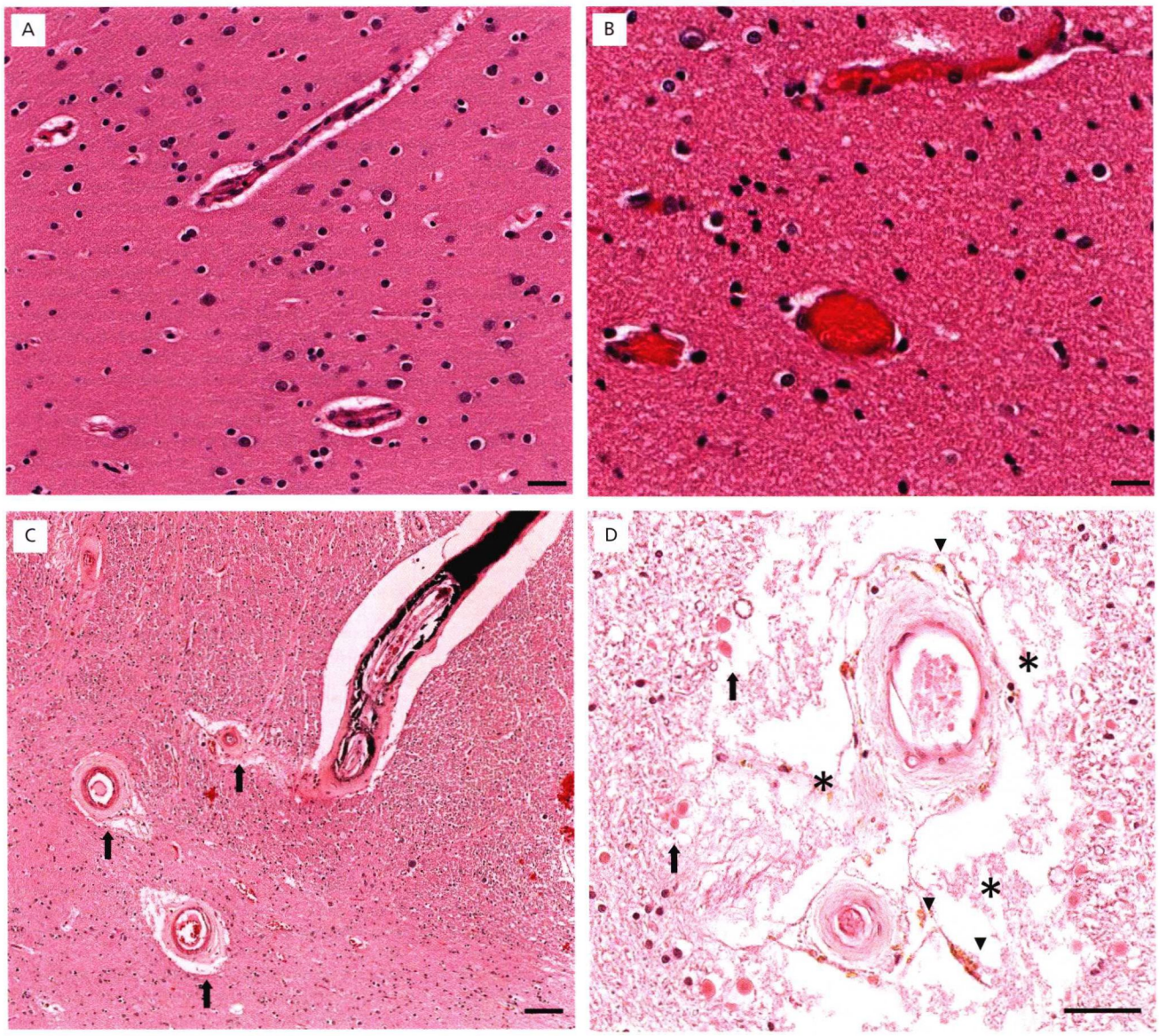

Figure 1.5 Small vessel morphology. The small blood vessels of the gray and white matter of most younger subjects (A, B, respectively) are thin walled, with minimal enlargement of the Virchow–Robin spaces. With age, these vessels often show arteriolosclerosis and lipohyalinosis (short arrows), usually accompanied by a widening of the perivascular spaces (*) with rarefaction of the surrounding white matter, an abundance of corpora amylacea (long arrows), and the presence of pigment-laden macrophages (arrowheads) (C, D). The vessels of the basal ganglia (particularly within the globus pallidus) also frequently undergo extensive mineralization (C). [Scale bars: A, B: 20 μm; C, D: 50 μm.]

there are indeed some genetic factors that strongly contribute to AD pathogenetically.

The highly penetrant human gene loci that alter risk for developing AD are APP, PSEN1, PSEN2, and APOE. None of these genes is known to be directly related to the aging process, nor to aging-related processes such as combating oxidative stress. These AD-affecting genes all influence processing of APP and provide support for the "amyloid cascade hypothesis" [118, 119], in which APP/Aβ dysfunction is a key pathogenetic mechanism in AD. The triplication of APP in the context of Down syndrome can induce AD-like pathology in the human brain as young as 8 years of age [120] with precursor lesions present even during infancy [3]. Even outside of Down syndrome, the focal duplication of the APP gene, and mutations in APP promoter regions that increase APP production, can cause AD [121, 122]. AD-relevant mutations in the APP gene affect its proteolysis, as do mutations in PSEN1 and PSEN2 [106].

By far the strongest risk factor for late-onset AD is the ε4 variant of the APOE gene [123, 124]. The impact of the APOE ε4 allele in terms of boosting brain Aβ deposition is well established [125–127]. The presence of APOE ε4 alleles correlates with much higher Aβ plaque densities and more extensive cerebral amyloid angiopathy [128, 129]. By contrast with AD, APOE ε4 is not a risk allele for HS-Aging [2, 77]. The strong genetic risk for AD in persons aged 50–80 leads to a survival bias in terms of individuals beyond that age range. Relatively few individuals with APOE ε4 allele (much less with APP or PSEN mutations) survive AD-free past age 90 [130–133]. This survival bias has been discussed previously [3, 134].

There are relatively recently discovered single nucleotide polymorphisms (SNPs) that alter AD risk and these include alleles in CLU, PICALM, and BIN1[135–138] in genome-wide association studies (GWAS). The penetrance of these genes is far weaker (i.e., the effect of the mutation on risk for the disease phenotype is less predictable) in comparison to mutations in APP, PSEN1, PSEN2, or APOE. SNP/GWAS data remain to be fully understood both in normal brain aging and in relation to AD or other brain disease manifestations.

In summary, AD appears to be a predominantly genetic disease that most often manifests in aged individuals but is not inevitable among the "oldest-old" and not necessarily linked to aging mechanisms per se. There are many other genetic diseases (linked to other genetic loci) that manifest late in life with neurodegeneration: trinucleotide repeat diseases, familial prion diseases, familial motor neuron diseases, FTD-MAPT, FTD-TDP, and dozens of other genetic diseases (see for example [139–143]) which also are not necessarily associated with "aging"-linked genes. HS-Aging seems to peak later in the aging spectrum than AD [2] but the genetic substrates of HS-Aging have not been elucidated. Although genetic diseases provide important insights into human aging and senescence, more work remains to be done to understand these complex ideas.

Summary

In the "oldest-old", numerous brain diseases, as defined by histopathologic characteristics, can be correlated with the severity of cognitive impairment [3, 144, 145]. Some of the neurodegenerative diseases (such as AD) appear to be linked with specific genetic changes rather than to "brain aging" per se. But as individuals advance into their ninth decade and beyond, there are many additional contributors to clinical dementia including CVD, HS-Aging, α-synucleinopathies, hematomas, argyrophilic grain disease, neuropsychiatric disorders and their therapies, failure of other organ systems, diabetes, hypertension, chemotherapy, and other side effects linked to medications [71, 81, 146–150]. These diseases are important to consider and inevitably have an impact on clinical trials: since most elderly individuals have comorbid pathologies in their brains, a therapeutic strategy that is effective for a particular disease process may seem to fail because of the presence of other brain diseases in the treated cohort of aged individuals.

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