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REVIEW ARTICLE

Brain pathological changes from population-based studies

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ABSTRACT

Brain structural and cerebrovascular changes and neurodegenerative pathologies are common and inadequately elucidated health problems in aging brains. Prospective population-based neuropathological studies play a unique role in neuropathological research. Brain weight decrease, arteriopathy, venular collagenosis, capillary loss, and accumulation of abnormal proteins are significant pathologies in the aging process. However, studies based on true population samples are scarce, and there is an ambiguity regarding the pathogenic proteinopathy between normal aging and neurodegenerative disease. Therefore, together population-based pathological studies offer an insight into the brain changes and diseases in the aging process, which could bring progress in the research for mechanisms and therapeutic interventions. Here, we reviewed findings from truly population-based pathological studies of brain aging and a range of neurodegenerative markers to better characterize brain pathological changes.

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1. Introduction

The increase in average life expectancy warrants insight into aging. Neuropathologically, brain weight decrease, arteriopathy, venular collagenosis, and capillary loss become more notable with aging, and some neurodegenerative changes, accumulation of abnormal proteins in brain tissue and cerebrovascular walls, are also prevalent in the old (Dugger & Dickson, 2017). Thus, companies with normal aging, and neurodegenerative diseases are common and complex health problems in the more ageing population (Hou et al., 2019; Kritsilis et al., 2018). Despite considerable advances in understanding its molecular and cellular underpinnings, neurodegenerative diseases with aging remain neither elucidated nor curable.

In particular, population-based clinicopathological studies might reveal new leads toward healthy aging and potential clues to overcoming age-related diseases (J. Zaccai et al., 2006). The neuropathologic biospecimens should come from prospective population-based cohort studies. Before autopsy, their participants should have long follow-up phases with well-recorded cognition, motor performance, and personality assessments. However, few cohort studies can fulfil such requirements.

Population studies can be generally divided into two categories: one conducted in patients or specific special populations, and the other shown in the local community intending to represent the general population. Studies focusing on Alzheimer's disease, Parkinson's disease, and other neurodegenerative markers, including the Hisayama

study, the Cambridge City over-75s Cohort (CC75C), the Vantaa 85+ Study, the Cognitive Function and Ageing Study (CFAS), the Honolulu-Asia Aging Study (HAAS), the Cache County Study on Memory and Aging (CCSMA), and the Adult Changes in Thought (ACT) Study, are strengthened in minimizing selection bias; however, they still face challenges in terms of keeping longitudinal follow up over decades and increasing tissue donation rate. On the other hand, studies among community-dwelling or specific selected populations may be less representative of the whole population due to sample selection bias. At the same time, they have the advantage of high clinical follow-up and autopsy rates. A combination of these approaches can be used to clarify the remaining areas of uncertainty.

Here we review evidence from population-based, clinicopathological studies of brain aging and neurodegenerative diseases to describe the changes, examine various hypotheses, and rationally select avenues for future investigation.

2. Characteristics of population-based prospective cohort studies

Seven studies were eligible as accurate population-based neuropathological studies among older people with standardized enrollment, regular follow-up assessment, and proper neuropathological methods.

The earliest neuropathological study among the general population is the Hisayama study, a prospective cohort study in a typical rural area in Japan from 1961, to evaluate the risk factors for lifestyle-related diseases (Ninomiya, 2018; Julia Zaccai et al., 2006). The study recruited 1,436 eligible subjects aged 40 or older in the beginning, and from 1985, the prevalence of dementia was investigated among residents aged 65 and over.

In Europe, CC75C (http://www.cc75c.group.cam.ac.uk), one of the oldest old's most extensive population-based pathological studies begins in 1985 and aims to measure the prevalence of dementia (Fleming et al., 2007). The original project enrolled 2,166 men and women aged 75 and above in Cambridge with a high response rate of 95%, and followed over the next 2 years after enrollment, as early named the Hughes Hall Project for Later Life and in publications. Then this cohort changed its name to the Cambridge Project for Later Life since the population has continued to follow up to the present day supported by a college of Cambridge University. Participants were then assessed with similar questionnaires every 3 or 4 years until 10 waves of data were collected. Another European study, the Vantaa 85+ Study, enrolled individuals at least 85 years old from 1991 in the city of Vantaa in Southern Finland. Among 553 subjects enrolled in the study, the response rate was about 92%. The Vantaa 85+ study focused on the characterization of the common age-related pathologies in the elderly Finnish population and the identification of their genetic background. CFAS (http://www.cfas.ac.uk), also known as the Medical Research Council (MRC) CFAS, was the most extensive population-based clinicopathological study in Europe and was designed to test for geographical differences (in six geographical areas) in dementia prevalence in the UK among adults over 65 years from 1989 to 1994 (Brayne et al., 2006). Indeed, the UK CFAS included three programs (Matthews et al., 2013). Data from Cambridge shire, Newcastle, and Nottingham of MRC CFAS were selected to provide CFAS I estimates. Between 2008 and 2011, to compare with CFAS I, CFAS II estimates in the same geographical areas were conducted. Recruitment for CFAS Wales, which aimed to interview a representative sample of 3,750 people aged 65 and over in two regions of Wales (Gwynedd and Swansea), began in 2011, with the follow-up wave completed in early 2016.

Longitudinal population-based studies in the USA started in the 1990s. HAAS is a part of the Honolulu Heart Program, and it prospectively collected information from the cohort of Japanese-American men to compare rates of dementia. CCSMA started in 1995, and the study enrolled 5,092 permanent residents of Cache County, Utah (USA) (Tschanz et al., 2005). The study was designed to investigate environmental and genetic factors related to the risk for Alzheimer's disease (AD) and other forms of dementia.

The above studies are truly population-based but with relatively low autopsy rates as a potential weakness. Studies among community-dwelling elderly and religious orders who agree to annual clinical evaluation and organ donation could make up for the shortcomings.

ACT study, a prospective community-based cohort study, enrolled men and women older than 65

who are members of the Group Health GH in the Seattle region, a well-established health maintenance organization. The original cohort enrolled 2581 individuals between 1994 and 1996, and an expansion cohort enrolled 811 individuals between 2000 and 2002. To replace people who die or drop out, the study re-enrolled in 2004.

The Nun Study enrolled individuals of Catholic School Sisters of Notre Dame, the USA, from 1986. The Nun Study remains one of the few longitudinal studies with complete records, including early life risk factors, the incidence of dementia, and neuropathologic findings at autopsy. Confounding from a wide variety of factors was minimized. The Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP) also enrolled selected populations with high follow-up rates (>90% among survivors) and autopsy rates (> 90%). ROS began enrolling Catholic nuns, priests, and brothers across 1994 the USA. To register participants with a much more comprehensive range of life experiences and socioeconomic status, in 1997, MAP enrolled 952 persons with an emphasis assessment on cognition, motor function, and risk of AD (Bennett et al., 2012; Bennett et al., 2005).

In addition, some autopsy cohorts are selected from a defined population, such as the Georgia Centenarian Study, the Mayo Clinic Study of Aging, and the Vienna Trans-Danube Aging study et al., which have revealed extensive findings concerning dementia and aging process. However, different selection biases exist in these studies, resulting in limitations in the inferences drawnfrom the community.

3. Gross neuropathology

At autopsy, brain structure is one of the first observations and undergoes considerable changes throughout human life. Average fresh brain weight is 1200-1400g, which for the adult male was 1336g and for the adult female 1198g (Hartmann et al., 1994). Brain weight and volume start to decline at around 45 to 50 years and reach their nadir after 70-86 years (Dekaban, 1978; Peters, 2006). As for gender, brain weight decreases by 2.7g in males and by 2.2g in females per year (Hartmann et al., 1994). In particular, specific areas of the brain responsible for cognitive functions, namely the frontal lobe and hippocampus, shrink more than other areas. The previous study showed that the average brain weight of 100-year-olds was 1097g, and it was relatively well-preserved in centenarians (aged 100 or more) (J. Zaccai et al., 2006) and supercentenarians (aged 110 years old or more) (Takao et al., 2016). The gross neuropathological findings of no severe brain atrophy and well-preserved brain shapes in centenarians are surprising (Ganz et al., 2018; Takao et al., 2016). However, brain morphometry is recorded only in some brain banks' hemispheres, leaving neuropathological analyses of aging brains to remain limited.

Atherosclerosis of the intracranial vessels, including the circle of Willis and the basal arteries, is macroscopically staged by experienced neuropathologists. Intracranial atherosclerosis is common in subjects older than 50, and it is one of the most important causes of stroke (Suemoto et al., 2018). The prevalence of intracranial stenosis (obstruction ≥ 50%) in the Brazil autopsy study is 59% (387/661) (Suemoto et al., 2018). However, for supercentenarians, the atherosclerosis of major cerebral arteries might be mild, as the well-preserved arteries might be an essential element associated with human longevity (Takao et al., 2016).

4. Cerebrovascular pathology

Cerebral microinfarcts are typically defined as sharply delimited microscopic regions of cellular death or tissue necrosis, sometimes with central fluid-filled cavitation. HAAS found that microinfarct number was independently associated with poor cognition (White et al., 2002), and in ACT, > 2 cerebral microinfarcts were statistically significant as correlates of dementia status (Sonnen et al., 2007). These results suggested that microinfarct burden may have a role in dementing illness.

Age-related brain microvascular pathologies are widespread in population-based autopsies. A previous study reported that moderate-to-severe arteriolosclerosis was noted in about 36% of subjects and was associated with microinfarct burden (Arvanitakis et al., 2017). With aging, arteriolosclerosis was not very severe in centenarians (Takao et al., 2016). "Cerebral age-related TDP-43 pathology and arteriolosclerosis" (CARTS) was proposed in a recent study as brain arteriolosclerosis together with TDP-43

deposition in the amygdala and limbic system, as well as hippocampal sclerosis (Nelson et al., 2016). Moreover, large amounts of arterioles become tortuous after age 50, with an intrinsic vulnerability of the white matter (Brown & Thore, 2011; Hassler, 1967). Apart from arteriopathy, in 1995, Moody et al. identified a new type of cerebral vascular pathology in subjects with white matter lesions, periventricular venous collagenosis. In our findings, moderate-to-severe venular collagenosis was also commonly observed in the white matter regions and was significantly correlated with age (unpublished data). The reason the veins become thickened in the deep white matter is not apparent, while a potential mechanism was proposed as the mechanical damage to small vessels due to abnormally high pulsatile motion in the periventricular white case (Henry-Feugeas, 2008). Capillaries, another main component of microvasculature, decrease in aging (average 16%) and lose their endothelium as string vessels (Bell & Ball, 1981; Brown & Thore, 2011). In this context, string vessels increase in aged brains, while the density in white matter lesions decreases and disappears (Brown & Thore, 2011). Overall, the pathogenesis seems to be a putative vicious cycle of cerebrovascular angiogenesis decline and hypoxia-induced capillary loss.

In population-based samples, the prevalence of cerebral amyloid angiopathy (CAA) is higher in the demented than the non-demented. On average, 55–59% of those with clinical dementia have CAA compared to 28–38% of the non-demented (Keage et al., 2009). One of the critical issues is that the optimized staining methods to examine CAA has not been well-recognized, including Congo red, thioflavin-S, anti-Aβ immunohistochemistry, and Weigert's haematoxylin conducted in previous pathological studies. Another limitation is that no consensus has been reached on how to sample or grade CAA severity. The current approach isolates cerebral and leptomeningeal vessels from the brain and staining for amyloid with Thioflavin (Roher et al., 2003; Weller et al., 1998). Given that the distribution is variable, a standard recognized method for assessing CAA is required for future population-based multi-center studies.

5. Alzheimer's disease neuropathological changes

Dementia affects about 55 million people worldwide, for which AD is the most common single cause and is paid much attention in community-based cohort studies. The CC75C research reported in 1998 that the average annual incidence rate of AD was 2.7 (1.6-4.4) in people aged over 75 years, with a marked increase with age (aged 75-79 years, 1.1; aged 80-84 years, 2.5; aged 85 years and older, 6.2) ("Incidence of dementia and cognitive decline in over-75s in Cambridge overview of the cohort study," 1998).

Alzheimer's disease neuropathological changes (ADNC) are defined by the 2012 NIA guidelines as including amyloid β (Aβ) plaques, neurofibrillary tangles (NFTs), and neuritic plaques and are assessed by a three-tiered staging system which quantifies the severity of ADNC as "not", "low", "intermediate" and "high" based on individual classification of these three pathological hallmarks (Hyman et al., 2012; Montine et al., 2012). Namely, this ADNC staging system includes ABC scores, combining assessment for amyloid plaques (A score), NFTs (Braak stages, B score), and neuritic plaques (CERAD scores, C score). Higher ADNC scores are strongly associated with cognitive decline and dementia, and a score of "high" or "intermediate" is considered a sufficient explanation for clinical cognitive impairment (Hyman et al., 2012). ADNC is commonly assessed in autopsy cohorts and brain banks.

ADNC correlates well with clinical symptoms of dementia in population-based autopsy cohorts. Findings from autopsy cases from the ROS MAP study (mean age at death: 88.5 years) showed that about 90% of patients with clinical AD met the pathological criteria for AD, and about 50% of patients with mild cognitive impairment met the pathological criteria, while 1/3 of people without clinical symptoms met the criteria ("Overview and Findings from the Religious Orders Study," 2012; "Overview and Findings from the Rush Memory and Aging Project," 2013). Combined analysis of the Nun and ACT studies found that 50%/51% of participants with dementia showed Braak stage V/VI, while 8%/12% of participants without dementia were assessed as Braak stage V/VI (Santa Cruz et al., 2011). Higher Braak stage was strongly associated with cognitive decline, memory impairment, and decreased hippocampal volume in the Nun study ("The Nun Study_ risk factors for pathology and clinical-pathologic correlations," 2012; Riley et al., 2002). The CC75C and CFAS studies confirmed the association between

dementia and type- and position-specific ADNC, with the odds ratio of neuritic plaques and NFTs for dementia far exceeding that of diffuse plaques, especially in the neocortex (Brayne et al., 2009; "Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales," 2001).

While studies confirmed the association between ADNC and cognitive decline, this association also appears to weaken with age, and many cases with substantial AD neuropathology at autopsy exhibit few, if any, clinical symptoms of dementia during their lifetime, a phenomenon termed resilience to AD (Arenaza-Urquijo & Vemuri, 2018). Among centenarians aged 98 years or older, 45% of non-demented individuals had intermediate or high AD pathology, and the distributions of neuropathology (except for NFTs) were similar among individuals with different cognitive states (Tanprasertsuk et al., 2019). The CFAS study assessed 456 brains (age at death: 69-103 years) and found that the associations between ADNC (neuritic plaques and NFTs) and dementia were strong at 75 years of age but much reduced at 95 years of age when ADNC showed considerable overlap between people with and without dementia ("Age, neuropathology, and dementia," 2009). When Braak and CERAD criteria were examined separately in a sample of 209 brains (mean age at death: 86 years), neither performed well enough to predict dementia status ("Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales," 2001). Lower neocortical pTau burden and lower TDP-43 encephalopathy neuropathologic change may assist in the resilience to clinical AD in those with sufficient ADNC burden (Latimer et al., 2019).

6. Other neuropathological markers

6.1 Lewy bodies

Lewy bodies are lamellated, eosinophilic hyaline, intracytoplasmic neuronal inclusions of densely packed fibrillated aggregates that include α-synuclein and ubiquitin (Spillantini et al., 1997). Lewy bodies (LBs) within neurons and Lewy neurites in neuronal processes are the microscopic pathological hallmarks of Lewy body diseases (LBD), which include Parkinson's disease (PD), Parkinson's disease with dementia (PDD), dementia with Lewy bodies (DLB), and other less common neurodegenerative disorders (Jellinger, 2003; Outeiro et al., 2019). However, pathological findings of LBs in routine postmortem examination are much more common than the incidence of clinical PD, PDD, and DLB (Foltynie et al., 2006). When LBs were found in the brains of normal individuals, it was often referred to as incidental LBD (Ben-Shlomo & Wenning, 1994).

Using alpha-synuclein immunohistochemistry, LBs occur in 8-36% of elder subjects in community-based populations (Bennett et al., 2006; Brenowitz et al., 2017; Buchman et al., 2018; Ganz et al., 2018; Knopman et al., 2003; Markesbery et al., 2009; Mikolaenko et al., 2005; Oinas et al., 2009; Schneider et al., 2009; Schneider et al., 2012; Wakisaka et al., 2003; Wennberg et al., 2019). One of these studies showed an age-related increase in Lewy pathology (Wakisaka et al., 2003). Still, other studies have found no significant difference in the mean age of those with and without Lewy pathology. The most common affected regions are the cerebrum and brainstem. Still, studies have also reported Lewy pathology of the spinal cord, dorsal root ganglia, and peripheral autonomic nervous system in neurologically healthy elderly subjects (Bloch et al., 2006; Buchman et al., 2018; Klos et al., 2006; Sumikura et al., 2015). Studies including a higher proportion of AD cases found that Lewy pathology frequently coexists with ADNC (Brenowitz et al., 2017; Jellinger, 2004; Mikolaenko et al., 2005; Parkkinen et al., 2003). The results from clinical studies only assessing participants with AD have been inconsistent (Chung et al., 2015; Hamilton, 2000; Stern et al., 2001). In a study of the mixed clinic and community-based samples, a high proportion (over 50%) of participants with ADNC had co-occurring LBs. It provided evidence for a positive association between ADNC and Lewy pathology in either clinic or community-based samples (Brenowitz et al., 2017). The discrepancies regarding Lewy pathology and AD pathology might come from the heterogeneity of the studied populations and neuropathological assessment methods.

6.2 TDP-43 proteinopathy

Transactive response DNA-binding protein of 43 kDa (TDP-43) is an RNA and DNA binding protein responsible for transcriptional repression, RNA metabolism, and RNA splicing during the

stress response (Buratti & Baralle, 2012). TDP-43 pathology was first considered as a disease protein in amyotrophic lateral sclerosis and frontotemporal lobar degeneration with ubiquitin-positive inclusions (Neumann et al., 2006; Xu et al., 2010), but to date, it has been reported as a common co-pathology in many age-related neurodegenerative disorders, including AD, PD, Huntington's disease, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and Guam Parkinson dementia complex, etc. (Amador-Ortiz et al., 2007; Koga et al., 2018; Liao et al., 2022; J. L. Robinson et al., 2018; Schwab et al., 2008; Wilson et al., 2011; Yokota et al., 2010). The prevalence of TDP-43 pathology has been reported as ranging from 25–50% in AD (Nakashima-Yasuda et al., 2007; Uryu et al., 2008; Wilson et al., 2011).

TDP-43 proteinopathy can also be observed in normal elderly. Several community-based cohorts studies indicate that TDP-43 pathology is common in neurologically normal elderly (the frequency ranging between 10.5% and 46.4%) (Arnold et al., 2013; Ganz et al., 2018; Keage et al., 2014; Nag et al., 2017; Nascimento et al., 2016; Nelson et al., 2019; A. C. Robinson et al., 2018; Uchino et al., 2015; Wennberg et al., 2019; Wilson et al., 2013), and the frequency of TDP-43 increased with age (Keage et al., 2014; Nag et al., 2017; Nascimento et al., 2016; Wennberg et al., 2019). One multiethnic study even suggested a higher prevalence of TDP-43 pathology in Asians than Caucasians (Nascimento et al., 2016), but evidence from more studies is lacking. As for other commonly concomitant neurological pathologies in normal elderly, those with TDP-43 were reported to have a higher prevalence of hippocampal sclerosis (Cykowski et al., 2016; Ganz et al., 2018; Nag et al., 2017; Nelson et al., 2019; Wilson et al., 2013) and argyrophilic grains (AGs) (Arnold et al., 2013), but no robust associations were found for neuropathological variables like LBs, NFTs or Aβ, etc. These studies failed to identify a definite link between TDP-43 pathology and dementia, though a trend was observed in different studies (Keage et al., 2014; Nag et al., 2017; A. C. Robinson et al., 2018; Wilson et al., 2013).

6.3 Argyrophilic grains

AGs are Gallyas-positive, spindle- or comma-shaped, four-repeat (4R) tau protein-positive lesions which are selectively accumulated in neuronal dendrites and axons, serving as the pathological hallmarks of argyrophilic grain disease (AGD) (Togo et al., 2002). AGD often coexists with other neurodegenerative diseases, including PSP (Ikeda et al., 2016; Kovacs et al., 2016; Masliah et al., 1991; Santpere & Ferrer, 2009), CBD (Tatsumi et al., 2014), AD (Braak & Braak, 1987; Mattila et al., 2002; Thal et al., 2005), PD (Grau-Rivera et al., 2013; Homma et al., 2015), and TDP-43 (Fujishiro et al., 2009), etc. It has been reported that in PSP cases, the frequency of AGs ranges from 18.8% to 80%, and CBD cases range from 41.2% to 100% (Yokota et al., 2018). In general, in a population ranging in age from 25 to 96 years, the frequency of AGs tended to be much lower (125/2661, 5%) than that in PSP or CBD cases and showed a significant increase with age (Braak & Braak, 1998). Another study, including 300 consecutive autopsies of subjects over age 30, found 17/300 or 5.6% of those cases showed AGs (Martinez-Lage & Munoz, 1997). The prevalence of AGs in centenarians reached 31.3% (Ding et al., 2006). Four population-based studies have confirmed that AGs are present at a frequency of 15–31% in neurologically normal elderly (Josephs et al., 2008; Knopman et al., 2003; Rodriguez et al., 2016; Sabbagh et al., 2009). AGs are primary age-associated tauopathies. Thus, it is understandable that in both clinical and community-based studies, AGs were never observed in persons younger than their mid-fifties and the prevalence increased with age (Ding et al., 2006; Saito et al., 2002; Saito et al., 2004). To date, age has been the sole risk factor for AGs. None of these studies has confirmed any distinctive health features associated with AG cases. Although two studies have reported a cognitive decline in AGD cases (Braak & Braak, 1998; Tolnay et al., 1997), AGs can occur without significant cognitive decline or even show protection against cognitive decline (Grinberg et al., 2013; Sabbagh et al., 2009). Prior studies suggested that AGs might be benign.

7. Conclusion

Given the irreplaceable advantages of population-based clinical-pathological studies in investigating age-related disease, here we review 7 such studies to describe their findings of neuropathological changes. Decreases in brain weight and volume, atherosclerosis, arteriolosclerosis, venular

collagenosis, capillary loss, and amyloid deposits in brain tissue and vascular walls, and characterized neuropathological changes of AD, PD, and other neurodegenerative disorders generally become prevalent with increased age at autopsy. However, most neuropathological changes are less prominent in centenarians due to selection bias by death. Aging is the fundamental risk factor for most neurodegenerative diseases, and typically, most pathological hallmarks of neurodegenerative disorders, including ADNC, LBs, TDP-43, and AGs, also manifest in the elderly. Proteinopathy is also commonly observed in the brains of aged individuals without severe cognitive deficits or motor dysfunction. Thus, abnormal protein deposits have been considered essential hallmarks in normal brain aging and neurodegeneration.

Population-based autopsy studies have unique advantages in the characterization of brain aging, and are necessary for exploring mechanisms and therapeutic targets of late-life neurodegeneration with less bias. However, they would be hindered by the difficulties in obtaining large amounts of donation resources. Thus, the integration of autopsied resources should be driven. Another crucial point for further research lies in whether the proteinopathy found in healthy individuals represents the preclinical phase of neurodegenerative disease or could be part of normal aging. In other words, whether normal aging and neurodegeneration are two quite distinct processes or co-development and where aging stops and pathological neurodegeneration begins, remainchallenging problems for future research.

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Abbreviations

CC75C, the Cambridge City over-75s Cohort; CFAS, the Vantaa 85+ Study, the Cognitive Function and Ageing Study; HAAS, the Honolulu-Asia Aging Study; CCSMA, the Cache County Study on Memory and Aging; ACT, the Adult Changes in Thought; MRC, the Medical Research Council; ROS, the Religious Orders Study; MAP, the Rush Memory and Aging Project; CARTS, cerebral age-related TDP-43 pathology and arteriolosclerosis; CAA, cerebral amyloid angiopathy; AD, Alzheimer's disease; ADNC, Alzheimer's disease neuropathological changes; Aβ, amyloid β; NFTs, neurofibrillary tangles; LBs, Lewy bodies; LBD, Lewy body diseases; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies; TDP-43, DNA-binding protein of 43 kDa; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; AGs, argyrophilic grains.