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Asymptomatic Alzheimer's Disease: A Prodrome or a State of Resilience?

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Abstract

Neuritic plaques and neurofibrillary tangles, the neuropathological hallmarks of AD, are not limited to individuals with dementia. These pathologic changes can also be present in the brains of cognitively normal older adults – a condition we defined as Asymptomatic AD (ASYMAD). Although it remains unclear whether these individuals would remain clinically normal with longer survival, they seem to be able to compensate for or delay the appearance of dementia symptoms. Here, we provide a historical background and highlight the combined clinical, pathologic and morphometric evidence related to ASYMAD. Understanding the nature of changes during this apparently asymptomatic state may shed light on the mechanisms that forestall the progression of the disease and allow for maintenance of cognitive health, an important area of research that has been understudied relative to the identification of risks and pathways to negative health outcomes.

Keywords

Normal aging; MCI; AD; neuropathology; beta-amyloid; neuronal hypertrophy

INTRODUCTION

“At the command of King Charles I, William Harvey (Philosophical Transactions, 1635) conducted a post-mortem examination on the famous Thomas Parr, of Great Wollaston, Shropshire, who died at the age of 154 years. Harvey describes the brain as ‘healthy, very firm and hard to the touch’. “Critchley, Brist, and Lond (Lancet, 1931) [1].

Alzheimer's disease (AD), an age-related neurodegenerative disorder, is the most common cause of dementia in older individuals and one of the leading causes of death in the developed world [2]. AD is characterized by a progressive loss of cognitive function and represents the culmination of neuropathological changes [3,4] thought to evolve over several decades [5–8]. With the mean population age rising steadily and some predicting as much as a four-fold increase in AD prevalence by 2050 [9,10], it is increasingly important to find effective strategies, be they diagnostic, preventative, or therapeutic.

It has become evident in recent years through prospective longitudinal studies with autopsy data that 1) neuropathological changes precede neurodegeneration, atrophy, and clinical

symptoms by perhaps decades [8,11–13], with clinical impairments detectable much later after substantial neurodegeneration has already taken place [14]; 2) therapy is likely to be most effective at symptom onset or earlier and the early diagnosis of AD is highly desirable before irreversible degeneration becomes severe and widespread; and 3) the identification of protective and/or compensatory factors, and thereby the prevention of disability and disease, has been understudied relative to the identification of pathways to negative health outcomes [15].

A substantial part of our efforts has been devoted to the understanding of the morphological substrates and underlying mechanisms by which some individuals remain cognitively intact despite the presence of considerable AD pathology. Our investigations have largely focused on the Baltimore Longitudinal Study of Aging (BLSA), established in 1958 [16]. The BLSA is supported by the National Institute on Aging (NIA) intramural research program with a mission to study the normal aging process and how it might differ from explicit age-related disease. An autopsy program, combined with comprehensive neurologic and cognitive evaluations, was established in 1986 in collaboration with the Johns Hopkins University Alzheimer's Disease Research Center (ADRC).

Here, we provide a historical background and review the key findings from the BLSA autopsy series focusing on the changes that occur in normal aging and early AD. Our goal is to highlight the combined clinical, pathologic and morphometric evidence of asymptomatic AD (ASYMAD), a state characterized by the presence of AD pathology in individuals with normal clinical evaluations. Understanding the nature of changes during this apparently asymptomatic state may shed light on the mechanisms that forestall the progression of the disease and allow for maintenance of cognitive health.

DIAGNOSTIC CRITERIA

Clinical diagnosis is based on the Diagnostic and Statistical Manual (DSM)-IIIR definition for dementia and AD criteria set forth by the joint working group of the National Institute of Neurologic and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) [17]. Although accuracy has improved over the years, especially when using consensus criteria in specialized AD centers, the clinical diagnosis of AD is still considered imprecise, with diagnostic accuracy lowest for early stages of AD [18] where age-related changes seem to overlap with pathological changes of the disease. Hence, the definitive diagnosis of AD requires *post-mortem* confirmation of neuropathological hallmarks – amyloid- β plaques (A β) and neurofibrillary tangles – along with clinical history of dementia. Currently, neuropathological diagnosis of AD is based on the frequency of neuritic plaques in neocortex determined according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria [19] while the Braak scores [20] define the distribution of neurofibrillary tangle (NFT) pathology in the entorhinal cortex, hippocampus, and neocortex.

Alois Alzheimer is credited to have been the first to describe the tangles at the 1906 Meeting of the Psychiatrists of South West Germany, where he presented the details of his now famous case, Auguste D [4]. He discussed the clinical features of the case which included a progressive dementia and described the pathological features, including plaques (miliary foci) and tangles (fibrils). The plaques, however, had already been described a few years earlier [21], while the documentation of clinical features of the disease dates back to the ancient Greeks [1]. It is useful to remark that two other important pathological changes of AD, i.e. degeneration of synapses [22, 23] and loss of neurons [24–26] arguably have better correlation with cognitive decline than plaques or NFTs, but are not part of the standard

pathologic diagnostic protocol. The loss of neurons in the CA1 region of the hippocampus is characteristic of AD and distinctly separates this entity from normal aging [25, 26].

ASYMPTOMATIC AD

Although current neuropathological criteria for AD still rely on densities of plaques and tangles to discriminate AD from normal aging, it has become apparent that the distinction between the two conditions seems to be quantitative rather than qualitative [27, 28]. Neuritic plaques and neurofibrillary tangles (NFTs), the neuropathological hallmarks of AD [29], are not limited to individuals with dementia and can be present in the brains of cognitively normal older adults [8, 13, 30–37].

In general, it has become apparent that as many as 30%–50% of older individuals (mean age = 85.5; age range 57–102) who come to autopsy as clinically normal have AD pathology present in the brain [38, 39]. Some have suggested that such individuals are in the preclinical stages of AD [40–44] while others view it as a part of the normal aging process [45–47]. The diagnostic category of cognitively normal individuals with pathology at autopsy has been termed preclinical AD [36, 48], high pathology controls [49] or high plaque non-demented subjects [50].

In the BLSA autopsy series, which is a non-representative sample of older, predominantly white, highly educated individuals with good access to health care, ASY-MAD subjects represent approximately 50% of individuals with preserved cognition beyond 75 years of age [38]. Initially, our group defined this condition as preclinical AD [13], but subsequently we used the term asymptomatic AD (ASYMAD) [51, 52] because we do not know *a priori* whether with longer survival these individuals would have remained clinically normal or not.

Reports of substantial brain degeneration and AD-related neuropathology in non-demented individuals are not novel. Tomlison, Blessed and Roth [37] reported numerous plaques in the brains of 8 out of 28 individuals who were intellectually preserved prior to death. Katznam and colleagues [33] reported plaque counts in 10 individuals with preserved mental status comparable to those commonly seen in individuals with dementia. Around the same time, Crystal and colleagues [30] evaluated 28 individuals who were followed longitudinally, nine of whom were non-demented. Numerous plaques were found in the brains of six out of those nine individuals. Similar observations have subsequently been reported by several different groups over the years [13, 32, 34, 53–58].

Although the number of studies is growing, it remains unclear whether the non-demented older individuals who harbor AD pathology would become demented given longer survival or whether they would be able to stave off cognitive impairment indefinitely.

COGNITION IN ASYMPTOMATIC AD

In the field of definitive AD cases with both pathological and clinical abnormalities, the severity of clinical impairment is significantly associated with the neuropathologic staging for both tangle and plaque classifications [59]. These findings, however, have often been criticized for leaving a large part of variability in cognitive performance unexplained given that amyloid-based staging accounted for only 13%, and tangles accounted for 26.5% of the variability in AD clinical severity. Subsequent studies employing more sensitive scales and more detailed neuropathological assessments show that a very high proportion of the variability in global cognition was explained by the tangle and neuronal counts in the hippocampal CA1 field, entorhinal cortex, and area 9 [60].

Although the studies are mounting [32, 33, 36, 39, 61–63], associations between cognition and AD neuropathology in clinically unimpaired individuals remain unclear. In 10 individuals whose plaque counts were 80% of those with dementia, Katzman and colleagues [33] found cognitive performance as good as or better than the performance of the upper quintile of those free of AD neuropathology. Hulette and colleagues [32] reported a trend for worse performance on tests with a memory component in 12 non-demented individuals with AD neuropathology. Schmitt and colleagues [36] reported worse immediate paragraph and delayed word-list recall in non-demented individuals meeting the NIA-Reagan criteria for AD. In addition to small sample sizes, however, the concern with the above mentioned studies is that all were possibly biased by inclusion of individuals with Mild Cognitive Impairment (MCI) [64] who also often have the pathology of AD [61,65], which was not widely recognized at the time. Although these individuals did not meet criteria for dementia, they may not have been clinically unimpaired.

A more recent study by Galvin and colleagues [65] reported stable cognition paired with the absence of practice effects on cognitive tests in individuals with histopathologic AD who were not demented at death. A study by Bennett and colleagues [11], also the largest study of AD neuropathology and cognition in non-demented individuals to date, reported that the presence of sufficient AD pathology to meet criteria for intermediate or high likelihood AD by NIA-Reagan criteria was associated with subtle deficits in cognitive function, specifically on tests of episodic memory. More recently, Price and colleagues [39] reported a significant association between AD lesion burden and worse cognitive performance at last available assessment, although none of the 97 autopsied were considered cognitively impaired even though up to 40% of these individuals met criteria for neuropathologically confirmed AD.

Through the BLSA autopsy series, we examined a sample of 81 elderly individuals who underwent prospective neuropsychological and neurological evaluations before coming to autopsy [62]. Our objective was slightly different from that of studies mentioned above. We asked whether the trajectory of change in cognitive performance with age of ASYMAD individuals was more similar to that of clinically normal individuals free of AD neuropathology or to the trajectory of individuals with MCI and AD. Trajectories of change over up to 16 years of follow-up were estimated for several cognitive domains, including memory, word knowledge, attention, executive function, and visuospatial abilities. Cognitive trajectories of clinically normal elderly individuals with (ASYMAD) and without AD-type neuropathology were similar across different cognitive domains. This stood in contrast to cognitive trajectories of clinically impaired individuals (MCI and AD) who exhibited an accelerated rate of cognitive decline that could be detected even in years prior to the diagnosis of dementia.

With recent advances in neuroimaging, amyloid deposition in clinically normal older individuals has also been documented *in vivo* [66–69]. For example, Aizenstein and colleagues [66], who characterized the prevalence of amyloid deposition *in vivo* in clinically unimpaired older individuals using Pittsburgh Compound B (PiB) positron emission tomography (PET) imaging, reported frequent amyloid deposition in non-demented older individuals, confirming that persons with significant amyloid burden can indeed remain cognitively normal well into advanced age. Moreover, amyloid-positive and amyloid-negative participants performed similarly on a battery of neuropsychological tests. A note of caution is in order when interpreting PiB studies, as PiB binding is highly selective specifically for insoluble (fibrillar) amyloid-beta deposits [70] and is currently not approved as a clinical diagnostic tool.

Clearly, significant progress has been made in the characterization of AD pathology and its relationship to cognitive function in clinically normal older individuals. With the possible

exception of subtle decrements in performance specific to episodic memory and the lack of benefit from practice, ASYMAD individuals seem to perform cognitively as well as their counterparts free of AD neuropathology. Still, we have little understanding of the underlying mechanisms and the apparent functional preservation in face of substantial AD pathology.

COGNITIVE RESERVE AND ASYMPTOMATIC AD

The idea of reserve against brain damage was born from the observations of functional preservation in the face of damage or pathology and it can manifest as either cognitive or brain reserve. Cognitive reserve refers to flexibility and efficiency of use of available brain reserve and is often proxied by education, IQ, and more recently literacy, occupational attainment, engagement in leisure activities, and the integrity of social networks. Brain reserve refers to quantitative measures of brain integrity, such as size or neuronal count. In the Nun Study, Iacono and colleagues [71] reported two observations that appear to link ASYMAD with cognitive reserve. First, significantly higher idea density scores reflecting linguistic abilities in early life were observed in controls and the ASYMAD group compared to MCI and AD. Second, the ASYMAD group had significantly more years of education (master degree) compared to MCI or AD (bachelor degree). Although the study by Iacono and colleagues [71] hints at potential protective properties of cognitive reserve against the negative effects of AD pathology, much work is clearly needed in this area of future research.

NEURONAL HYPERTROPHY IN ASYMPTOMATIC AD

Hypertrophy of cortical neurons has recently been described in ASYMAD. Riudavets and colleagues [52] focused their investigations in the BLSA on morphometric changes of cortical neurons. Stereological methods were used to compare cell bodies and nuclear volumes in anterior cingulate gyrus and the hippocampus in autopsy brains of ASYMAD, with AD, MCI, and age-matched controls. Lower neuronal volumes were observed in MCI and AD compared to controls, while no neuronal atrophy was present in ASYMAD. In fact, Riudavets and colleagues [52] found a significant increase in nuclear volumes in ASYMAD compared to not only the control group, but also MCI and AD for both the anterior cingulate gyrus and CA1 hippocampal region.

Iacono and colleagues [71] followed up by extending the investigations to four cerebral regions, including anterior cingulate gyrus, posterior cingulate gyrus, primary visual cortex, and CA1 region of hippocampus. In addition to neuronal cell bodies, investigators also measured volumes of nuclei and nucleoli. Significant hypertrophy of the neuronal cell bodies, nuclei, and nucleoli of CA1 of hippocampus and anterior cingulate gyrus neurons in ASYMAD subjects was confirmed, while the hypertrophy in the posterior cingulate gyrus and primary visual cortex was limited to the nuclei and nucleoli.

The morphological substrates of ASYMAD were also investigated in a sample from the Nun Study [66]. Volumes of neuronal cell bodies, nuclei, and nucleoli in the CA1 region of hippocampus (CA1) were measured using designed-based stereology in four diagnostic groups: ASYMAD, MCI, AD, and age-matched controls. A significant hypertrophy of the cell bodies, nuclei, and nucleoli in the CA1 neurons was reported in ASYMAD compared with MCI and a similar trend was observed in comparison with controls.

Together, these findings suggest that neuronal hypertrophy may represent an early reaction to the presence of neurotoxic A β or tau, or a compensatory mechanism that prevents the progression of the disease into dementia despite substantial AD lesions. Non-human animal literature hints at neuronal hypertrophy as a potential compensatory morphological mechanism in response to injury. For example, an increase in neuron size was observed in

environmentally enriched rats [72]. In an unrelated study, p75 knockout mice exhibited an increase in cholinergic cell size in the basal forebrain which was associated with better spatial learning [73]. Hypertrophy of dopamine neurons was observed in primates following ventromedial mesencephalic tegmentum resection and is suggested to be a compensatory mechanism of dopaminergic neurons in response to partial lesions of the striatal dopaminergic innervations [74]. We have also demonstrated hypertrophy of dopaminergic nigral neurons in normal older subjects from the BLSA [75]. Hence, it is not unreasonable to presume that neuronal hypertrophy observed in the human brain may represent a morphological compensatory response to AD pathology.

SUMMARY

Here we review the accumulating body of knowledge pertaining to asymptomatic AD, a condition characterized by the lack of notable cognitive impairment despite the presence of substantial AD pathology. Studies assessing longitudinal cognitive course of non-demented individuals who came to autopsy are still a few. Of these studies, some have reported a negative effect specific to episodic memory and not other cognitive domains. [11, 32, 33] Other studies report no relationship between AD pathology and any cognitive measures [34, 62]. The comparison of results has been difficult because neuropathological methods and criteria differ between studies. It is likely that methodological differences combined with relatively small sample sizes in most studies are contributing to conflicting findings pertaining to the relationships between AD neuropathology and cognition in the non-demented individuals.

Still, the observation that some older individuals escape notable cognitive impairment even when faced with substantial AD pathology is continuing to puzzle the field of AD research. One interpretation of the lack of cognitive decline in association with AD neuropathology in clinically normal individuals may be that there is a threshold beyond which AD neuropathology causes negative functional outcomes. Another possibility is that some protective mechanism is working in favor of cognitively normal elderly with AD neuropathology. Identification of protective as opposed to risk factors, and thereby the prevention of disability and disease, has been understudied relative to the identification of pathways to negative health outcomes and merits additional emphasis in future research. It is possible that factors such as pathological aging [31], cognitive and brain reserve [76], ApoE-2 genotype [66] or others yet to be identified may compensate for or delay the appearance of dementia symptoms in these individuals.

Recent advances in neuroimaging, namely the advent of amyloid tracers [77–80], hold promise for molecular imaging as an *in vivo* diagnostic and prognostic tool. Given the lack of differences in the rates of cognitive decline between clinically unimpaired elderly with and without AD neuropathology, however, it seems that merely getting a snap-shot of who has β -amyloid present in their brain is not as diagnostically useful as originally hoped. Amyloid imaging, however, will remain critical in tracking the time-course of deposition. Longitudinal amyloid imaging studies will be essential in testing the hypothesis of a threshold for amyloid deposition which results in functional deficits and whether that threshold is uniform across individuals or varies according to other risk and protective factors and may ultimately aid in defining new preventative, diagnostic or treatment tools. Finally, we believe that the combination of longitudinal clinical follow-up, *in vivo* imaging of brain β -amyloid, and postmortem neuropathological examination will contribute to better classification of ASYMAD. As of now, the jury is still out on whether ASYMAD constitutes a prodrome to dementia or a state of resilience.

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