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What does it take to stay healthy past 100?:

Commentary on No disease in the brain of a 115 year old woman

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Abstract

The description of an 115 year old woman without dementia or Alzheimer's disease (AD) is remarkable, but fits well with previous accounts of aging and AD. Several similar non-demented cases aged 85 to 105 years have been reported previously, who had neurofibrillary tangles in the medial temporal lobe, but no deposition of amyloid plaques. Together with observations on other aging and very mild AD cases, these can be related to a model of aging and AD. In this model, tangles develop independently but relatively slowly during aging; these represent neurodegeneration, but by themselves may not represent AD. In contrast, amyloid may be the driving factor in AD, exacerbating neurofibrillary changes and other neurodegeneration. There is a pre-clinical period when the process has begun but has not produced sufficient degeneration to produce clinical symptoms. Critical questions raised by the present report include what genetic or other factors allowed healthy survival to age 115, and whether anti-amyloid therapies will allow more general survival in good mental health beyond age 100?

Although there are limits to the generalizations that can be drawn from a single case, the individual brain reported in this paper is quite remarkable. Not only was the subject the oldest known living human at the time of her death, but she also had very little cognitive decline, and her brain was found to be remarkably healthy, even for someone much younger than 115 years. As the authors point out, this indicates that brain disease is not inevitable, even in super-centenarians. Unfortunately, the bad news that must accompany this report is that the number of people who can maintain a healthy brain for this long is very small. Unless medical or other interventions are developed, the majority of us must expect cognitive decline before 100 years of age. The incidence of AD and other causes of dementia increases exponentially between ages 65 and 95 (15,16). Although estimates of prevalence vary, as many as 50% of people aged 85 to 95 years appear to have some level of dementia (5,6). If individuals are included who have begun to develop lesions indicative of preclinical AD but have not yet developed clinical symptoms, the proportion affected probably would be much greater.

It is worth separating the two elements of this report, the lack of cognitive decline, and the relative absence neuropathological lesions, especially amyloid plaques. As is well known, lesions related to Alzheimer's disease (AD) are found prior to the onset of detectable cognitive decline or dementia. Except for the special case of Down's Syndrome, neurofibrillary tangles in medial temporal lobe structures usually precede the onset of amyloid deposition into plaques.

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In their neuropathological study of 2661 cases, Braak and Braak (4) reported that the majority of cases with neurofibrillary stage 1 or II, and some of those with stage III/IV did not have amyloid plaques. Even in cases older than 90 years of age, about 20% did not have plaques. On the other hand virtually all of the cases with plaques, or those over 80 years of age, had tangles. In our study of 39 well characterized non-demented cases aged 63 to 89 years, we found the same relationship, with the initial tangle formation preceding plaque deposition (24). Apart from her extreme age, the current subject would seem to fit into this pattern, with a moderate number of neurofibrillary tangles but no plaques.

There have been previous reports of relatively elderly individuals with relatively healthy brains, although none as old as the current subject. Price and Morris (24) reported three well characterized, non-demented individuals between 85 and 90 years of age who had no plaques. These cases also had tangles in the entorhinal cortex and hippocampus, but very few tangles in the neocortex. In addition to the study by the Braaks mentioned above (4), another study by Giannakopoulos et al. (8) of 1258 cases from a geriatric hospital, indicated that 11 of 37 cases aged 95 to 105 years did not have senile plaques, at least in the inferior temporal cortex. Thus, the pattern of neuropathology in the current case is in line with that seen in other elderly cases.

Neurofibrillary tangles are clearly pathological, and appear to represent sick, dying or dead neurons. For example, the documented pattern of cell death in the entorhinal cortex and hippocampal field CA1 matches closely the pattern of tangle formation in those areas in AD (9,13,14,25). On the other hand, the consistent relationship of tangles to aging suggests that they may represent an aging phenomenon and not necessarily AD as such. Tangle density in vulnerable areas such as the entorhinal cortex and CA1 increase almost exponentially with age (1,23,24). Further, tangles in medial temporal lobe regions are nearly ubiquitous in aging, reaching 50% prevalence (at least at Braak stage I) before 50 years of age, and approaching 100% prevalence by about 80 years of age (4,5,29). Although it is hard to be definitive, this pattern resembles an aging phenomenon, and without the concomitant presence of amyloid plaques does not appear to represent AD.

In contrast, there is compelling evidence that β -amyloid is the causative agent in AD. This comes particularly from observations on genetic mutations that cause familial forms of AD, all of which produce an elevation in β -amyloid or its more toxic form, β -amyloid 1–42 (27, 28). These mutations occur directly in the gene for amyloid precursor protein (APP) or occur in the genes for the Presenilin proteins, which form an important part of the γ -secretase complex that cuts APP to liberate β -amyloid. The triplication of chromosome 21 in Down's Syndrome also results almost invariably in AD; because the gene for APP is on the chromosome 21, the triplication produces an excess amount of β -amyloid. Although these genetic conditions account for only a small fraction of the total number of AD cases, the associated pattern of neuropathological lesions is essentially the same as that in "sporadic AD".

The widespread deposition of β -amyloid in plaques also appears provides the best neuropathological distinction of aging from AD (20,22,30,21,17). Studies on carefully assessed cases have indicated that although even very mild AD cases have widespread and substantial numbers of plaques, most non-demented cases do not (22,30). There are some non-demented cases with large numbers of plaques, however, which resemble the very mild AD cases; these appear to represent the "preclinical" stage of AD, in which the underlying disease process has begun, but has not yet produced sufficient neuronal damage to be clinically or psychometrically detectable (24,25,11). Recent positron emission tomography (PET) observations on carefully assessed non-demented cases with the [11C]PIB compound confirms that a portion of these cases show amyloid deposition similar to that seen in very mild AD cases (19). Longitudinal studies should be able to determine whether these cases progress to clinically detectable AD.

These observations, taken together, support a model in which neurofibrillary tangles form as a function of age, independent of β -amyloid. While tangles increase with age and clearly represent neuronal damage, in the absence of β -amyloid, their numbers are relatively low and they are largely restricted to the medial temporal lobe, as seen in the current case. It is possible that if humans lived long enough, the slow accumulation of tangles eventually would result in sufficient neuronal degeneration to cause clinically meaningful deficits, but the relevance of this outcome for the current human lifespan (up to 122 years) is unclear. The development of significant amounts of β -amyloid, however, as either plaques or diffusible oligomers, appears to exacerbate the formation of tangles and possibly also cause other types of neurodegeneration, resulting in the synaptic and neuronal destruction that is characteristic of AD. Perhaps the most striking evidence of this process is the development of dystrophic neurites within “neuritic” amyloid plaques. These neuronal processes contain the same tau-based paired helical filaments as seen in tangles, and form specifically within the β -amyloid-rich environment of a plaque.

A major question raised by the current report is what genetic or other factors enabled the subject described by Dunnen et al. to survive to 115 years of age without developing even pre-clinical indications of AD. Probably the major deficit in the report is that the authors did not at least determine the ApoE genotype. While ApoE ϵ -4 is recognized as increasing the risk of AD and AD-related changes at an earlier age, ϵ -2 is often thought to be beneficial, possibly increasing the clearance of β -amyloid from the brain (2). This subject may have been one of the rare individuals who are homogeneous for ApoE ϵ -2. Other centenarians have been reported who were ApoE ϵ -4 but disease free, however (18).

If the anti-amyloid therapies that are currently being developed prove to be efficacious and safe (3,7,10), it may become possible to prevent the formation of excess β -amyloid, or even to remove it from the brain. In that case, we may be faced with the ability to remove the scourge of AD, and allow more individuals to live with good mental health to 115 years of age or beyond.

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