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# Clinicopathologic correlates in the oldest-old Commentary on "No disease in the brain of a 115-year-old woman"

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## Abstract

den Dunnen et al. [den Dunnen, W.F.A., Brouwer, W.H., Bijlard, E., Kamphuis, J., van Linschoten, K., Eggens-Meijer, E., Holstege, G., 2008. No disease in the brain of a 115-year-old woman. Neurobiol. Aging] had the opportunity to follow up the cognitive functioning of one of the world's oldest woman during the last 3 years of her life. They performed two neuropsychological evaluations at age 112 and 115 that revealed a striking preservation of immediate recall abilities and orientation. In contrast, working memory, retrieval from semantic memory and mental arithmetic performances declined after age 112. Overall, only a one-point decrease of MMSE score occurred (from 27 to 26) reflecting the remarkable preservation of cognitive abilities. The neuropathological assessment showed few neurofibrillary tangles (NFT) in the hippocampal formation compatible with Braak staging II, absence of amyloid deposits and other types of neurodegenerative lesions as well as preservation of neuron numbers in locus coeruleus. This finding was related to a striking paucity of Alzheimer disease (AD)-related lesions in the hippocampal formation. The present report parallels the early descriptions of rare "supernormal" centenarians supporting the dissociation between brain aging and AD processes. In conjunction with recent stereological analyses in cases aged from 90 to 102 years, it also points to the marked resistance of the hippocampal formation to the degenerative process in this age group and possible dissociation between the occurrence of slight cognitive deficits and development of AD-related pathologic changes in neocortical areas. This work is discussed in the context of current efforts to identify the biological and genetic parameters of human longevity.

### Keywords

Disease; Brain aging; Centenarians; Longevity; Neuronal vulnerability

The growing evidence for a steady increase in the number of centenarians worldwide is paralleled by several community-based longitudinal and cross-sectional studies aiming to determine possible psychobiological particularities of these individuals (Gueresi et al., 2003; Nybo et al., 2003; Silver et al., 2002; Stek et al., 2004; von Heideken Wagert et al., 2005;



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von Strauss et al., 2000). These studies showed that the known predictors of mortality such as sociodemo-graphic factors, smoking and obesity are less important in this age group. Centenarians are less prone to oxidative stress and are thought to have better antioxidant defences, nutritional status, immunologic resistance, endocrinologic and metabolic reserves than younger elderly cohorts (Andersen et al., 1998; Moroni et al., 2005). Psychologically, they report greater satisfaction with life as well as social and family relations, and display lower scores for anxiety and depression and better coping abilities compared to less old individuals (Dello Buono et al., 1998). Although prevalence and incidence data are still scarce in this age group, it has long been thought that very old age is associated with the highest prevalence of dementia (Blansjaar et al., 2000; Schneider, 1999; Thomassen et al., 1998). However, the clinical diagnosis of dementia made by primary care physicians is generally based on global decline of cognitive performances rather than on a detailed analysis of each cognitive function leading to an overestimation of the prevalence of dementia in the oldest-old. In fact, recent epidemiological studies in larger cohorts of very old individuals showed prevalence rates which varied from 27% to 62% pointing to the fact that dementia is not inevitable in very old individuals (for review see Ankri and Poupard, 2003; Fichter et al., 1995; Howieson et al., 1997; Kliegel et al., 2004; Lautenschlager et al., 1996).

den Dunnen et al. (2007) had the unique opportunity to explore both the cognitive functions and neuropathological changes of one “longevity champion” who died at the age of 115 in the Netherlands. Two neuropsychological investigations were performed 1 and 3 years before her death. The neuropathological analysis included classical histological stains and immunocytochemistry to visualize AD-related lesions (as well as Lewy bodies, ubiquitin and α-synuclein positive inclusions) as well as counting of neuromelanin-containing neurons in the locus coeruleus. The examination of a supercentenarian with limited visual acuity is a hard task and one should consider that several aspects of the cognitive functioning (i.e., visuoconstructive and visuospatial abilities) were not assessed in this case. From a neuropathological viewpoint, in contrast to the thorough investigation of neurodegenerative changes, informations about vascular (and mainly microvascular) lesions are scarce so that it is not possible to exclude the participation of this type of alterations to the observed slight changes in cognition. Despite these limitations, the observations reported by den Dunnen et al. point to the marked resistance of both cognitive abilities and brain structure in this exceptional case. Overall, only a one-point decrease on the MMSE score occurred (from 27 to 26) reflecting the good preservation of cognitive abilities. Two important issues merit further comments.

First, consistent with the paucity of lesions in the hippocampal formation (Braak NFT stage II), immediate and, in to a lesser degree, delayed recall were strikingly preserved at age 112 (unfortunately, the results at age 115 are not complete). Several neuropathologic analyses postulated that in contrast to younger cases where dementia is mainly related to severe NFT formation within adjacent regions of the medial and inferior temporal neocortex, the extent of NFT development in the hippocampus is the key determinant of dementia after 90 years supporting the notion of limbic dementia in this age group (Delaère et al., 1993; Giannakopoulos et al., 1993, 1996, 1997). However, more recent data challenged this view (Green et al., 2000). In particular, a recent stereological study of 12 nonagenarians and centenarians showed that the progression of NFT formation in both the CA1 field and the entorhinal cortex from CDR 0 to CDR 2) groups was significantly slower in nonagenarians and centenarians compared to younger cases. Even cases with moderate dementia display only mild NFT formation in the CA1 field and entorhinal cortex with more than 60% and 80% of preserved neurons, respectively (von Gunten et al., 2005). Similar observations were made in respect to total amyloid volume and neuronal loss in hippocampal subdivisions (von Gunten et al., 2005). In conjunction with these stereological observations in cases aged from

90 to 102 years, the case report of den Dunnen et al. (2007) in a case of extreme aging provides additional support to the notion that the occurrence and progression of AD-related pathologic changes are not a sine qua non-concomitant of increasing aging (Giannakopoulos et al., 1994, 1995, 1996; Green et al., 2000).

Second, despite preserved attentional capacities, performance in frontal-lobe-related tests such as digit span backward, word fluency and mental arithmetic was affected at age 115 in the absence of specific neuropathological changes not only in the frontal cortex but also in the other neocortical association areas studied. Although slight in this particular case, the dissociation between clinical and neuropathological findings in the oldest-old is an intriguing issue. In fact, even a careful assessment of the classical AD-related pathological hallmarks does not make it possible to predict reliably the cognitive status indicating that independent morphometric variables may decisively contribute to the cognitive decline in this age group (von Gunten et al., 2005).

The debate whether there is continuity or not between normal brain aging and dementia has a long history and is not only of academic interest. The hypothesis that AD is an aging-related condition is supported by the nearly ubiquitous presence of AD-related pathologic changes in the course of brain aging and by the exponential increase of AD prevalence after 65 years of age. Contrasting with this conception of aging, the neuropathological studies of oldest-old individuals indicate that the occurrence of AD pathology is not a mandatory phenomenon of increasing chronologic age and point to the fact that very old individuals display a striking resistance to the neurodegenerative process. The remarkable contribution of den Dunnen et al. remembers the first descriptions of “supernormal centenarians” with minimal AD pathology and preserved cognitive functions made by Mizutani and Shimada (1992) and Delaère et al. (1993) almost 15 years ago. The biological background of the increased resistance to AD lesion development after 90 years is still poorly understood. Evidence from genetic studies of aging and AD implies that a number of susceptibility genes may modify or delay the onset of late-life brain failure. These gene families form a natural target for developing strategies to delay the onset of late-onset dementia (Kaye, 1997). More recently, the importance of genetic factors has been further stressed by studies of centenarian pedigrees showing increased relative survival probabilities in centenarian siblings compared to the general population (Perls et al., 2002). The first community-based linkage and association studies identified two candidate genes predisposing to longevity. Both of them were related to lipoprotein synthesis suggesting that protection against cardiovascular diseases may be primordial to achieve extreme old age (Barzilai et al., 2003; Geesaman et al., 2003; Puca et al., 2001). With the population of centenarians growing at such a rapid rate, complex longitudinal studies including functional neuroimaging, quantitative assessment of microvascular parameters in neocortical areas and differential gene expression may provide additional informations about both the genetic and neurobiological dimensions of longevity.

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