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Neurofibrillary changes of the Alzheimer type in very elderly individuals: Neither inevitable nor benign Commentary on "No disease in the brain of a 115-year-old woman"

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> "Our observations indicate that the limits of human cognitive function extend far beyond the range that is currently enjoyed by most individuals and that *brain disease, even in supercentenarians, is not inevitable*."
>
> Excerpt from den Dunnen et al. No disease in the brain of a 115-year-old woman. Neurobiol Aging 2008

The most widespread degenerative disorder of the human nervous system, Alzheimer's disease (AD), progresses over decades without spontaneous remission. Two of its conventional histopathological hallmarks are intraneuronal protein aggregations in the form of neurofibrillary tangles (NFTs) and neuropil threads (NTs) (Arriagada et al., 1992; Giannakopoulos et al., 2003). Although entangled neurons are capable of surviving for a long time, they almost certainly become functionally impaired before cell death occurs (Callahan et al., 1994; Coleman et al., 2004; Morris, 2006; Morsch et al., 1999). The neurofibrillary degeneration is confined to specific nuclei, areas, and cortical laminae (Hyman and Gómez-Isla, 1994) and, based on its topographical distribution pattern in the brain, can be staged (Braak and Braak, 1991; Braak and Del Tredici, 2006; Braak et al., 2006). The pattern of the disease-process is reminiscent of the inverse pattern of cortical maturation (myelination) during both phylogenesis and ontogenesis (Arendt et al., 1998; Braak and Braak, 1996; Miller et al., 2008; Moceri et al., 2000; Rapoport, 1988; Rapoport, 1990; Reisberg et al., 2003).

The initially subtle neurofibrillary lesions can, ultimately, induce clinically detectable symptoms (Morris, 2006; Petersen, 2003; Petersen et al., 2001; Thal et al., 2004), whereby decades may elapse between the first NFTs/NTs and phases of the disorder in which the pathology is extensive enough for clinical symptoms to become apparent (Braak and Braak, 1997; Davis et al., 1999; Grober et al., 1999). The diagram shows the percentage of nonselected autopsy cases at each of the six NFT-stages for various age groups and it is evident that some degree of neurofibrillary degeneration becomes increasingly prevalent at later decades (Fig. 1, Table 1). In addition, the diagram reveals that considerable differences exist with respect to the age at which the earliest NFTs/NTs actually are detectable. Stage I–II lesions appear in persons under 25 years of age, thereby implying that advanced age is not a prerequisite for their occurrence (Fig. 1, light gray). This indicates that the pathological process that underlies AD is not an age-dependent process but, instead, appears to be age-related since the arithmetic means of NFT-stages increase with age (Braak and Braak, 1995, 1997; Braak et al., 2003; Gold et al., 2000; Gómez-Isla and Hyman, 2003; Jellinger, 2000; Powell, 1994).

The white columns in the diagram represent individuals whose brains were found to be entirely devoid of NFTs/NTs (Fig. 1). This means that a tiny minority of persons, even at 95 years of age, refrain altogether from developing AD-associated cytoskeletal abnormalities (Braak and Braak, 1997; Jicha et al., 2005; Knopman et al., 2003; Mizutani and Shimada, 1992). By extrapolation, the 115-year-old woman described in the case study by den Dunnen et al. (see also (Coles, 2008; Ritchie, 1995; Robine and Allard, 1998)) also would find her place within this schema, having achieved exceptional longevity without progressing beyond NFT-stage II and, apparently, without developing

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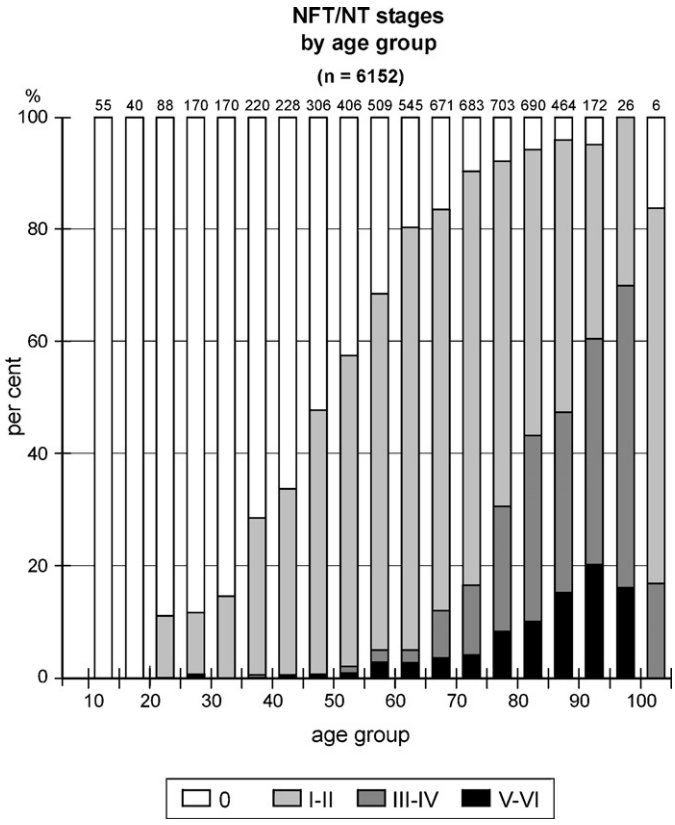

Fig. 1. Schematic diagram showing the breakdown by age groups and percent for 6,152 nonselected autopsy cases according to neurofibrillary stages (NFTs—neurofibrillary tangles and NTs—neuropil threads): 0 (white), I–II (light gray), III–IV (gray), and V–VI (black). Neurofibrillary degeneration occurs with greater prevalence at later decades. Considerable variability exists with regard to the age at which the first NFTs/NTs develop: Stage I–II lesions are present in some cases even before the age of 25, which implies that advanced age is not required for their development. The white columns represent individuals whose brains lacked NFTs/NTs. Thus, a tiny minority of elderly persons, even at 95 years of age, refrain altogether from developing AD-associated cytoskeletal abnormalities.

any clinical signs of neurodegenerative (e.g., AD-, Parkinson's disease-, or vascular-related) cognitive decline. Given the postulated estimated transition time between NFT-stages I and II, the first neurofibrillary changes in this instance might have developed in her brain in her late nineties (see (Finch, 2005)).

Just as the first malignant cells in cancer, regardless at which age they occur, fail to produce any clinically

Table 1
NFT/NT stages by age group ($n = 6152$)

Age group (years)	NFT/NT 0	NFT/NT I–II	NFT/NT III–IV	NFT/NT V–VI	Totals
0–14	55	0	0	0	55
15–19	40	0	0	0	40
20–24	78	10	0	0	88
25–29	150	19	0	1	170
30–34	145	25	0	0	170
35–39	158	61	1	0	220
40–44	152	75	0	1	228
45–49	161	143	1	1	306
50–54	174	224	5	3	406
55–59	162	328	10	9	509
60–64	108	410	13	14	545
65–69	113	478	57	23	671
70–74	69	502	86	26	683
75–79	58	435	154	56	703
80–84	44	354	225	67	690
85–89	21	227	148	68	464
90–94	9	60	69	34	172
95–99	0	8	14	4	26
100–104	1	4	1	0	6

detectable symptoms but represent a larger and potentially life-threatening pathologic process, the presence of NFTs/NTs constitute a true threat. They are insidious lesions rather than harmless or normal concomitants of aging (Green et al., 2000; Hyman and Trojanowski, 1997; Thal et al., 2004). By "aging," we understand the continuum of biological changes and changes in independent living skills that transpire in the course of a lifetime but which, in themselves, do not necessarily represent a disease-process (Swerdlow, 2006). In closing, the following points are meant to serve as a very brief summary: (1) Cytoskeletal abnormalities (e.g., NFTs) are not found at autopsy in every aged individual. Even centenarians or supercentenarians such as the woman here, may show only very mild involvement. These very old individuals or "super normals" most probably constitute a minority. (2) NFTs/NTs are seen at autopsy in a very few young, cognitively unimpaired adults, i.e., at a point in life when other "age-related" or "old age" changes, such as accumulation of lipofuscin granules, neuronal atrophy, and cerebrovascular pathology (Finch, 2003, 2005; Finch and Sapolsky, 1999), are not anticipated or routinely seen. (3) Large quantities of NFTs/NTs in the transentorhinal and entorhinal regions are inevitably associated with "disease" in the form of progressive cognitive decline accompanied by impaired activities of independent daily living over time, and, as such, almost certainly do not speak for a benign process (Riley et al., 2002). (4) Thus, although NFTs/NTs are not inevitable, i.e., inevitably integral to aging, they are pathologic (nonbenign, premorbid) markers in neurons no matter at what age or end of the life spectrum they occur.

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