ELSEVIER

Alzheimer's & Dementia 8 (2012) 227–233

Alzheimer's & Dementia

Perspectives

Alzheimer's disease: Pathogenesis and prevention

Heiko Braak*, Kelly Del Tredici

Clinical Neuroanatomy Section, Department of Neurology, Center for Biomedical Research, Ulm University, Ulm, Germany

Abstract Tau lesions (pretangles, neuropil threads, neurofibrillary tangles) in select neuronal types are essential to the pathogenesis of Alzheimer's disease. Pretangle formation marks the beginning of the pathological process and is of particular interest because it is temporally closer to the prevailing conditions that induce the pathological process underlying Alzheimer's disease in contrast to late-stage disease. However, not all pretangles convert into neurofibrillary tangles. We propose that the development of tau lesions in Alzheimer's disease is traceable to differences between early- versus late-maturing oligodendrocytes and to the exceptionally protracted myelination of late-developing portions of the human brain. Conclusions drawn from these considerations should encourage development of new preventative and disease-modifying strategies.

Keywords: Alzheimer's disease; AT8; Brain evolution; Evolutionary medicine; Hyperphosphorylated tau protein; Neurofibrillary tangles; Neuropil threads; Pretangles; Myelination

1. Introduction

The formation of abnormally altered microtubule-associated tau protein in select types of human nerve cells is crucial to the pathogenesis of Alzheimer's disease (AD) [1–3]. Tau lesions are present from the beginning until the end phase of the disorder and are not known to be subject to remission [4]. The earliest disease phase is of particular interest because only abnormal tau is involved at that point and, in contrast to the end phase, it is temporally much closer to the prevailing conditions that induce the pathological process underlying AD. Because extracellular deposition of amyloid-β protein occurs later in the disease process, it is not discussed here [4–7].

Clinically, AD develops only in humans and is unknown in nonhuman primates or subprimate mammals. In this perspective article, we propose that the development of the intraneuronal tau lesions that characterize the pathological process underlying AD is traceable to idiosyncrasies within the human brain, namely, the exceptionally protracted myelination process of phylogenetically late-appearing portions of the brain and possible differences between early and late maturation of oligodendrocytes [8–10].

2. Pretangles and neurofibrillary tangles

For unknown reasons, particularly vulnerable projection cells in the human brain begin to produce an abnormally phosphorylated tau protein that does not bind to microtubules and lies free, in high concentrations, in cytosol. Under such conditions, abnormal tau tends to form nonbiodegradable aggregates. It is unknown why cellular clearance mechanisms do not dismantle or eliminate the abnormal material. The aggregates accumulate intraneuronally—initially as nonfibrillar and nonargyrophilic inclusions visible under the light microscope and referred to as "pretangles." Pretangle material can (but does not always) evolve into rigid fibrillar and argyrophilic (Gallyas-positive) neuropil threads (NTs) in dendritic processes and neurofibrillary tangles (NFTs) in cell bodies. Both types of abnormal tau (pretangles and argyrophilic NTs/NFTs) stain robustly in immunoreactions with the antibody AT8 [11,12].

3. NFT stages

The intraneuronal disease process progresses in a topographically systematic manner, and it may require an extended period—nearly a lifetime—to reach its full extent [4,13–15]. Late disease stages cause recognizable symptoms and correlate with the clinical picture of AD dementia [16–18]. The prevalence of clinically observable AD cases

*Corresponding author. Tel.: 0731-500-63111, Fax: 0731-500-63133.
E-mail address: heiko.braak@uni-ulm.de

1552-5260/$ - see front matter © 2012 The Alzheimer's Association. All rights reserved.
doi:10.1016/j.jalz.2012.01.011

increases markedly with age, thereby imposing major socioeconomic burdens on all societies in which life expectancy is still increasing.

The formation of the tau lesions is recapitulated in reverse below, beginning with the clinically recognizable final stages of the AD process and concluding with early stages, i.e., the preclinical or prodromal phase. NFT stage VI represents end-stage AD. Macroscopically, all cortical regions display severe lesions on Gallyas silver staining and AT8 immunoreactivity studies (100-μm-thick double-hemisphere immunostained section in Fig. 1A) [19,20]. In NFT stage V, the cortical pathology is somewhat less extensive but still severe. Individuals with this degree of neuronal damage are no longer in possession of a fully functional cerebral cortex and are nearly always demented. However, this is also the point at which the initial provisional clinical AD diagnosis is usually made. Initiation of therapeutic interventions is useless when the pathological process is so advanced. Currently available antidementia drugs can neither arrest, reverse, nor otherwise modify tau pathology, and there are no causal or preventative therapies for AD [21,22].

During NFT stage IV, most areas of the neocortex are uninvolved, and in stage III, the pathology is restricted to a few regions in medial portions of the temporal lobe (Fig. 1B). At this point, some patients are diagnosed with mild cognitive impairment [23,24]. Imaging techniques capable of detecting the degree of pathological tau changes observed in autopsy material are still unavailable but in the pipeline [25,26]. Large autopsy-controlled prospective studies that can confirm the reliability of current biomarkers, particularly in mild cognitive impairment, are also needed [27].

In NFT stages II and I (Fig. 1C), tau lesions are mainly localized within the entorhinal region of the temporal lobe, particularly within the superficial entorhinal layer of medium-sized multipolar neurons. During NFT stage I (Fig. 1C), the cortical neurons that are susceptible to the AD process occupy mainly the laterally adjoining transentorhinal region of the temporal lobe [4,20]. In some NFT stage I cases, the cortical pathology is confined to a single Gallyas-positive pyramidal cell.

4. Frequency of NFT stages I to VI in a large autopsy series

Fig. 2 provides an overview of the relative frequency of occurrence of NFT stages and recently described pretangle stages in various age-groups stratified by decade. NFT stages V and VI still represent end-stage AD (Fig. 2F). These and the clinically less remarkable NFT stages III and IV begin to occur between the ages of 31 and 40 years and increase thereafter in frequency (Fig. 2E). The prodromal NFT stages I and II begin in teenagers and increase steadily up to the ages of 51 to 60 years (Fig. 2D). Slightly more than 8% of all teenagers in the study cohort already had NFT stages I or II pathology. The frequency of NFT stages I and II decreases in patients aged 61 to 70 years, but only because they are replaced by more advanced NFT stages. The majority of the 2332 cases (i.e., 1990 individuals) could be assigned to one of the six NFT stages [4].

5. Frequency of pretangle stages (a-c, 1a, 1b)

As in section 3 above, the formation of the pretangle lesions is described in reverse, beginning with the last stage (1b) and working back to the initial stage (a). Of the remaining 342 of 2332 cases, 274 displayed pretangle material in vulnerable neurons or portions of nerve cells in the transentorhinal region (Fig. 2C). We refer to cases with involvement of entire pyramidal cells in that region as cortical pretangle stage 1b and, when only neuronal processes are involved, as cortical pretangle stage 1a. Additional studies are needed to see whether stage 1a nerve cell processes are terminal axons of brainstem nuclei that project diffusely to the transentorhinal region [4].

The cerebral cortex of 68 cases had no NTs/NFTs or pretangle-containing cell bodies or nerve cell processes. However, the majority of these (58 cases) had AT8-immunoreactive cells or cellular processes in subcortical nuclei. We refer to such cases as subcortical pretangle stages a to c (Fig. 2B). Such cases occurred mostly in younger individuals [4]. Finally, only 10 brains (i.e., 0.4% of 2332 cases) lacked abnormal tau lesions in both the cerebral cortex and the brainstem (Fig. 2A).

Pretangles in the brainstem were confined to projection neurons that generate a disproportionately long and poorly myelinated ascending axon with extensive and diffuse ramifications within the cerebral cortex (cholinergic nuclei of the basal forebrain, serotonergic nuclei of the upper raphe system, noradrenergic locus coeruleus) [28–30]. Pretangle material was observed most frequently in the locus coeruleus of the pontine tegmentum [31]. In pretangle stage c, immunolabeled neurons were found in some or all of the subcortical nuclei mentioned but nowhere else in the brainstem. In pretangle stages a and b, AT8-immunopositive material was only observed in coeruleus projection neurons; for this reason, the locus coeruleus is, in our opinion, most probably the site where AD begins. Moreover, after examining a large number of cases and coming to the same results, it appears that the AD process begins in the axon (pretangle stage a) and subsequently involves the somatodendritic compartment of affected nerve cells in the locus coeruleus (pretangle stage b). The youngest individual in whom pretangle material was found in axons within the locus coeruleus was 6 years of age [4].

Lesions that exist before clinical manifestation of most diseases (e.g., arteriosclerosis, malignant neoplasms, idiopathic Parkinson disease) are generally acknowledged as prodromes. NFT stages I and II and/or pretangle stages are not detectable using currently available diagnostic instruments or tests. Nevertheless, these abnormal tau lesions represent pathological changes. Do they represent prodromal

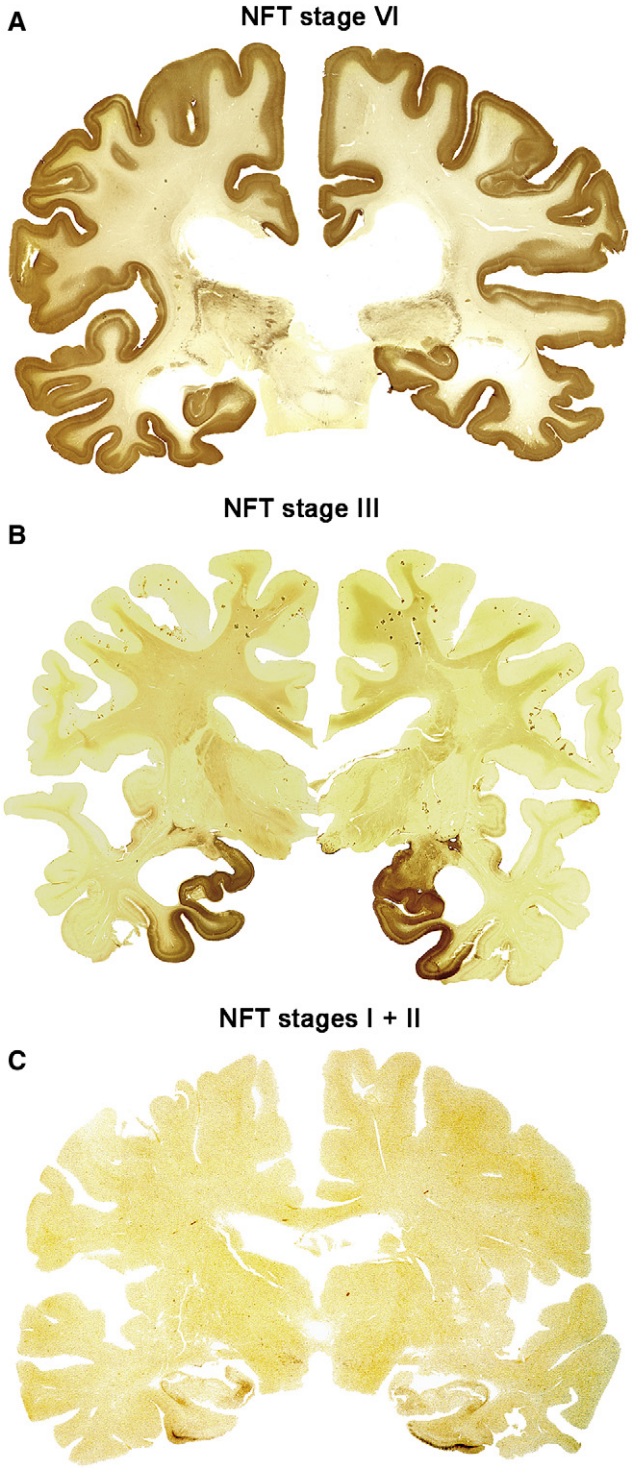

Fig. 1. Stages VI to I of cortical neurofibrillary changes of the Alzheimer type in 100-μm-thick double-hemisphere coronal sections cut perpendicular to Forel intercommissural axis and immunostained for abnormal tau (AT8). (A) Neurofibrillary tangle (NFT) stage VI. Section from a severely demented 72-year-old female patient with Alzheimer's disease who died of aspiration pneumonia. Note that NFTs/neuropil threads are visible in all portions of the cerebral cortex, including the primary fields of the neocortex that acquire abnormal tau lesions very late (note the primary auditory cortex in Heschl gyrus at the left). In addition, lesions are recognizable in intralaminar nuclei of the thalamus and in portions of the midbrain. (B) NFT stage III. The section is cut at the latitude of uncal portions of the hippocampal formation and originates from a 90-year-old woman who died of a malignant neoplasm of the pancreas. The tau lesions are located in the nuclear complex of the amygdala (at right) and hippocampal formation, as well as in the entorhinal region in anteromedial portions of the temporal lobe. The transentorhinal region in the rhinal sulcus is also involved as are the high-order sensory association areas of the basal temporal neocortex. At stage III, the lesions do not extend beyond the occipitotemporal and lingual gyri. (C) NFT stage I (at left) and II (at right). This section cut at the level of the uncus comes from a cognitively intact 80-year-old woman who died of myocardial infarction. At these early stages, lesions are mainly recognizable in the uppermost cellular layer of the entorhinal region at stage II. At stage I, involvement is slight and concentrated in the transentorhinal region located on the medial surface of the rhinal and/or collateral sulcus.

AD, or are they normal brain changes? The contention that the lesions are normal requires the problematic definition of a point at which "normal" abnormal tau converts into "disease-related" abnormal tau. Here, we think it is necessary to distinguish between AD as a clinical entity, which includes dementia, and AD as a pathological process, which includes a prodromal phase.

6. AD and the aging process

It has long been argued that AD is intrinsic to aging or, at least, indirectly attributable to the aging process [32]. Nevertheless, this does not take into consideration that although AD symptoms only become recognizable in old age and at an advanced phase of the disease-related process [33], the clinically mute, but pathological, process exists much longer. When the pretangle stages are incorporated into the natural history of the tau lesions, the result may be a preclinical phase of nearly a lifetime. Moreover, if, in fact, the NFT stages I and II in young individuals and the pretangle stages in children lie along a biological continuum and are not transient, this would mean not only that AD has one of the longest prodromal phases of all known neurodegenerative diseases but also that a much larger window of opportunity exists for causally oriented and disease-modifying interventions than previously imagined.

Numerous postmitotic cell types in the human body are markedly influenced by the aging process and, during the course of a lifetime, are subjected to a variety of influences (e.g., oxidative stress, mitochondrial dysfunction, and failure of the ubiquitin–proteasomal system). The extent to which these phenomena may be capable of exacerbating neurodegenerative diseases in the elderly population is still the subject of intense research. However, they cannot be anticipated as playing a pivotal role in the pathogenesis of pretangles during childhood, puberty, or young adulthood.

7. Nerve cell-to-nerve cell transmission of tau

One of the hallmarks of disease progression in AD is that a wide range of brain sites becomes involved in a systematic manner, with relatively little interindividual variability, and this makes it possible to assess the tau lesions neuropathologically [13,14,20]. Moreover, all of the vulnerable types

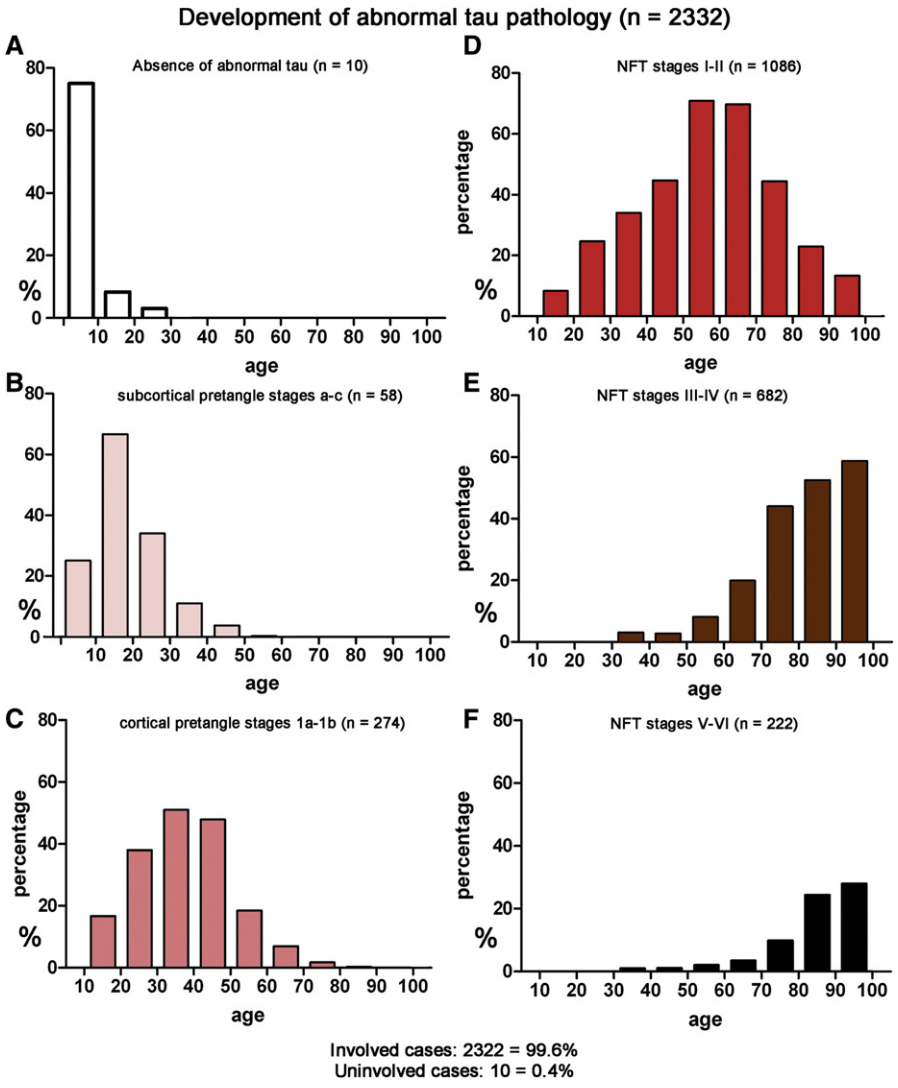

Fig. 2. The relative frequency of the occurrence of abnormal tau stages in 2332 nonselected autopsy cases. (D-F) Fibrillar and argyrophilic lesions characterizing the cortical NFT stages I to VI are color-coded. Stage V to VI cases, black (F); stage III to IV cases, brown (E); stage I to II cases, red (D). (C) Light red indicates nonargyrophilic and nonfibrillar lesions in either cortical pyramidal cells (pretangle stage 1a) or nerve cell processes (pretangle stage 1b) of the transentorhinal region. (B) Pink indicates pretangle material in nerve cells or nerve cell processes, this time confined to subcortical nuclei that diffusely project to the cerebral cortex (stages a-c pathology). (A) Brains of only a minority of cases show absence of any abnormal tau deposits (white bars).

of projection neurons in involved brain regions are interconnected anatomically, which indicates that physical contacts between affected neurons and regions play an important role in the pathogenesis of AD [34,35].

Initially involved projection neurons in the locus coeruleus are located at a considerable distance from the transentorhinal region, the site at which the next pretangle lesions have been observed to develop in stages 1a to 1b. Because both sites are connected by long ascending and weakly myelinated projections, we posed the question whether pathogenic molecules of abnormal tau in coeruleus nerve cells may be capable of propagating the disease process through transsynaptic transmission in far-removed projection neurons in the transentorhinal cortex [36]. The conditions and mechanisms required to promote the transfer of pathological tau species from one nerve cell to another are presently at the center of a new genre of experimental studies [37–40].

8. AD and evolution

The tendency to develop abnormal tau in predisposed neuronal types appears to be intrinsic to the human brain (99.6% of the cases recently examined by us had AD-associated tau lesions) [4] (Fig. 2). Furthermore, a comparable, but considerably lower, proclivity for abnormal tau formation has been reported in a few nonhuman primates [41] and subprimate mammalian species, including sheep, bears [42,43], and polar bears (Braak and Braak, unpublished data, 1998). As in humans, the phenomenon is confined to specific neuronal types, namely, those with disproportionately lengthy and weakly myelinated axons. However, in contrast to the

human brain, pretangle material develops only in the brains of very old animals, that is, at an advanced age that these species never reach in the wild.

The low proclivity shown by a few mammalian species to develop abnormal tau may have become much more pronounced during the last phase of evolution when humans appeared among higher primates. This phase was accompanied by a remarkable increase in brain weight and volume. Neocortical areas became more expansive, and the allocortical entorhinal region—chiefly devoted to processing olfactory data in lower macrosmatic mammals—underwent reorganization in microsmatic primates, thereby not only forfeiting most of its olfactory functions and forging new interconnectivities to the neocortex through a transitional area between the allocortex and neocortex, the transentorhinal region, but also preparing the way for massive indirect neocortical input to the hippocampal formation. These phylogenetically late events left their mark on late-differentiating and, for neurodegeneration, susceptible nerve cell types during ontogenesis [10].

The final step in neuronal differentiation is the production of the axonal myelin sheath that improves and optimizes nerve cell performance [44]. A singular feature of neurons that are susceptible to the AD process is that their axons undergo myelination postnatally by late-maturing oligodendrocytes, which, in contrast to early-differentiating oligodendroglial cells, myelinate large numbers of axons simultaneously. Thus, some axons simply may not have enough time to achieve an adequate degree of myelination. Although such neurons remain functional, they are less stable than those that have a thick myelin sheath, and perhaps this is why remarkably widespread production of abnormal tau is observed in the human brain compared with that found in other species. In other words, the marked propensity to produce abnormal tau may be associated with development of the human brain during evolution. Apparently, however, these same factors were not of evolutional significance for the propagation and survival of the human species because the resulting brain dysfunction would have occurred only in exceptional cases, that is, at an advanced age seldom reached by our ancestors with very limited life expectancies.

9. AD prevention?

Efforts to develop new tau protein-based therapies for AD have chiefly been aimed at preventing the development of pretangle material or NTs/NFTs [45]. It is still too early to tell whether these experiments will lead to success; however, while keeping this goal in sight, the reality is that 99.6% of our cases had some form of AD-associated tau lesions (Fig. 2). However, it is also important to point out that only a small percentage of those individuals will subsequently cross the threshold to clinically manifest cognitive dysfunction [4,46]. Why, in the population at large, does the AD process seldom progress so rapidly that individuals actually reach NFT stages V or VI (Fig. 2)?

Evidently, the rate of interindividual disease progression varies remarkably. The high degree of variability is best illustrated by NFT stages I and II (Fig. 2D). Approximately 8% of the individuals in our study were at NFT stages I to II as teenagers, whereas others were $\geq$90 years of age or older [4]. Presently, there are no convincing explanations for these interindividual differences. More information about the factors that determine or influence the pace of the pathological process is urgently needed.

In this context, we want to emphasize that the neuronal types that are especially susceptible to the AD process and develop the most severe AD-associated tau pathology not only appear late phylogenetically but also reach maturity late in life [47,48]. In these projection neurons, the development of the axonal myelin sheath takes place postnatally and continues into adulthood [9,49,50]. In contrast, neurons with a myelin sheath that is sturdy and matures early are resistant to the AD process and do not develop pretangles or NTs/NFTs. It should also be pointed out that nerve cell activity provides the physiological stimulus for the oligodendroglial cells that produce and sustain the myelin sheath [50]. The greater the degree of neuronal activity, the thicker the myelin sheath during the time of nerve cell differentiation and, ultimately, the better protected such nerve cells are against the AD process.

Can the maturation process of the myelin sheath be improved postnatally by placing higher functional demands on the brain, as is almost certainly the case when preschoolers receive musical training or are exposed to learning in a multilingual setting [51]? Prospective studies involving such individuals are necessary to determine whether vulnerable projection neurons can be protected by increased activity during myelination. Today, the demographic changes taking place in aging societies make it imperative that research efforts not only be limited to seeking measures directed at eliminating abnormal tau formation and against possible cell-to-cell seeding of tau but, rather, they also should include disease-modifying strategies aimed at postponing the AD process.

Acknowledgments

Funding for this article was provided by the German Research Council (Deutsche Forschungsgemeinschaft, DFG, grant # TR 1000/1-1) and the Michael J. Fox Foundation for Parkinson's Research (New York City). Tissue was provided by the Braak Collection (Goethe University Frankfurt). We wish to express our special thanks to Ms. Simone Feldengut (immunohistochemistry) and Mr. David Ewert (graphics) for technical support.

References

[1] Mandelkow E, von Bergen M, Biernat J, Mandelkow EM. Structural principles of tau and the paired helical filaments of Alzheimer's disease. Brain Pathol 2007;17:83–90.

[2] Alonso AC, Li B, Grundke-Iqbal I, Iqbal K. Mechanism of tau-induced neurodegeneration in Alzheimer disease and related tauopathies. Curr Alzheimer Res 2008;5:375–84.

[3] Iqbal K, Liu F, Gong CX, Alonso AC, Grundke-Iqbal I. Mechanisms of tau-induced neurodegeneration. Acta Neuropathol 2009; 118:53–69.
[4] Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathological process in Alzheimer' disease. J. Neuropathol Exp Neurol 2011;70:960–9.
[5] Schönheit B, Zarski R, Ohm TG. Spatial and temporal relationships between plaques and tangles in Alzheimer-pathology. Neurobiol Aging 2004;25:697–711.
[6] Korczyn AD. The amyloid cascade hypothesis. Alzheimers Dement 2008;4:176–8.
[7] Pimplikar SW. Reassessing the amyloid cascade hypothesis of Alzheimer's disease. Int J Biochem Cell Biol 2009;41:1261–8.
[8] Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A. Maturation of white matter in the human brain: a review of magnetic resonance studies. Brain Res Bull 2001;54:255–66.
[9] Bartzokis G. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. Neurobiol Aging 2004;25:5–18.
[10] Braak H, Del Tredici K. Poor and protracted myelination as a contributory factor to neurodegenerative disorders. Neurobiol Aging 2004; 25:19–23.
[11] Bancher C, Brunner C, Lassmann H, et al. Accumulation of abnormally phosphorylated tau precedes the formation of neurofibrillary tangles in Alzheimer's disease. Brain Res 1989;477:90–9.
[12] Braak E, Braak H, Mandelkow EM. A sequence of cytoskeleton changes related to the formation of neurofibrillary tangles and neuropil threads. Acta Neuropathol 1994;87:554–67.
[13] Arnold SE, Hyman BT, Flory J, Damasio AR, van Hoesen GW. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cerebral Cortex 1991;1:103–16.
[14] Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82:239–59.
[15] Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997;18:351–7.
[16] Nelson PT, Jicha GA, Schmitt FA, et al. Clinicopathologic correlations in a large Alzheimer disease center autopsy cohort: neuritic plaques and neurofibrillary tangles "do count" when staging disease severity. J Neuropathol Exp Neurol 2007;66:1136–46.
[17] Dolan D, Troncoso J, Resnick SM, et al. Age, Alzheimer's disease and dementia in the Baltimore longitudinal study of ageing. Brain 2010; 133:2225–31.
[18] Sabbagh MN, Cooper K, DeLange J, et al. Functional, global and cognitive decline correlates to accumulation of Alzheimer's pathology in MCI and AD. Curr Alzheimer Res 2010;7:280–6.
[19] Braak H, Braak E. Demonstration of amyloid deposits and neurofibrillary changes in whole brain sections. Brain Pathol 1991b; 1:213–6.
[20] Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol 2006;112:389–404.
[21] Molnar FJ, Man-Son-Hing M, Fergusson D. Systematic review of measures of clinical significance employed in randomized controlled trials of drugs for dementia. J Am Geriatr Soc 2009;57:536–46.
[22] Wollen KA. Alzheimer's disease: the pros and cons of pharmaceutical, nutritional, botanical, and stimulatory therapies, with a discussion of treatment strategies from the perspective of patients and practitioners. Altern Med Rev 2010;15:223–44.
[23] Markesbery WR, Schmitt FA, Kryscio RJ, Davis DG, Smith CD, Wekstein DR. Neuropathologic substrate of mild cognitive impairment. Arch Neurol 2006;63:38–46.
[24] Albert MS, Dekosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–9.
[25] Fodero-Tavoletti MT, Okamura N, Furumoto S, Mulligan RS, Connor AR, et al. 18F-THK523: a novel in vivo tau imaging ligand for Alzheimer's disease. Brain 2011;134:1089–100.
[26] Jensen JR, Cisek K, Funk KE, Naphade S, Schafer KN, Kuret J. Research towards tau imaging. J Alzheimers Dis 2011;26(Suppl 3):147–57.
[27] Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28.
[28] German DC, White CL, Sparkman DR. Alzheimer's disease: neurofibrillary tangles in nuclei that project to the cerebral cortex. Neuroscience 1987;21:305–12.
[29] Mesulam MM, Shaw P, Mash D, Weintraub S. Cholinergic nucleus basalis tauopathy emerges early in the aging-MCI-AD continuum. Ann Neurol 2004;55:815–28.
[30] Grinberg LT, Rüb U, Ferretti REL, et al., Brazilian brain bank study group. The dorsal raphe nucleus shows phospho-tau neurofibrillary changes before the transentorhinal region in Alzheimer's disease. A precocious onset? Neuropathol Appl Neurobiol 2009; 35:406–16.
[31] Grudzien A, Shaw P, Weintraub S, Bigio E, Mash DC, Mesulam MM. Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer's disease. Neurobiol Aging 2007; 28:327–35.
[32] Herrup K. Reimagining Alzheimer's disease—an age-based hypothesis. J Neurosci 2010;30:16755–62.
[33] Nelson PT, Head E, Schmitt FA, et al. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiologicical human studies. Acta Neuropathol 2011;121:571–87.
[34] Saper CB, Wainer BH, German DC. Axonal and transneuronal transport in the transmission of neurological disease: potential role in system degenerations, including Alzheimer's disease. Neuroscience 1987;23:389–98.
[35] Pearson RCA. Cortical connections and the pathology of Alzheimer's disease. Neurodegeneration 1996;5:429–34.
[36] Braak H, Del Tredici K. Alzheimer's pathogenesis: is there neuron-to-neuron propagation? Acta Neuropathol 2011b;121:589–95.
[37] Clavaguera F, Bolmont T, Crowther RA, et al. Transmission and spreading of tauopathy in transgenic mouse brain. Nat Cell Biol 2009;11:909–13.
[38] Frost B, Jacks RL, Diamond MI. Propagation of tau misfolding from the outside to the inside of a cell. J Biol Chem 2009;284:12845–52.
[39] Goedert M, Clavaguera F, Tolnay M. The propagation of prion-like protein inclusions in neurodegenerative diseases. Trends Neurosci 2010;33:317–25.
[40] Guo JL, Lee VM. Seeding of normal tau by pathological tau conformers drives pathogenesis of Alzheimer-like tangles. J Biol Chem 2011;286:15317–31.
[41] Schultz C, Dehghani F, Hubbard GB, et al. Filamentous tau pathology in nerve cells, astrocytes and oligodendrocytes of aged baboons. J Neuropathol Exp Neurol 2000;59:39–52.
[42] Nelson PT, Greenberg SG, Saper CB. Neurofibrillary tangles in the cerebral cortex of sheep. Neurosci Lett 1994;170:187–90.
[43] Cork LC, Powers RE, Selkoe DJ, Davies P, Geyer JJ, Price DL. Neurofibrillary tangles and senile plaques in aged bears. J Neuropathol Exp Neurol 1998;47:629–41.
[44] van der Knaap MS, Valk J, Bakker CJ, et al. Myelination as an expression of the functional maturity of the brain. Dev Med Child Neurol 1991;33:849–57.
[45] Bulic B, Pickhardt M, Mandelkow EM, Mandelkow E. Tau protein and tau aggregation inhibitors. Neuropharmacol 2010;59:276–89.
[46] Elobeid A, Soininen H, Alafuzoff I. Hyperphosphorylated tau in young and middle-aged subjects. Acta Neuropathol 2012;123:97–104.
[47] Braak H, Braak E. Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis. Acta Neuropathol 1996;92:97–201.

[48] Reisberg B, Franssen EH, Hasan SM, Monteiro I, et al. Retrogenesis: clinical, physiologic, and pathologic mechanisms in brain aging, Alzheimer's and other dementing processes. Eur Arch Psychiatry Clin Neurosci 1999;249(Suppl 3):28–36.
[49] Giedd JN. The teen brain: insights from neuroimaging. J Adolesc Health 2008;42:335–43.
[50] Ullén F. Is activity regulation of late myelination a plastic mechanism in the human nervous system? Neuron Glia Biol 2009; 5:29–34.
[51] Bengtsson SL, Nagy Z, Skare S, Forsman L, Forssberg H, Ullén F. Extensive piano practicing has regionally specific effects on white matter development. Nat Neurosci 2005;8:1148–50.