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Review Article

The Construct of Alzheimer's Disease Matured for Retirement

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Abstract

Histological observations, published in 1907-12 by A. Alzheimer and more thoroughly by O. Fischer, became source of the assumption that brain amyloid and neurofibrillary tangles are causing a specific disease leading to dementia. At a time, when research over the last 30 years has found a large variety of processes that impair the performance of the aging brain the construct of Alzheimer´s disease (AD) is losing its meaning. The communication among neuroscientists will therefore benefit from shedding the dichotomy of „healthy aging "versus„ AD"and embracing instead a multicausal model of senile presbyphrenia. In addition to eradicating semantic contradictions, this approach will also help to abandon ghostly visions of a global pandemic or personal tragedy of this „deadly disease".

Keywords: Dementia, mixed pathologies, vascular dementia, Alzheimer´s, neurofibrillary tangles, amyloid, brain atrophy, presbyophrenia, ischemic encephalopathy

Semantic specification of aging and degenerative processes

The prolongation of human life is now slowly approaching its maximum. The elimination of the main 3 causes of death in the population (cardiovascular disease, stroke and cancer) would result in an increase of only about 15 years and the resolution of Alzheimer's disease (0.7% likelihood of dying from) would add about 19 days onto the average life expectancy [1-3]. Providing the age-associated diseases would be successfully cured, then aging will be revealed as the leading cause of death, with maximal life-span somewhere around 125 years [2].

The processes of aging affect the life-span between the attainment of maturity and death. Aging occurs after reproductive maturation and results from the diminishing energy available to maintain molecular fidelity. This corresponds with the natural law, where age-weakened individuals living beyond reproductive success have diminishing value for the survival of a species and the genom that governs molecular synthesis and integrity from conception to sexual maturation is incapable of maintaining fidelity indefinitely [2]. This concept fully corresponds with Claude Bernard´s notion in 1865: „a cell after its birth has no other way of life as to proceed to death". Indeed, the general pattern of age changes following a linear decrement in function beginning about the age of 30 exerts later various slopes of regression (from 10 to 60%) in the particular somatic and mental functions [4].

Herman T. Blumenthal [5] provided a list of opinions on the semantic enigma, whether aging is a disease and what is the difference between pure senescence and aging-associated diseases. Some experts consider the forces of aging not being a sickness in the accepted sense of the word [6], others search for difference between genetically programmed aging phenomena and age-associated pathological phenomena acquired or initiated by external events [7]; others again hold a view that man will never die of old age but always from a disease [8] or that physiological and pathological aging are so interrelated as to make all attempts to separate them relatively abortive [9]. The disputed truth is hidden in the old latin saying „Senectus ipsa morbus est".

Strehler determines the following criteria of aging: intrinsicality, universality, irreversibility, progressivity and genetic programming [10]. However, not even these definitions would solve the immanent connection between aging and disease in regard to „Alzheimer´s disease"(AD). Being neither removable nor curable it is not a conventional disease, which would „attack "an otherwise healthy person among his peers. We have processes of aging and etiologies of diseases. Conventional diseases occur in a small percentage of population and are as such considered exceptions from majority/normality. This is not the case with senile dementia. If its prevalence surpasses 50% by age 85 or 90, it is no more an accident, nor a disease, but an expected event [11]. It

should be understood rather as an inevitable process, a toll for long life, where the individual has escaped the risks of more severe, namely somatic deadly diseases. Despite of the blurring distinction between biological and pathological aging [5], all attempts for understanding the degenerative processes and deferring their impact are of utmost importance.

Retrogenesis

A striking similarity has been observed between the progressive changes in clinical, electrophysiologic, histologic and neuroimaging features of the maturing brain and their reciprocal regression in old age. The order of acquisition in normal development is mirrored by the inverse sequence of losses during the clinical course of the degenerative dementia. The 16 subsequent stages of the Functional Assessment Staging (FAST) correlated in their progressive and regressive scoring in degrees of self-dependence, activities of daily living (ADL), cognition measures, primitive reflexes, EEG and the state of white matter (WM) myelination [12].

Having in mind the above mentioned inescapability and lawfulness of dementia in old age, as well as the phenomenon of the prosperity of developmental features versus retrogenesis in senium, one should be cautious in rendering dementia as a disease. Nevertheless, dementia is only a syndrome. Calling this „disease" a „biggest, relentless killer", „worldwide epidemics", and/or „devastating enemy to be eradicated" are misleading representations serving only to an improper fear induction [13-17].

Dementia can be caused by an indefinite list of illnesses [18], injuries or iatrogenic interventions. Many of them are ubiquitous processes, inseparable of standard living (like atherosclerosis or fading heart function).

Terminology inconsistency prevails also in terms like „sporadic AD", meaning rare. Simultaneously its „death toll" is dramatically proclaimed to be gradually outgrowing that of cardiovascular disease and malignancies. Also in the interpretation of cognition, cogitation and execution are considerable discrepancies, similarly to enrolling memory among the „cognitive functions". Memory is in fact a prerequisite for cognition, it is a basic function, on which any higher mental activities can only be superimposed.

The quality of mental abilities is changing throughout the life span. Vocabulary, verbal memory in immediate and delayed testing, manipulation of numbers, spatial orientation, inductive reasoning and perceptual speed/information processing when checked in 7 year intervals in the Seattle longitudinal study revealed a general immanent trajectory of human population [19]. The most conspicuous gradual decline was found in perceptual speed, being most linear and progressive, and starting already at 25 years. The other faculties, in particular the items of crystal intelligence (vocabulary) have shown decline only after 60.

Brain aging burdened by Alzheimer´s disease?

The traditional concept of AD derived from the historical papers of 1907 [20,21] posits that presenile dementia is a consequence of deposition of Amyloid (Aβ) and neurofibrillary tangles (NFT) in the brain parenchyma. However Alois Alzheimer, his collaborators Francesco Bonfiglio and Gaetano Perusini [22], as well as their rival Oskar Fischer in Prague [23,24], were well aware of the fact, that these two histological abnormalities do not suffice for the explanation of senile mental deterioration. Such doubts of A. Alzheimer are quoted in O. Fischer discussion with him (A.A. calls amyloid deposits according to Fischer „druses"): „…next question is now whether the druses or as Fischer referred to them, Sphaerotrichia, could be considered the cause of a fully specific, classifiable, and clinically diagnosable psychosis…… having cases of an unequivocal dementia senilis, in which the druses are not much numerable…Further we find also in locations, where there are in the cortex no druses, dispersed known senile changes: sclerotic-fatty-pigmented distorted ganglionic cells, changes in their fibrils – as described by Brodmann and Bielschowski, creation of fibers in glia, degenerative changes in the vascular wall. These we cannot interpret as being caused by druses" and „we must anyway come to the conclusion, that druses are not a producer of senile dementia, but only an accompanying feature of senile involution of the central nervous system" [25]. Thus the cautious approach of these pioneers is in concert with modern findings of an overlap of manifold etiologies of senile dementia [26]. Alzheimer and Fischer, limited by their historical possibilities of histological staining, have described just two out of a host of future structural causes of dementia. The remaining ones had to await the sophisticated methods of the next decades.

Aging in „normal adults".

Most neuroscientists wish to dichotomize senile mental capacity and its supposed patho-anatomical prerequisites into two categories: healthy aging and AD. Despite that, our practical experience doesn´t see any obvious border amidst the continuous spectrum of senile mental deficits. Attempts to distinguish „normalcy" from „morbid" senium are running in categories of psychometrics – e.g. memory, executive functions, as well as in their morphological and pathophysiological counterparts like brain volume, cortex thinning, amyloid depositioning, tau density, macro- and microvascular lesions, leukoaraiosis, metabolism, transmitters, water diffusivity, connectivity and many others.

A/ Functional mental capacity

In 1958, Wechsler stated, „Beginning with the investigation by Galton in 1883 and continuing up to and including the most recent studies by Pacaud, nearly all studies dealing with the age factor in adult performance have shown that most human abilities, in so far as they are measurable, decline progressively, after reaching a peak somewhere between ages 18 and 25. The peak age varies with the ability in question but the decline occurs in all mental measures of ability, including those employed in tests of intelligence".

Life-long changes in mental performance [19] are governed by processing speed, memory and executive functioning [27-47]. Mental processes, accelerating during maturation and decelerating

in the elderly, are best described by a „U"curve [34]. Declining speed, the main factor for the quality/capacity of working memory, for the manipulation of perceptual representational systems and for the recall from the semantic and episodic memory thus devalues fluid intelligence, individual cognitive control, inhibitory functions, reasoning and others [32,35-38]. While implicit memory with its dominant „integrative processing "remains relatively constant across the life span, the explicit memory, facilitated primarily by „elaborative processing"fades off more progressively [39]. Distinction is observed also in the life-span changes of episodic memory versus the semantic one. While the first one shows tendency to gradually deteriorate with an acceleration after 60 – 65 years, verbal abilities and world knowledge (crystal intelligence) tend to increase up to 55 and then are usually maintained longer [40].

Since 1949, the distinction of Short Term and Long Memory (STM, LTM) provides another important concept for understanding domains of past and recent memory engrams [41]. While STM is based on temporary electrical activation, LTM is stored by neuronal growth. In the late sixties the Atkinson-Shiffrin model of a series of temporary sensory registers transmitting the information into LTM gained broad credibility [42]. It has been further enriched into the contemporary scheme by the construct of working memory with its visuospatial sketchpad, phonological loop and their supervision by central executive according to Baddeley and Hitch [43-45]. Its functional importance dwells in its effect on a range of cognitive activities, such as reasoning, learning and comprehension [46].

Working memory declines with aging [47]. So does also the „supervisory activating system failing to maintain context representations in an active state"[38]. In addition to intellectual functions, elderly people are losing their skills due to progressing apraxia, due to a failure to access stored kinematic patterns or „space-time engrams"[48, 49].

The aging trajectories of mental profile in population based samples dissociate between „maintainers"(18%) and „decliners"(13%), while the followers of the „age-typical changes" (68%) are spread in-between [30].

B/ Morphological and histological changes.

To comprehend properly the lawful development of our brain tissue changes during life we need to prioritize studies, which analyze natural aging regardless of any „disease stickers". Many investigators in the magnitude, pattern and timing of brain atrophy, cortical changes, amyloid deposition and cognitive deficits come to the conclusion, that these changes are an inevitable part of normal aging and that age affects the brain independently of AD [50-57].

Atrophy

Between age 3 and 18, the brain increases in weight to about 5 times that of a newborn. At 45–50 years of age, a progressive decline in brain weight begins and reaches its lowest value after the age of 86. By then, it is about 11% smaller relative to the maximum brain weight attained around 19 years of age [50-52]. Both the cross-sectional and longitudinal studies by means of serial MRI in population-based studies revealed again decrease in both whole and regional brain volume accelerating over the age of 65 [53,54]. Observing the thinning of GM and WM separately helps to show that it starts in the white matter later. The progress of atrophy in non-demented persons makes 0.45% and in demented people 0.98% per year [55].

A meta-analysis of 56 longitudinal MRI studies with a total of 2211 participants aged 4 till 88 years, demonstrated a steady volume loss of 0,2% per year, accelerating gradually to 0,5% volume loss around 60 years and even stronger thereafter [56]. The annual atrophy rates have been discovered not only in the most suspected frontal lobes, but also in the temporal ones. Atrophy rates of 0.79 – 2.0% for the hippocampus and of 0.3 – 2.4% for the entorhinal cortex were reported from several studies quoted by Fell [57]. The late-maturing regions are most vulnerable to age changes. The predominance of such brain areas copies the pattern of cephalization in fylogenesis, rendering them most fragile on a principle „last in, first out"[57].

Amyloid (Aβ)

In their review of amyloid properties Greenwald and Riek [58] quote the pioneering discovery of 1935, that proteins, when aggregating, assume their energetically most favorable conformation, namely a cross β-sheet motif. This primitive folding process results in amyloid [59]. Its name comes from Robert Virchow who in 1854, considered this pathological protein to be a starch (in Latin amylum). The amyloid β-peptide is a normal component of serum and its precursor is permanently present in the cellular membrane. With its role in transmembrane processes and cellular adhesion it participates obviously in synaptic plasticity [60]. Deposition of amyloid in cerebral tissue occurs in two varieties: extracellular lenticular non-fibrilized diffuse plaques (called also benign) or more advanced neurotic plaques with a dense core [61]. Senile amyloidosis is a long documented phenomenon in both rodents and humans. Recognized as a posttranslational misfolding of proteins, amyloidosis in autopsy studies is found with prevalence of 80 – 100% in subjects of advanced age, thereby approaching universality [5]. When the delicate balance between protein folding and aggregation is disturbed, then under certain circumstances the amyloid can achieve even replication or transform into a prion [58]. The specific feature of a protein making it capable of forming amyloid-like fibrils is a segment permitting the formation of a steric zipper of two complementary beta sheets forming the spine of the fibril [62].

Since the advent of in vivo amyoid detection by PET [63,64] an extensive research looks for its correlation with: age, memory, cognition, neurofibrillary tangles (NFT), metabolism, atrophy, vascular lesions, connectivity and many others. In a longitudinal study with 741 participants amyloid deposits were first found in precuneus, posterior cingulate, insula and medial and lateral orbitofrontal cortices [65] in agreement with histological observations of the nineties [66]. Higher stages of amyloid depositioning were associated with accelerated cognitive decline and with atrophy [65]. Cerebral amyloidosis affects 4% of individuals already in their 40s and culminates in the 10th

decade with 75% of affected persons [67]. Despite of designating amyloid as the decisive culprit of senile dementia, its correlation with cognition, NFT, glucose metabolism or atrophy doesn´t fulfill a consistent relationship [68]. A progressive increase of amyloid first in neocortical, later in all cortical regions can be observed up to 75 years, whereas in the oldest olds it remains stable [69].

The link between amyloid and mental performance appears to be unreliable. Among cognitively well preserved individuals Aβ PET positivity was found between 14 and 47% [70-77]. Vice versa in persons with AD Aβ PET is often (32%) negative [78]. Therefore the causality between amyloid and dementia has been often put in doubt [79-81]. Elderly people with other structural brain biomarkers like hippocampal atrophy, FDG hypometabolism and white matter hyperintensities were designated as „sNAP - suspected non-Alzheimer pathway of dementia [80,82,83]. A meta-analysis of 64 studies representing 7,140 subjects revealed that the domains of working memory, processing speed, visuospatial function, and semantic memory did not have significant relationship with amyloid. Only episodic memory was associated with the increased amyloid burden [84].

Although some authors interpret cerebral amyloidosis as a process provoking formation of tau deposits [85], the majority believe in an opposite order [86-88].

Neurofibrillary tangles (NFT)

In the second half of the eighties paired helical filaments in neurofibrillary tangles gained new insights. Research using polyclonal antibodies discovered the importance of microtubule-associated phosphoproteins which under unpropitious circumstances degenerate into aggregates of tau protein [89,90]. Later six different isoforms of tau were described including their role in the dynamic equilibrium with the microtubules. Since the microtubule network plays an essential role in axonal transport, its disturbance very probably brings about synaptic dysfunction. Essential for the axonal function is trafficking of organelles, primarily of mitochondria. Neurites containing tau aggregates suffer disruption in human and in animal studies in an age-dependent manner [91,92]. Along with the interruption of axonal transport of organelles also the flow of amyloid precursor protein is altered, indicating a possible relationship of NFT with amyloid depositioning. Defects in mitochondrial function have in their wake decreased ATP synthesis, increased ROS production and impaired oxidative phosphorylation. It is still not elucidated, whether mitochondrial dysfunction is the cause or the consequence of pathological tau accumulation [93].

It is possible, or rather very probable, that mitochondrial dysfunction and related tau abnormalities are closely linked with ischemia. Since mitochondria play a pivotal role in regulating energy metabolism and apoptotic pathways including intracellular Ca homeostasis as the „powerhouse" of the neuron, providing energy for ATP generation, their dysfunction can be viewed as a prominent and early chronic oxidative stress-associated event [94]. The formation of intraneuronal NFT precedes that of the insoluble, aggregated amyloid- β protein; this fact excludes the often suggested idea that amyloid β would be driving the AD pathology and inducing secondarily the tau changes [87,95]. High burden of NFT was found to be associated with lower mental performance (MMSE <20) in a study of 168 autopsied persons [96]. Attempts of recognizing pathological P-tau levels in plasma resulted in some success in distinguishing AD from other tau-pathological diseases like PSP or CBD [97].

A large review of literature on senile neuropathological changes in 2012 came to the conclusion, that the cognitive impairment correlates best with the burden of neocortical neurofibrillary tangles [98]. In the last decade research profited from PET tracers (flortaucipir) binding to phosphorylated tau. In a study of 73 individuals of an average age 82.5, the sensitivity for postmortem histological confirmation was between 92 and 100%, with a specificity ranging from 52 to 92% [99]. The NFT, found often in other regions as in those with the highest content of amyloid usually spread from the medial and inferior temporal lobes into the neocortical regions. When combined with amyloid they were consistently associated with increased cognitive impairment [100].

Flortaucipir binding intensity enabled investigators to distinguish patients with AD dementia from individuals without cognitive impairment, outperforming MRI in its correlation of dementia with whole brain cortical thickness or with temporal lobe thickness. Moreover the NFT PET density also distinguished AD from frontotemporal dementia, progressive supranuclear palsy or dementia with Lewy bodies or with Parkinson disease [101,102].

Vascular components of dementia

The atherosclerotic deterioration in macro- as well as micro-vessels worsens circulatory efficiency in the brain, including decreased pulsatility and hemodynamic adaptability to the needs of metabolism. Not surprisingly, blood supply disturbances have been considered a main element in the senile degradation already in the 19. century [103] and repeatedly further elaborated under a term of subcortical arteriosclerotic encephalopathy [104-106]. The underlying neuropathological mechanisms are hypoperfusion [107] and defective cerebrovascular reactivity [108,109]. Ischemic effects on neuron and glia were intensively studied in animal experiments [110, 111] and found to produce histological markers of AD [112-114]. Thus ischemia is believed to trigger and amplify the soluble β-amyloid peptide and tau protein production [115]. Consequently the idea of ischemia as a driving force in AD clinics and tissue markers has many supporters [116-121].

As soon as we permit explaining AD pathology by ischemic failures of brain metabolism, we are approaching a blurred territory of clinical attempts to separate vascular dementia from the neurodegenerative one. The term „vascular dementia "with its heterogeneous nature [122-125] is losing practical value, since it covers minimally three causal categories: one strategic infarct, multiinfarct [124] – or no infarct, leukoaraiosis dementia [125]. These categories are largely different both in their etiology and their impact on mental capacities.

While no discrepancy prevails in understanding the role of major, demonstrable infarctions, more tricky is the effect of small vessel disease, manifesting in two distinct categories:

a/ microinfarcts: Minute lacunes or gliotic foci (50-400 μm) with neuronal loss and pallor in hematoxylin-eosin staining are found mainly in border zones between major arteries [126]; thus they prove their hypoperfusion etiology. In non-demented 1229 individuals of 12 studies in persons aged 70 – 95 years their frequency was 3% - 43%. Among 409 persons with AD they were found in 20% to 100%. However, owing to the limited sampling sites the actual number of micro infarcts could be several hundred times higher. The whole brain number could be up to hundreds or thousands. Their detection namely increases with high resolution (7T) MRI scanners. Even after subtracting AD histological pathology, small cerebral infarcts in general elderly population increase the odds of dementia 5 times and impair cognitive function [127-129].

b/ white matter lesions (WML) causing leukoaraiosis: Since the introduction of this term in 1984 [130], rarefaction of white matter is being found in cohorts of general elderly community in 50-98%, in stroke patients in 67-98%, in „Alzheimer´s disease" labeled persons in 28,9-100% and in Parkinson´s patients in 30-55% [131]. Obviously, leukoaraiosis accompanies aging along all categories of neurodegeneration. These hyperintense lesions in T2-weighted MRI, better in FLAIR sequence, were detected already in persons of forty [132] and grow in frequency and extent with aging [133]. Progression of these WM lesions in a metaanalysis of 46 longitudinal studies paralleled cognitive decline, most intensively in processing speed and executive functions. It appeared, not surprisingly, also associated with increased risk of stroke [134]. Their impact on mental impediment can be observed also in practical behavior, like driving car: Among 3930 „healthy" automobile drivers involvement in traffic accidents in subjects with multiple lesions surpassed that of persons with single subcortical foci more than three times [135]. Progression of WML according to the Austrian Stroke Prevention Study makes a total increment of 2,7 – 9,3 cm3 per year [136,137]. Faster progression is associated with more severe cognitive deterioration [138].

White matter rarefaction with demyelination of cerebral tracts is histologically characterized also by apoptosis [139] and results into an elevated mean water diffusivity and reduced fractional anisotropy (FA) in DWI [140-144]. Their associations with cognitive decline were documented not only in humans, but analogically also in other primates [145,146]. Although vascular mechanisms for brain tissue deterioration account for a particular etiological factor for any dementia, many authors consider them as contributing to „Alzheimer´s disease"[147]. One reason for this could be a close association of higher intensity of these lesions with higher amyloid content in the tissue and an elevated CSF-tau. In preclinical AD the amyloid burden doesn´t necessarily coincide with increased mean diffusivity or decreased FA [148].

Periventricular hyperintensities are associated with hypometabolism on FDG-PET [149]. Special attention deserve comparisons of normative aging in non-human primates, where immediate histological research following the moment of death is possible. These studies show a more pronounced deterioration of WM than GM. Demyelination with splitting of the sheaths along with axonal loss affect conduction (e.g. in corpus callosum and cingulum) which is in concert with loss of fractional anisotropy, leukoaraiosis, prevailing loss of WM weight and volume in manifold human and non-human studies [145]. Astrogliosis sets in and provides another marker of brain aging [150].

Some authors attempt to dissociate the deleterious effects of ischemia from those of amyloid and NFT. They found a closer association of WM hyperintensities with frontal hypometabolism, while higher CSF Aβ corresponded with metabolic abnormalities in the temporal lobe [151]. Impact on cognitive performance due to a decreased cerebral perfusion, although so tiny, that proven only by an increased Oxygen Extraction Fraction, was documented in persons with one-sided carotid artery occlusions [152].

The mechanism of ischemic damage to the brain tissue deserves special attention. The prosperity of neuronal and glial metabolism is dependent on proper coupling of blood flow with metabolic demands. That´s why the neurovascular unit is intensively studied [153,154]. An insufficient oxygenation, mainly in WM may occur with fluctuations of hypercapnia combined with hypotension – a mechanism of steal syndrome [155].

Another crucial phenomenon of aging vessels is their blood-brain-barrier (BBB) damage, documented in cognitive dysfunction irrespective of the Alzheimer's Aβ and/or tau biomarker changes in these individuals [156]. Consequences of a broken BBB are then not only leakage of blood-derived proteins but also cerebral microbleeds [157,158].

Traumatic reasons for dementia

Nobody doubts the effect of macrotrauma. The brain is however exposed also to microinjuries, like heading in football which were usually not counted until recently. Sports related head injury induce focal astrocytosis, microbleedings documented by hemosiderin, axonal dystrophy and can be experimentally demonstrated also in mice [159]. Chronic traumatic encephalopathy in football players resulted into white matter rarefaction and NFT burden in line with the number of years of play [160-163].

Inflammatory etiology of dementia

Treponema species, viruses and yeasts are also considered a plausible etiology of late onset AD. They could enter the brain via broken BBB in the elderly, or via the missing BBB in choroid plexuses. Detectable evidence of brain infection dramatically increased odds ratio for AD. Spirochetes, Treponema pallidum and Borrelia burgdorferi achieved the strongest association with dementia [164-169]. TBC is also one possible etiology [168].

Connectivity with a special role of fornix

With progressing technics, especially with diffusion-weighted imaging (DWI) and fractional anisotropy (FA) dementia is increasingly studied as a disconnection syndrome.

Whether disruption of WM tracts should be blamed for MCI and dementia, can be well documented by fibre-specific macro- and microstructural investigations, recently employing an improved fixel-based methodology. The extent to which WM degeneration is related to Aβ pathology remains however unclear [170,171].

Another diagnostic tool for comparison of intact vs disrupted functional network in WM is functional MRI (fMRI). The key regions of mental operations, including memory performance [172,173] like prefrontal cortices, hippocampal formation, fusiform cortices and cingulate structures are found to suffer deficits of their functional activity with age and with higher amyloid load in both healthy persons [174-176] and AD [177,178] as well as in leukoaraiosis patients [179,180].

A central structure for memory manipulations is fornix. Its higher, preserved FA was found to be associated with better working memory, episodic memory, and with both verbal and visual recall tasks. Its microstructure had the greatest impact on both functional connectivity and memory performance [181-186].

Mixed pathologies in mental deterioration of elderly people

Late onset dementia, following mild cognitive impairment, is a phenomenon, overlapping with trajectories of mental deterioration in cross-sectional as well as in longitudinal studies of general population. Steeper preclinical cognitive decline predicts faster fall into a diagnosis of AD [187]. Although a higher content of the traditional markers of AD, Aβ and NFT may accelerate this process [188], the final state depends still on a number of other factors in cerebral microstructural deterioration, mentioned above. Consequently insistence on individual/particular „diseases "causing dementia quite often fails in its practical application. Clinical practice scrutinized by autopsy revealed, that only 64% of all cases were deemed to match clinically and pathologically; in the clinical AD group 37% did not directly match pathologically. The majority of these had AD pathology, but with additional prominent Lewy Body or cerebrovascular pathology [189-191]. Distribution of AD pathology, varying among individuals, dictates different syndromological patterns, but practically always co-occurs with other pathologies, like Lewy body, white matter hyperintensities, TAR DNA-binding protein 43 and many others [192]. Also other issues than Aβ and NFT, e.g. loss of neocortical synapses are often more influential on the progress of dementia [193] and thus put doubt on the singularity of the whole traditional triad. A key study elucidating manifold etiological processes in brain has been provided by Patricia Boyle with co-authors. In a big cohort of octogenarians, observed for 9 years using 21 psychological tests annually, the final autopsy at 90 years of age revealed 7 other pathologies in addition to Aβ and NFT being substantial attributes to dementia. The authors were thus able to declare AD as no longer a singular disease process but most commonly the result of mixed pathologies [194]. Such an opinion is also in full agreement with our own understanding for senile dementia [195].

When age is recognized as the main risk factor for dementia, we must pay attention to genetic factors causing rapid or slower aging processes. Younger epigenetic age, estimated using the DNA-methylation on specific genomic positions has shown indeed a difference between memory maintainers and memory decliners throughout an observation period of 15 years [196]. Some other, psychosocial, health, life-style and biologic factors for preserving good memory were also identified [197,198].

Fornix plays a key functional role in connecting memory deposits with limbic association centers of integrated awareness and with frontal supervisory centers. If having only about one million axons even minimal lesions in these fasciculi are capable of causing much bigger functional deficits than major lesions elsewhere in the hemispheres.

Several markers of senile encephalopathy are mutually interconnected. Most prominent is the link between oxidative stress [199] and the rise of tauopathy [200]. Being more influential on mental deficits than amyloid, the Primary age-related tauopathy (PART) was suggested as a clinical unit [201]. Its cellular mechanisms were documented in histological studies that show aberrant modifications of neuronal microtubules via hyperphosphorylation after induction by oxidative stress [202]. ROS production may increase the permeability of mitochondrial membranes and thereby initiate cell death through release of apoptosis.

Recent investigations shed new light on the subcellular processes regarding protein misfolding. Such observations link our amyloid fibril hypotheses with oligomer and protofibrillar intermediates which influence the permeability of cellular membrane. In the same time they can be neurotoxic. They are common findings in several neurodegenerative diseases, like AD, PSP, MSA, ALS, Parkinson´s or Huntington´s disease [203]. Even more intriguing is the conjunction of these protein conformational isomeric changes with the innate immune system. Certain similarities have been found in amyloidogenic proteins with α-synuclein, huntingtin and even with the prion protein (PrP). Based on a phenomenon of switching from innate immunity complexes into the pathogen-like immune complexes, neurodegeneration could be eventually interpreted as a process, activated by neurotropic viruses [204-206]. The interaction between Aβ oligomers and PrP may further impact synaptic plasticity functions.

In agreement with the influential paper of Clifford Jack´s committee we also believe, that „The term "Alzheimer's disease" refers to an aggregate of neuropathological changes" and that dementia is not a "disease" but rather is a syndrome composed of signs and symptoms that can be caused by multiple diseases [207,208]. We cannot however support the idea, that the whole-life progressing histological changes should be promoted to a „disease" ignoring absence of its actual clinical manifestation. Not only because „disease" traditionally designates subjective complaints with obvious clinical objective symptoms, but also because it should be reserved for a deviation from a standard life-long development.

Conclusion

Mental decline from normal over MCI to dementia is a lawful and inevitable process of human aging. The term „healthy aging", „contradictio in adjecto "refers only to relative advantage of slower decliners compared to the faster ones. Among the many processes of the histological tissue degradation the amyloid beta and NFT, traditional markers of AD are only two among many others; all together they cause and fulfill in an additive and synergistic manner, often in mutual potentiation, the trajectory of human life from its conception through maturity to its senescent impairment.

Throughout the century since Alzheimer´s and Fischer´s discoveries a number of new techniques have made it possible to increasingly recognize the degradatory processes that are immanent to human aging: the fluctuating ischemia due to cardiovascular insufficiency, microtrauma, infection, metabolic, immune and hormonal disorders or alcohol and other addictions. The fascinating results of the worldwide research call for a new approach in understanding dementia as our common destiny. Placing AD markers in a humbler position among other components of cerebral deterioration should not diminish the fame and merit of its pioneers. Simplifying mental aging to a handful of specific diseases is no longer sustainable.

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