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Recent discoveries widen the basis for future research in Alzheimer´s disease.

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Abstract. Intended as food for thought this revue offers a general orientation on Alzheimer´s disease (AD) with comments on the brain changes and clinical features. But more importantly, it points out recent research findings which may offer new alleys for AD research pertinent to the etiology and pathogenesis of AD and alternatives to the so far rather unfruitful and costly amyloid research trail. This new knowledge thus comes from various fields of research such as epigenetics, pointing to possible environmental etiologic factors. Further exosomes may provide information on the state of the neuronal population for diagnostic purposes and might become useful as carriers of therapeutic substances. The newly disclosed protein complexity of the synapses may harbor a large yet unexplored field for neurochemical research pertinent to the early or likely initial loss of synapses in Alzheimer disease. The finding of a more generalized neuronal gene disturbance in Alzheimer´s disease shifts the focus from age related changes to developmental disturbances and increased neuronal vulnerability. BBB incompetence with a start in the *hippocampus* has also recently been pointed out and may initiate the degenerative process of Alzheimer´s disease. Finally, recent basic research findings on glial evolution, underscoring the distance between humans and rodents, our prime disease model animal, points to several new unexplored mechanisms, which may be relevant for the understanding of neurodegenerative processes. Also stressed is the need to institute treatment at an early stage of the disease, necessitating research for markers, which will enable a diagnosis way ahead of the widespread damage present at the time of clinical debut.

Keywords: Alzheimer´s disease, Dementia, Epigenetic factors, amyloid hypothesis, Blood-Brain barrier, exosome, synapses, astrocytic syncytium, evolution.

Alzheimer´s disease (AD) is a global curse not just for the diseased but also for the relatives. It is the most common form of dementia, followed by vascular or infarct dementia, which also very often complicates Alzheimer´s disease. Even if the disease is most common among elders, about 10% of the victims are below retirement age in Sweden, or 10000 persons. Today about 40 million people worldwide suffer from Alzheimer´s, and with a calculated doubling of the number of victims every 20 years it

will become a very heavy burden for the society as commented upon by US president B. Obama. The World Health Organization considers dementing disorders one of the greatest global health challenges. The real incidence is underrated since death certificates in USA had AD as cause of death in 86000 cases while in reality they were 500 000, most of which were instead reported to have died from pneumonia and other terminal complications. This makes AD the third most common cause of death after cancer and heart disease, while the costs for AD is larger than those for stroke, heart disease and cancer taken together.

Dementia may be defined as a condition with acquired longstanding decline of mental functions such as memory, spatial orientation, language, and practical abilities. The clinical debut of AD often occurs around 50 yrs. of age and the course is 5-15 years or more. The start is insidious, marked by difficulties regarding memory and spatial orientation but also fatigue, depression and poor concentration. With the following disease progress, there are added difficulties to recognize even close relatives, inability to button clothes or handling knife and fork. On the other hand, judgment, personality and emotional functions are long preserved. In late stages, there is often epileptic seizures and the patient becomes bed ridden and in need of care in all respects. The disease profile varies however from case to case depending on individual differences with regard to e.g. previously acquired functional loss of capacity and complicating other brain disorder, especially vascular lesions.

The debut of the disease is usually defined as the point of time when symptoms become noticeable, enabling a diagnosis. By then, however, the disease is already well established in the brain. A closer analysis reveals a decline of spatial orientation capacity on the average three years ahead of diagnosis, and of general cognitive skill two years before, while verbal memory difficulties appear one year ahead of definite diagnosis. There are however many indications that the disease starts even earlier! Down's syndrome, nearly always complicated by AD, in my experience shows typical and increasing brain changes in their late teens, 20 – 30 years before the clinical debut. This is also true for other types of AD with PS-1 gene mutations, where early signs of AD include disturbed amyloid metabolism (raised cerebrospinal fluid levels of amyloid, but not reduced levels as in established AD) and altered activity e.g. in the memory center (hippocampus) long before the clinical debut. These changes might begin before biomarker evidence of *Amyloid beta* ($A\beta$) plaque deposition and may have a degenerative or a developmental background (1). Dominantly inherited forms of AD show reduced cerebrospinal fluid levels of amyloid and raised levels of tau as in established AD 20 years before the clinical debut with appearance of plaques and tangles. Further, other forms of AD with a common gene abnormality (APOE ϵ 4 allele) show changes already in

adolescents and even in fetuses in areas much later to be hit by AD, such as reduced hippocampal volume and abnormal nerve cell contacts and mitochondria (2). Here one could thus trace the disease long ahead of its clinical debut. This may presently be true just for these genetically based forms, but raises the thought of a similar very early debut also in other forms given the commonality of genetic aberrations to be described in what follows. We therefore need to take into account also the possibility of a parallel disturbance of the brain development and maturation, in addition making the brain more susceptible to degenerative processes!

The reason why symptoms are delayed is in part an ongoing repair of deranged structures, but above all a reserve capacity of the brain, an affluence of neuronal functional components, which are the targets of AD. This allows an ability to compensate for damage for a time and thus postpone noticeable dysfunction. A recent report has shown that higher education adds to this richness and thus increases the reserve capacity, thereby delaying the dementia phase with up to 7 years from the first phase with mild cognitive decline.

Is the cause of the disease genetic abnormalities, which may be far more general in AD than assumed, as in the forms just mentioned? This may be the case in Down's syndrome, which regularly is complicated by AD. It has been thought to be due to an extra chromosome 21, but recently a more general genetic abnormality has been found. AD without Down's syndrome has also been found to show a widely disseminated variation and abnormality in the gene material, an aneuploidy, which may be expected to cause an increased vulnerability of the neurons as well as a disturbance of neuronal development (3). Such gene abnormalities may concern not just AD, but be a more general principle for all post mitotic neurons. Lu and Yankner (2004) concludes: "*During life accelerated DNA damage may compromise systems that sub serve synaptic function and neuronal survival*" and "*this could be a starting point for trying to understand why aging of the brain is a major risk factor for AD*" (4). This opens up a host of new probable disease causes and mechanisms. Of the previously described mutations, some have been linked to abnormal amyloid accumulation, but since the majority of AD cases have accumulation of amyloid without a presently demonstrable such gene mutation this link may not be crucial. There remains of course the possibility of one yet not detected mutation e.g. one that fails to inhibit amyloid overproduction.

Epigenetic factors may lie behind such mechanisms, silencing or activating DNA genes. This is of particular interest since our environment plays on the epigenes, why we will be obliged to look closer at the environment in our search for causes of AD. The epigenome is now being mapped beginning with normal tissues. The epigenome might vary from

person to person and in an individual between regions of the same organ such as the brain, something of interest with regard to the striking cerebral regional vulnerability patterns of neurodegenerative disorders including Alzheimer's disease. Depending on exactly where on the DNA the epigenetic factors occur, these modifications help determine whether a gene is read or ignored by the transcription apparatus. Data suggest that changes to gene expression in immune cells initiate Alzheimer's disease, but it could also be the result of environmental factors such as education playing on other cell systems (5)

The immune system has been implicated also in other neurodegenerative diseases such as amyotrophic lateral sclerosis, which co-occurs with frontotemporal dementias, and Parkinson's disease (6). This opens up a basic research field where we have already begun see the first results pertaining to AD.

The amyloid hypothesis. The currently dominating opinion is that a misfolded protein, amyloid, triggers the disease according to a mechanism much like how prions cause mad cow disease (Creutzfeldt – Jacobs disease) which however is an entirely different disorder. This principle may also be relevant for the hyper phosphorylated protein tau (τ) always present in neurons in AD. Above described research findings do however cast some doubt upon the amyloid hypothesis providing a wider basis for the causes of neurodegeneration, which in addition occurs long before the amyloid and other characteristic AD changes appear and which form diagnostic criteria for AD (amyloid accumulation, plaques and tangles). Amyloid as a cause of AD has been maintained since 40 years but still without conclusive evidence in spite of massive research efforts and costs, at the expense of support for alternative research ideas. Some researchers point out that the accumulation of amyloid is out of pace with the degenerative process and that therefore the accumulation is an independent biological process. Amyloid may promote and speed up the degeneration, but not be the cause of the disease. Many anti amyloid therapeutic attempts have also been discarded due to lack of effect, such as the recent phase 3 trial on *Gantenerumab* (7). Treatment Alzheimer patients with *Aducanumab*, monoclonal antibodies directed against forms of β -amyloid, was recently found to be associated with a statistically significant dose- and time-dependent reduction in amyloid plaque (8).

Further new research has shown that amyloid may accumulate without dementia in many cases, and, conversely there are cases of AD without much amyloid accumulation in spite of ongoing neuronal degeneration (9).

Other etiological suggestions involve abnormal oxidation or oxidative stress, leading to membrane damage at subcellular and cellular levels.

Accumulation of amyloid could here instead be seen as an expression of properties of amyloid in the adult brain, viz. an attempt to protect from membrane damage and to support repair mechanisms.

The blood brain barrier. In addition, vascular disease has been thought to be involved in the etiology given the very common co-occurrence of AD and vascular brain disease. Here previous hypertension can have left behind a vessel wall damage involving also the blood brain barrier, which then no longer prevents unwanted blood substances from penetrating into the brain. Incompetence of the blood brain barrier has also been pointed out, starting in the hippocampus in both ageing and early stages of Alzheimer's disease. That would allow circulating toxic substances to reach the brain and start a degenerative process (10). This calls for means to close the barrier, or to identify and neutralize released substances responsible for the neural degeneration. As in all similar biological situations one should consider the opposite alternative, in this case that the opening of the BBB is secondary, a call for delivery from the blood of cells or substances needed for the repair of degenerative damage to the brain structures!

In addition, there are in AD very often cerebrovascular lesions and especially scattered white matter infarctions of the incomplete type, which will complicate or confuse the symptom picture and add a component that would resist AD therapy and attenuate the results of treatment attempts.

Alzheimer and Cancer. Interesting information might be gained from a study of factors leading to cancer, since several investigations including one recent study of more than 1 million Northern Italy residents found that the risk of cancer in patients with AD dementia was halved, while one-third (11) reduced the risk of AD in patients with cancer.

The main microscopically changes are loss of synapses, deposition of amyloid in meningeal and cortical but rarely in white matter vessels walls, an interesting but evidently unexplored discrepancy. Amyloid is also deposited in the center of rounded scar formations consisting of deranged neurites and dendrites, so called plaques, which may have a more rapid turnover than previously assumed. Also the "skeleton" of the neurons, their internal transport channels, degenerate to form tangles marked by hyper phosphorylation of the constituent protein tau. Consequently, the neurons shrink probably at least in part due to reduced impulse input after loss of synapses and connecting wiring. These structures may regenerate if given the opportunity, creating a late window for treatment. The brain reacts with increase of supporting cells or gliosis and shrinkage of the most deranged parts, and may lose almost half of its weight! This results in a rather disease characteristic pattern that we showed in 1976 with atrophy of the

hippocampus in the basal medial temporal lobe, starting already at the stage of mild cognitive impairment and progressing with the transition to AD (12). The changes then spread to medial structures of the hemisphere, especially and early to the posterior cingulate gyrus and adjoining cuneus, posterior lateral portions of the parietal lobes and later to the frontal lobes, for long usually sparing the phylogenetically old and therefore more robust sensory and motor gyri. This pattern is reproduced on functional brain imaging. This spreading pattern is now believed to be due to transport along nerve tracts between cooperating and therefore physically connected neurons of "toxic" substances such as misfolded proteins type tau or amyloid and others. A transport mechanism may also be at fault, such as the protein TDP43, something relevant also for other neurodegenerative disorders such as frontotemporal dementia.

The exosome system. Also relevant in this context of the march of the disease is the recently Nobel prized research finding regarding small circulating transporters, exosomes. They carry protein messages, good or bad, to and from normal and diseased neurons (13). This raises hopes of future possibilities to diagnose the disease through an analysis of their contents and, even treat the disease by adding a therapeutic substance to said contents.

Loss of synapses is the probably most important change for the dysfunction in AD and the earliest to occur. Synapses are the dominating part of the reserve capacity structures of the brain and the one that can be restored and improved through training. This is the reason for the widespread opinion that acquired raised brain capacity resulting in an enriched supply of contact structures delays or postpones the dementia stage, although at the prize of a faster downhill course when symptom finally appear. The synapses have recently been found to contain thousands of different proteins normally involved in the activity and metabolism of the synapses, including amyloid and alfa-syncline, markers of AD and Lewy body dementia. This opens up a new, gigantic virgin research field that may hold keys to the cause/causes of the degeneration (14).

The retina, a representation of the central nervous system accessible for direct inspection, may offer an opportunity to detect and diagnose neurodegeneration since the retina has been found to undergo atrophy in MCI and more extensively so in Alzheimer's disease (15). The retinal changes may be of particular diagnostic interest since they seem to be early features of neurodegeneration. Maybe imaging methods now in use to demonstrate amyloid and tau deposits in the brain could be applied and add further, more specific information, as well as novel retinal microvascular network and retinal ganglion cell imaging. Is also macular degeneration

paralleled by central nervous system neurodegenerative changes? Also in other neurodegenerative conditions such as frontotemporal dementia, the retina should be investigated along these lines of thought.

Evolutional sophistication. The last few years have seen interesting basic research results pointing out that not only have neurons undergone remarkable evolutionary modifications but also the astroglial cells which have developed new properties and even new forms in primates and have become distinctly different from those of inframammals, e.g. rodents. These evolutionary changes have resulted in an astrocytic syncytium, which modulates and coordinates neural signaling and takes part in neural maintenance. "*The evolution of human neural processing, and hence the species-specific aspects of human cognition, may in part reflect the course of astrocytic evolution*" (16, 17). This means that we have here got new mechanisms to consider in the research on neurodegeneration. It also means that our brain disease model animals, the rodents, are even more remote from the human brain regarding structure and function than previously assumed and accepted, making rodent disease models seem less realistic and adequate for the purpose. Several new papers allude to glial incompetence in relation to the neuron and its axon as a possible cause of Alzheimer.

A skin Test for Alzheimer's and Parkinson's Diseases may become available in the shape of a skin biopsy showing significantly higher concentrations of the proteins tau in neurodegenerative diseases. In addition alpha-synuclein is associated to Parkinson's disease (Dqghwrg/#533;,, compared to non-degenerative controls, according to a report from Hospital Central, San Luis Potosi, Mexico, referred to by Pauline Anderson in February 25, 2015 Medscape Medical News, conference News, awaiting later publication. Such a test would serve to support a tentative diagnosis and aid in the differential diagnostics. Many questions are unanswered for the time being, such as the possibility of a more generalized metabolic perturbation related to the PNS and skin nerves or of an export and deposition of the substances from the CNS, and if this may be applicable to also other disorders such as LBD, Huntington and other.

Treatment.

Vaccination for AD. Many attempts to vaccinate against amyloid have failed or ended in catastrophe. Presently hopes are set on a modified method at an early stage of the disease, with antibodies against various species of the amyloid molecule. Its curative effect remains to be shown, but it has had a certain ameliorating effect (18). One can only hope that

the so far promising effects on both amyloid and cognition will hold up in a longer perspective. (Daniel M. Keller, PhD March 23, 2015 Medscape Medical News) (9). Other attempts have employed anti tau vaccination with some effect in mice but hardly in man so far.

Neuronal contact enhancers, such as acetylcholine esterase inhibitors, improving signal transmission between neurons, dominate drug treatment for AD. These are unfortunately effective only in a certain proportion of cases though with improved effect if combined with the receptor antagonist Memantine. As for other therapeutic measures these would gain from an early introduction, before the degenerative process has consumed too much of the structures which can be influenced by treatment. One plausible reason for lack of success with this treatment or rather persistence of symptoms may be the very frequent and treatment refractory vascular lesions, in particular the incomplete white matter infarctions, which should be treated preventively.

Non-drug treatment through brain stimulation is based on the finding that mental and physical activity enriches neuronal connectivity in terms of additional receptors and synapses, resulting in improved cognition and memory. Again, such training has to be instituted before late stages of the disease to be of benefit. Studies has shown that brain training postpones with several years the stage when care is needed, though then the course becomes faster, shortening the long-term care. Along the same line of reasoning reduction of brain input due to loneliness or isolation, and hearing and visual difficulties should be counteracted. They may otherwise cause "loneliness dementia", a rediscovery of sensory deprivation from the fifties (19), with frontal subcortical damage to oligodendroglia cells and demyelination, something that is reversible on stimulation (20).

In conclusion recent progress in basic brain science and neurodegenerative diseases has provided an unprecedented number of new tools and theories for both clinical and basic research that promises to allow safer evaluation of previous research results and offer new openings in the hunt for the cause of Alzheimer's disease.

MicroRNAs (miR-), small non-coding RNAs that regulate gene expression, are increasingly recognized as players in Alzheimer's disease (AD). miR-9, miR-106, miR-107 are all downregulated in the brain, while miR-34 and miR-146a are upregulated in the AD hippocampus. miR-29 and miR-181 may also be involved in Alzheimer's processes (21,22).

In addition, the recently discovered glial syncytium and disturbances in its capacity to care for the neurons has emerged as a possible source of neurodegeneration.

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