***Review***

# □ Alzheimer's dementia

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***SUMMARY:*** *I was given the task of reviewing current knowledge on Alzheimer's disease. Each of us, professional clinician, is daily confronted with cases and persons of disparate origin who complain of memory failures and increasing disorientation or naming difficulties with aging. The diagnosis is often very simple. However not necessarily our guess meets the canonical criteria designed by our colleagues who are mainly involved in research. Literature on the topic is vast and anyone can absorb desired information to guide clinical skills and treatment methodologies over the myriads of scientific papers or international meetings. There is no need to provide you with a boring summary of what is known in the field since last twenty-five years. It would be more profitable, I hope, to share with you our personal clinical experience hoping to open new windows and unexplored trails which can more adequately address the real needs of our patients starting with a better recollection of the history of their life, long time before they eventually develop the disease.*

***KEY WORDS:*** *Amyloid beta Alzheimer Dementia, CT, Cerebrospinal fluid, FDG, Magnetic Resonance, PET.*

Aging is not a disease. Good aging however is a luxury not for many.

Today, our society cannot allow to bear heavy loads. Bad (pathological) aging becomes a double disease. First for those affected (*at an individual level*); secondly for the entire society, upon which all incident cases impact (*social or group level*). Nobody is yet prepared to adequately overcome this new epidemic, nor our society, or our public health system. Even less prepared are caregivers, often left alone to fight the very challenging and devastating battle of populations' aging.

Dementia is a biological process of cerebral degeneration, which reduces and thins neurons and knowledge within the human brain, progressively and irreversibly. It begins in a subtle way but soon becomes inexorable. The affected individual is not completely aware of her/his difficulties; relatives also minimize at first the magnitude of their symptoms and the impact on everyday life. Very often these failures become apparent around the retirement phase of life and easily these are misdiagnosed as "depressive" reactions. Instead this is a very slow neurodegenerative process of exfoliation of premorbid acquired skills, which has no equals in neuropathology, where cerebral, and cognitive rearrangements finally result devastating. Among all forms of dementia, Alzheimer's disease represents almost 50% of all recognized cases[16].

Current research assumes that 1% of western population might be affected by Alzheimer's disease at age 60. This rate doubles every 5 years, so at age 80 almost 16% of resident population results affected by the disease, and at age 90, more than half of

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***LIST OF ACRONYMS AND ABBREVIATIONS:*** **Abeta** = Amyloid beta; **AD** = Alzheiemer's Disease; **CSF** = CerebroSpinal Fluid; **FDG** = Fluoro-Dexosi-Glucose; **MRI** = Magnetic Resonance Imaging; **PET** = Positron Emission Tomography.

survived individuals might be affected by such pathological process. Early forms of dementia of Alzheimer's type (age 40 to age 60) although less frequent, are diagnosed as well; their pathological and clinical progression is actually worse and faster. In Italy it is calculated that 12 new cases/1000/year could be an overall good estimate for those individuals over 65 years of age. Therefore almost 100.000 new cases are diagnosed every year with early or advanced clinical symptoms of this degenerative form of dementia.

Alzheimer's disease was labeled after Alois Alzheimer and Gaetano Perusini's description of a relatively young lady manifesting with cognitive as well as behavioral disturbances which were not related to any known disease at that time. It was discovered more than a hundred years ago, however only in the last twenty years there has been sufficient recognition and improved medical care for patients affected and their caregivers. Since 1984, when diagnostic criteria were first generated[13] our perception of the disease and our clinical approach has completely changed. Also, new criteria are continuously elaborated rearranging our understanding, our approach and our clinical taste. This review will briefly cover a few general topics of the diagnostic process and will soon move to the latest significant selection of newly generated research frameworks.

First, contrary to the old 1984 diagnostic guidelines, Alzheimer's disease covers a continuum from initial changes of asymptomatic subjects to late accumulation of changes characteristics of very old and very severe demented patients. Alzheimer's disease is now labeled "Alzheimer's dementia" to describe patients in the spectrum of the disease, confirmed with neuroimaging and/or cerebrospinal fluid.

Second, initial symptoms are mainly involving short-term or recent memory and the learning system, although very soon language, reasoning, orientation, self-perception, awareness and executive behavior become affected.

Third, as the disease progresses, cognitive, behavioral and functional abilities worsen to the point that people become totally dependent upon others, also for very basic activities of day living, such bathing, eating, or dressing.

The pathological markers of the disease is the accumulation of amyloid beta (between brain neurons) and tau protein (inside the neurons). Beta amyloid plaques deposition contribute to functionally disconnect neurons and synapses. Tau tangles inside the cells block the transport of nutrients and kill the brain neurons[11]. Inflammation due to several causes provokes shrinkage and cell loss contributing to the widespread atrophy. As neuronal damage progresses, the brain can no longer compensate for such changes and the individuals begin to show subtle-to-marked signs of cognitive breakdown. These brain changes start years before clinical manifestation; sometimes twenty or more years. This makes even more difficult our effort of early diagnosis and treatment.

Alzheimer's dementia recognizes various known promoting factors. The first and most acknowledged factor is *age*. Increasing age by itself is the most important factor contributing to trigger the pathological process linked to dementia. Also, *low education* has been found a significant factor by many researchers. Adequate formal education lowers the risk of developing the disease, contributing to build our "cognitive reserve"[17], a sort of "parachute" which delays, slows down the initial manifestation of the disease although never can impede the progression once started. Several *vascular factors* may as well contribute to increase the risk of developing dementia: hypertension, cholesterol, diabetes all contribute to lower the resistance of brain cells under the weight of time and promoting negative factors.

Their contribution has always been postulated in the pathophysiology of dementia, however never fully confirmed. The key point might be the role of these vascular factors upon neurodegeneration itself, due to pro-inflammatory activity now being studied at length. *Familiarity* of dementia is a strong factor, in combination with previous factors, triggered by a genetic predisposition linked to the apolipoprotein E gene[15], especially when two homologous E4 forms are found.

Other important factors, less known and less caught, are *chronic depression*, untreated depression and history of *head trauma*, all factors which inhibit cellular activity at the hippocampal level. The convergence of some of these factors negatively

influences the resistance of the brain apparatus (resilience) and cognitive symptoms start to emerge. If they remain underreported and under investigated, such deviant processes may continue to impact upon the level of cognitive activity which in turn reduces concentration, short-term memory, confidence, and general activity, building up a pathological loop of extreme severity, if left undiagnosed.

A special note deserves a topic often neglected in research and in clinical routine. It is our personal experiences that *general anesthesia*, especially if repeated, long lasting (at least two hours) and after age 55, cumulate a rapid, often devastating pro-inflammatory process that facilitates neuro-degeneration. It is not known at this moment yet, if the anesthetic itself is responsible of the devastation or the prolonged activity under narcosis, but this is a very frequent finding in routine clinical practice (if investigated). Our patients and their relatives come to our laboratories after reporting a recent major surgery, and they often overtly offer such evidence, although clinicians are not ready yet to take into consideration the relevance of such a common event. Very recently, no more than a month ago, a major journal reported cognitive decline in middle-aged individuals who underwent surgery and general anesthesia[2,7]. Reduced concentration, reduced flexibility, reduction in immediate memory and working memory were significantly found and they were correlated to the number of operations and the length of anesthesia. This is a very crucial factor in our experience, increasing the risk of developing dementia in those patients who already have other risk factors (known), serving as a "strong and rapid" stimulator or trigger.

Our patients, and their families complain of such events and we need to listen more carefully. The effect of general anesthesia is visible among individuals who were free of cognitive disturbances; it can be devastating for those who already have developed an initial process of cognitive worsening and cerebral atrophy, as serial neuroradiological and imaging findings show distinctively. In summary, we may list "*general risk factors*" such as chronic consumption of alcohol, vascular pro-inflammatory comorbidities, diabetes, thyroid dysfunction and, "*specific risk factors*" which could be either "genetic" or "epigenetic". Among these, relevant events which occurred during pediatric or adolescence life (*completely neglected*) but also and more importantly during the early mature phase of life, such as traumatic brain injury, untreated depression, neuro-immunitary and dis-immune conditions such as thyroiditis or major allergic reactions.

These mentioned conditions and risk-generating factors all increase neuroinflammation which plays a significant role in degenerative diseases. Toxic substances including cytokines, tumor necrosis factors, glial activation are very harmful. Especially in the very early stages of the underlying disease, a vicious cycle of glial priming, release of pro-inflammatory factors and neuronal damage which influence the systemic inflammation[3,9,12] and contribute to reduce the intrinsic capacity of the central nervous system of progressive elimination of debris, then increasing the amount of amyloid between the neurons and interrupting connections and signal transmission. Functional disorganization of cerebral networks starts at a certain age, but this process may become pathological when a series of different mechanisms co-occur and interrupt the regular biochemical and neurochemical transmission. Symptoms of cognitive decline are not yet visible at this stage and this is the reason why the earliest disturbances remain often undiagnosed and un-mentioned.

The most common and prototypical clinical debut is a progressive, frustrating and embarrassing incapacity to form new memories, or to recall recently acquired verbal and non-verbal information. Names become very difficult to recall, faces are forgotten, places and roads appear inextricable. The progression is also predictable. Soon the patient becomes disoriented, displaces common objects, finds problems in organizing her/his life and becomes more confused, fatigued, irritable and forgets the meaning of words or finds difficult to manage money, familiar instruments, confuses day and night and even familiar faces. Language becomes scanty, non-fluent, confused and very poor of communicative information. Behavioral disturbances follow after a few years, agitation takes place and the patient is unable to autonomously live her/his life. This process may take almost 15-20 years before becomes clear, but once diagnosed, progression commonly takes its worst scenario within ten more years.

In the pre-dementia period, cognitive dysfunctions have a specific pattern. Episodic memory becomes faulty, object names are nor easily recallable, even name-face association of familiar people becomes a hard task. Handling more than two activities at once results very challenging and many errors appear in

conducting activities of daily life. Irritability becomes apparent and, at first, also depressive mood appears mixed with anxiety for the perceived incoming difficulties. After a few years though, especially if disturbed behavior is left undiagnosed, patients develop unawareness of their deficits, become fatuous and they loose insight into their own difficulties.

Cognitive testing has become the easiest and more requested valuation, often without significant results, early defective performance being "within normal limits"[8,14,18]. Neurological attention is seldom requested and more appropriate instrumental assessment is not given, loosing precious time and alternative treatment strategies. Basic CT scanning is not appropriate, MRI imaging is not specific and clinical interpretation assumes the style of "wait and see". After the 2007 criteria spread by Dubois and colleagues though, dementia in not an "exclusion diagnosis" but conversely an "inclusion diagnosis", that is, if cognitive disturbances surge to assume a significant impact on daily and working living, the first think we are forced is to pursue a "pattern of dementia"[6]. Still now though this is not the common approach. Diagnosis of dementia, preclinical or presenile, is not frequently made, often remaining in search of the "Alzheimer's pathognomonic findings.

Pathological Alzheimer's findings are also found in normal brain but these patients are not demented. Conversely patients diagnosed with "Alzheimer's disease very often do not show the pathological marks of the disease at autopsy. Alzheimer's disease has been conceived so far as a "*clinical-pathological construct*": if a person had amnestic symptoms they would have AD neuropathologic changes at autopsy; if the symptoms were absent, they would not have AD at autopsy. Cognitive dysfunction and disease became interchangeable[10]. Recently the most common construct to be utilized has been the "*clinical-biomarker*" approach[5,6], where biomarkers have been used to support and confirm a diagnosis of AD in symptomatic individuals. As a cognitive neurologist, one lesson I have learned in recent years is that amnestic multidomain dementia is neither sensitive nor specific for AD neuropathologic change, suggesting that cognitive disturbances and cognitive assessment can remain not an ideal way to investigate and define Alzheimer's disease.

Very recently, the National Institute on Aging-Alzheimer's Association set up a research framework[10] which is replacing our traditional knowledge and may serve as an updated guideline for clinical diagnostic procedures and therapeutic intervention. Although, they say, this a research framework not for clinical use, their conclusions are very strong and linear contributing to review our thoughts, diagnostic patterns and outcome consideration. The main contribution of this research paper could be summarized as follows:

1. We currently use the term Alzheimer's disease *indistinctly* to describe clinical syndromes that resemble the classical pattern of AD, but also to refer to the neuropathological hallmarks of the disease.
2. Disease-modifying substances being studied can only be applied in the very early (preclinical phase) of the disease; these individuals could not yet be labeled patients.
3. The disease once was confirmed only at autopsy. After 2011, with the advent of the biomarkers-approach, the disease could also be diagnosed reasonably well in the living brain.
4. To make a diagnosis of AD we must either perform a PET Amyloid or PET tau scan or (at least) quantify beta amyloid and/or tau in the CSF after lumbar puncture
5. Neurodegeneration, visible on MRI is not sufficient to enter the Alzheimer's spectrum, nor is a defective neuropsychological examination documenting multidomain areas of impairment, which could be not specifically related to other causes.
6. Biomarkers (either Imaging or cerebrospinal fluid) are a continuous measure of disease, which starts preclinically, before the symptoms start. Amyloid PET is a valid in vivo surrogate of the Abeta deposition in the brain, so is CSF Abeta 42 or the ratio Abeta 42/Abeta 40. The first biomarkers to become abnormal are those of Abeta.
7. There seems to be a causal upstream role for Abeta in the pathogenesis of AD. Amyloid biomarkers represent the earliest evidence of AD.
8. Both Abeta and pathologic tau biomarkers need to be present to apply the label of "Alzheimer's disease" in living individuals.
9. Neurodegenerative changes, both neuroradiological or neurocognitive, remain indicators of the severity and the progression of the disease; they cannot define the presence of the disease.
10. Cognitive performance then exists on a continuum and contribute to define categorical stages and progression of the disease, from a pre-clinical

| AT (N) biomarker grouping |
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| **A = aggregated amyloid-beta or associated pathologic state** |
| • CSF Abeta 42 or Abeta 42/Abeta 40 ratio<br>• Amyloid PET |
| **T = Tau pathology: aggregated tau (neurofibrillary tangles) or associated pathologic state** |
| • CSF phosphorylated tau<br>• Tau PET |
| **(N) = Neurodegeneration or Neuronal injury. Not sufficient for "in vivo" pathologic definition of AD** |
| • Anatomic MRI<br>• FDG PET<br>• CSF total tau |

**Table 1.** Recent criteria: AT (N) biomarker grouping (*adapted from Jack et al., 2018*[10]).

phase of pauci-symptomatic or good aging to mild cognitive impairment, to early dementia, till the most severe stages of the disease. Even the most severe cases of dementia (clinical syndrome) may not be attributed to Alzheimer's pathology (non-Alzheimer's dementia).

This new paradigm of pathological definition of Alzheimer's disease greatly contributes to speak the same language between clinicians and researchers. It poses unquestionable clarity in the diagnostic process and relegates cognitive assessment to its role: a quantification of the relative cognitive devastation secondary to underlying degenerative pathology represented by AD, rather than a synonymous of AD. This paradigm makes light into the *neurobiology* of this common process linked primarily with aging (bad aging). This newly developed framework allows also a better patients' segmentation in clinical trials[4]. Biomarkers are invasive and expensive though and not easily implemented into our daily clinical activity. In the future we hope that other biomarkers could be available, less invasive and less expensive as well more at hand. But in the meantime every clinician needs to face a major problem, that is daily confrontation with the many questions of patients at their early symptomatic stage or their relatives who are first concerned for their dears but also make increasingly more questions about their future and the risk that they might develop of the same cognitive failures or the same disease. To their many questions indeed we have no answers, nor we can continue to use the answers available to us till a few months ago. Alzheimer's disease is a pathological process, which could be diagnosed "in vivo" following the specific and costly patterns of investigation as mentioned above. The shortcut of cognitive assessment and the lapidary diagnosis of Alzheimer's disease based on these results are no longer appropriate. Each of us need to clearly differentiate both clinically and discursively, the *neurodegeneration* responsible of the syndrome of dementia, illustrated on MRI or on cognitive evaluation, from Alzheimer's disease itself which needs to be ascertained with biomarkers, either on Imaging or with CSF findings.

## □ FINAL REMARKS

Alzheimer's disease is a recently coined clinical-pathological entity, which was labeled after the work of Alois Alzheimer and his school more than a hundred years ago. For many decades it remained neglected, unknown, undiagnosed. By the end of the 20$^{th}$ century there was a surge of interest as a result of reduced mortality, better living and increasing "survival of civilized society". Pathological determinants of the disease were postulated and confirmed. Amyloid plaques and fibrillary tangles were discovered a hundred years earlier but the mechanisms of the neuronal degeneration, network disintegration, cognitive collapse and neuroimaging of the living brain made our clinical work more interesting and more incisive. Anticholinesterase medications came into the market and each of us cultivated the unconfessable certainty that a cure for the disease was soon arriving. After twenty and more

years of hope, of regenerated diagnostic criteria, of detailed guidelines, and of countless money investment in drug research, we must admit that a cure is not available. Biomarkers were emphasized in the living persons, which allowed us to make a step forward in understanding the early stages of the disease. However, we begin to understand that this "endemic" diagnosis is maybe the result of an increased survival of our society and the most "civilized " western (so far) populations. Centuries ago mortality reached astronomical numbers in the mid-ages: wars, pestilences, famines, childhood mortality, absence of surgical intervention, un-diagnosed diseases, etc. In current era childhood mortality is reduced significantly, youngsters survive even to the most dangerous and severe traumatic injury, surgical advancement has become impressive, late stage mortality due to vascular, inflammatory, neoplastic diseases have reached minimal terms. Survival is the norm. In the aging brain consequently neurodegeneration is a common finding and a frequent diagnosis. Neurodegeneration though is not synonymous of Alzheimer's disease and one more effort is due: correctly subdividing Alzheimer's disease from non-Alzheimer's pathology.

The last research effort by the group of Jack et al.[10] is in this direction. Now we need to get the most out of this "biomarkers' driven methodological diagnostic process". All the risk factors previously mentioned need to be explored and properly investigated, starting from the day of birth. Epigenetic factors are very crucial "starting" mechanisms of cognitive decline and dementing process[1]. However these environmental, life-related events and comorbidity causes may "trigger" and amplify what is already taking place, which is chronic inflammation, neurodegeneration and network disintegration of our once efficient brain.

The final last comment, from a clinical point of view remains the same: why do we make such refined taxonomies and diagnostic procedures to separate Alzheimer's from non-Alzheimer's pathology, if there is yet no medication available and there is no immediate future hope for any treatment of this *endemic result of "survival of the species"*?

*To posterity the arduous sentence, said the poet. Or, "Posterity will judge"*.

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