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Alzheimer's Disease: Definition, Contexts, Neural Correlates, Strategies and Clinical Approaches

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Abstract

Starting from the definition analysis of Alzheimer's disease, we proceeded to study the clinical, psychological and socio-environmental context, to better analyze the intrinsic and extrinsic aspects of this chronic progressive neurodegenerative pathology. The present contribution focuses in particular on all the most significant elements, also from an etiological and neurobiological point of view, in order to present the best therapies and treatments known today in medical and neuropsychotherapeutic profiles.

Keywords: Neurology; Neuroscience; Alzheimer; Alzheimer's Disease; Dopamine

Definition and Clinical Contexts of Alzheimer's Disease

Historical profile

Alzheimer's disease is the most common form of progressive and debilitating degenerative dementia, with onset mainly in presenile age (over 65 years) and classified in Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as one of the classified neurocognitive disorders [1].

In 1901, Dr. Alois Alzheimer, a German psychiatrist, identified the main symptoms of this disease in a 51-year-old woman named Auguste Deter (1850-1906). Questioning her patient, the lady could not remember the objects seen a short time before: this condition, first identified by the same doctor as "writing amnesia disorder", was then reclassified, also thanks to the contributions of the young Italian doctor Gaetano Perusini, who was commissioned by Alzheimer himself to collect information and data on similar cases. The description of the cases was so accurate as to investigate the clinical aspects with different hand drawings, then published in 1910, in the journal ("Histologische und histopathologic Arbeiten über die Grosshirnrinde"-Histological and histopathological studies on the cerebral cortex), even if the name the Italian doctor was omitted. In the following years, eleven other similar cases were recorded in scientific literature, so as to be inserted by the German psychiatrist Emil Kraepelin in his book "Manual of Psychiatry", in the same year of the publication, with the words "Alzheimer's disease", or "Presenile dementia" [2].

The etiopathological profile

The cause, in most cases of Alzheimer's, is still mostly unknown, except for a small percentage, less than 5, where the origin appears to be genetic.

Several hypotheses try to explain the cause of the disease, but without reaching a definitive and exhaustive conclusion:

The genetic cause: The genetic heritability of Alzheimer's disease, based on twin and family studies, includes 49% to 79% of cases [3]. About 0.1% of cases are autosomal familial forms (not related to sexual chromosomes), with dominant inheritance, which have an onset before the age of 65 [4]. This form of the disease is known as "Juvenile Alzheimer's" [5]; most of these cases, transmissible as autosomal dominant Mendelian characters, can be attributed to mutations in one of the three genes: gene encoding the Amyloid Precursor Protein (APP 1) the genes coding for Presenilins 1 (PS-1) and 2 (PS-2). Most mutations in the APP [6] and PS 1 and two genes increase the production of a small protein called Aβ42 [7], which is the main component of senile amyloid plaques. Some of the mutations alter the relationship between Aβ42 and other major firms such as Aβ40 (non-pathological) without increasing Aβ42 levels. This suggests that presenilin mutations can cause disease even if the total amount of Aβ produced is lower. There are also variants of the APP gene that are protective. Most cases of Alzheimer's disease do not have an autosomal dominant inheritance and are referred to as sporadic AD, where environmental and genetic differences can act as risk factors. The best known genetic risk factor is the inheritance of the ε4 allele of

Apolipoprotein E (APO-E) [8]. Between 40 and 80% of people with the disease are in possession of at least one APOEε4 allele [9]. The APOEε4 allele increases the risk of the disease three times in heterozygotes and 15 times in homozygotes. Like many human diseases, environmental effects and genetic modifiers cause incomplete penetrance. In the first screening attempts, about 400 genes associated with sporadic AD with late-onset (LOAD) were recognized; this resulted in a low screening yield. More recent Genome-Wide Association Studies (GWAS) have found 19 areas in genes that appear to be associated with risk. These genes are [10-12]: CASS4, CELF1, FERMT2, HLA-DRB5, INPP5D, MEF2C, NME8, PTK2B, SORL1, ZCWPW1, SlC24A4, CLU, PICALM, CR1, BIN1, MS4A, ABCA7, EPHA1, CD2AP and after BA1-42/1-40 [13]. Mutations in the TREM2 gene have been associated with a 3 to 5 time's higher risk of developing Alzheimer's disease [14,15].

Amyloid plaques: The disease is notoriously due to the widespread destruction of neurons, mainly attributed to beta-amyloid, a protein that, depositing itself between neurons, acts as a sort of glue, absorbing "Neurofibrillary" plaques and tangles [16]. The disease is also accompanied by a sharp decrease in acetylcholine in the brain, a neurotransmitter (or a fundamental molecule for communication between neurons, and therefore for memory and any other intellectual faculty). The consequence of these cerebral modifications is the impossibility for the neuron to transmit the nerve impulses and therefore the death of the same, with consequent progressive atrophy of the brain as a whole. On a macroscopic neurological level, the disease is characterized by a decrease in the weight and volume of the brain, due to cortical atrophy, also visible in a widening of the furrows and corresponding flattening of the convolutions. At the microscopic and cellular level, neuronal depletion, senile plaques (also called amyloid plaques), neurofibrillary clusters, congophilic angiopathy (amyloid) are found [17]. From the post-mortem analysis of brain tissues of Alzheimer's patients (only at this time can the clinical diagnosis be confirmed from an anatomopathological point of view), an extracellular accumulation of a protein, called beta-amyloid. The Amyloid precursor protein/Amyloid Progenitor Protein (APP) that is produced is degraded during the transport process on the cell surface (APP degradation process) and involves three enzymes that operate proteolytic cuts: α-secretase and β-secretase at first and then γ-secretase. Through two successive cuts operated first by α-secretase and then by γ-secretase, a harmless peptide called p3 is produced. The β-secretase operates a different cut that, following the subsequent cutting by γ-secretase, leads to the production (amyloidogenic pathway) of two peptides of 40 and 42 amino acids, called beta-amyloid (Aβ40 and Aβ42): the second (Aβ42) is considered the most toxic at the neuronal level. In healthy subjects, the degradation process of the APP appears to be operated mainly by α-secretase. For reasons not fully clarified, in the sick subjects, the enzyme that intervenes on the APP is not α-secretase but β-secretase, with a large production of beta-amyloid protein. This β-amyloid does not have the biological characteristics of the natural form, but has even a toxic effect on the neuron; this is already in itself an atypical aspect for an amyloid pathology, in which generally the damage is mediated by cytolysis, compressive and trophic aspects given by the fibrillar deposit itself (the amyloid fragment is generally inert from a functional pathophysiological point of view). At the death of the neuron (due, in the early stages, to the aforementioned toxic effect) the amyloid fragments are released into the extracellular space, tending to deposit themselves in insoluble fibrillar aggregates, gradually getting larger, forming the so-called amyloid plaques, detectable on examination histological. These neuronal plaques trigger a reactive inflammatory process mediated by astrocytes and microglia, activating an immune response by recalling macrophages and neutrophils, which will produce cytokines, interleukins and TNF-α that irreversibly damage neurons [18]. Recent research, however, would highlight the failures of clinical trials in the anti-amyloid antibody space: the drugs tested, such as bapinuzumab, aducanumab, AC-1204 and lilyopirdine, would have been ineffective to eliminate amyloid plaques. The research on this hypothesis, for now, is firm or otherwise oriented elsewhere.

Tau proteins: In the wake of the aforementioned failures, further studies point out that in Alzheimer's patients, a further pathological mechanism intervenes: within the neurons, a Tau Protein, anomalously phosphorylated, accumulates in the so-called "neurofibrillary aggregates" (or neurofibrillary clusters). Particularly affected by this pathological process are cholinergic neurons, especially those of the cortical, subcortical areas and, among the latter, the hippocampal areas. In particular, the hippocampus is the anencephalic structure that plays a fundamental role in learning and memorizing processes; therefore the destruction of the neurons of these areas is considered to be the leading cause of the patients' memory loss [19].

Non-Ceruloplasmin plasmatic copper: Always recent hypotheses assume the association of the early onset of the disease with the presence of non-ceruloplasmin copper in the blood. The anomaly in the levels of copper in fact, detected in time, also helps to better identify those pre-symptomatic cases (the so-called Mild Cognitive Impairment=MCI) that have a high risk of developing the disease in the following 5-6 years [20]. Always recently, the Canox4drug company, in collaboration with the AFaR, has developed C4D, an innovative test capable of measuring the quantity of Non-ceruloplasminic copper in circulation with rapidity, very high precision and repeatability. On this hypothesis, however, the research is still embryonic, even if it has been talked about for over five years, and has not been published with definitive evidence.

Herpes-Virus: A published study has shown the involvement of two viruses of the herpes virus family (HHV-6A and HHV-7). Specifically, the genes of the two viruses can interact with the gene networks of neurons, altering their metabolism and favouring the development of amyloid plaques and tangles of Tau proteins [21].

Dopaminergic hypothesis: Another hypothesis, Italian, indicates how potential causes the death of neurons in the ventral tegmental area responsible for the production of dopamine. In the early stages of the disease, the end of dopaminergic neurons is recorded in the ventral tegmental area of the brain: this generates deficiency of the neurotransmitter in the hippocampus, thus leading to the typical symptoms of memory loss [22].

The epidemiological profile

Alzheimer's disease can be defined as a degenerative process that progressively affects the brain cells, gradually rendering the individual who is suffering from it incapable of healthy life and eventually causing death. Recent estimates speak of about 30 million people suffering from this pathology [23], although the estimates are certainly underestimated.

At the epidemiological level, except in rare "early-onset" family genetic forms (i.e. with juvenile-onset), the factor most closely related to the incidence of the disease is age. The incidence of Alzheimer's varies according to the presence of a genetic and demographic risk factor such as APOE, sex and race. In Europe, it is estimated that Alzheimer's dementia represents 54% of all dementias with a prevalence in the over-65 population of 4.4%. The prevalence of this pathology increases with age and is higher in women, who have values

ranging from 0.7% for the age group 65-69 years to 23.6% for women over 90, compared to men whose costs vary respectively from 0.6% to 17.6%. The incidence rates for AD, observed in Europe, indicate an increase in males from 0.9 cases per 1,000 person-years in the age group between 65 and 69 years to 20 cases in those with age greater than 90 years; in women, however, the increase varies from 2.2 in the age group between 65 and 69 to 69.7 cases per 1,000 person-years in that> 90 years [23].

The clinical and symptomatic profile

The course of the disease can be different, in the times and in the symptomatological modalities, for each individual patient; however, there are a series of common symptoms that are frequently associated in the various phases with which, clinically, and the course of the disease is divided by convention. The course of the disease is divided into 4 phases, with a progressive model of cognitive and functional deterioration:

Pre-dementia: The first symptoms are often subtle and wrongly attributed to ageing or stress. In fact, detailed neuropsychological tests can reveal mild cognitive difficulties up to eight years before a person meets the clinical criteria for diagnosis without manifesting the classic symptom clearly [24,25]. The first symptoms can affect many activities of daily living, such as the difficulty in remembering the facts learned recently and the inability to acquire new information [26-28]. Small problems of attention, of planning actions, of abstract thought, or problems with semantic memory, as well as apathy, are recorded in this phase, while depressive symptoms, irritability and poor awareness of memory difficulties are prevalent [29]. This pre-clinical phase of the disease, also called "Mild Cognitive Impairment" (MCI) is therefore characterized by occasional forgetfulness, distractions, erroneous placement of objects of common use, apathy and attention deficit [30,31].

Initial phase: In this phase, the patient begins to suffer from a significant decrease in the ability to coordinate muscles for small movements, such as weaving; then the impairment linked to memory and learning continues, up to a beginning, albeit sketchy and not in all cases of difficulty in language, spatial processing capacity, perception (agnosia) and execution of complex movements (apraxia) [31,32]. Old memories of personal life (episodic memory), the notions learned (semantic memory), and implicit memory (the body's memory of how to do things, such as using a fork to eat) is instead less affected than to concepts learned recently [33,34]. The linguistic problems are characterized mainly by an impoverishment in the vocabulary and a decrease in fluency, which lead to a general impoverishment of oral and written language [35].

Intermediate phase: The progress of the AD hinders independence in the subjects, who are slowly no longer able to perform daily activities [1]. The linguistic difficulties become evident due to aphasia, which frequently leads to replacing words with others that are wrong in the context (paraphasias). Reading and writing are slowly abandoned [16]. Complex motor sequences become less coordinated with time and increase the risk of falls. At this stage, memory problems worsen, and the person may not recognize close relatives [17]. Long-term memory, which was previously intact, becomes compromised. Behavioural and neuropsychiatric changes become more evident. One can pass quickly from irritability to crying; rages of anger or resistance to the "caregiver" are not rare. The subjects also lose awareness of their illness and the limits that it entails (anosognosia). Urinary incontinence may develop [18].

Final phase: During the final stages, the patient is completely dependent on the "caregiver" [1]. The language is reduced to simple sentences or words, even single ones, eventually leading to the complete loss of the word [16]. Despite the loss of verbal language skills, some people can often still understand and return emotional signals. Although aggression can still be present, apathy and fatigue are the most common symptoms [17]. People with Alzheimer's disease will eventually not be able to perform even the simplest tasks independently; muscle mass and mobility deteriorate to the point where they are bedridden and unable to feed themselves. The cause of death is usually an external factor, such as trauma, infection or pneumonia [18].

The differential diagnosis

From recent and less recent estimates it is becoming increasingly clear that among dementias, vasculopathy diseases cover 15%, Parkinson's and Lewy bodies 12%, other dementias 8%, while Alzheimer's is as high as 65%. All involve cognitive and behavioural deficits, as well as impairments of functional abilities. However, each of them has specific characteristics, and only the comparison between history, family history, nuclear and genetic radiological investigations can clarify the mystery [16].

From the first symptoms, more or less visible, the severe decline, with serious functional impairment, occurs within the first decade (except for rare exceptions that arrive until the middle of the second decade), with the appearance of a slightly varied constellation of symptoms: psychomotor agitation, agnosia, hallucinations, myoclonus, epileptic seizures. On neuromotor examination, the patient manifests slow gait, bright ROT and supraspinal and extrapyramidal signs. Death occurs within the next 6-18 months [36].

In frontotemporal dementia, the first significant clinical signs concern the absence of awareness, personality changes, emotional flattening, disinhibition, reduction of judgment and critical capacity of logical reasoning, the presence of stereotyped behaviors, reduction of verbal initiative or hyperorality, echolalia and palilalia, with irritability, early incontinence and forgetfulness of everyday objects (eg phone, home keys) [37].

In hypoxic vasculopathy, the subject is more irritable, nervous, argumentative, often suffers from memory lapses associated with daily activities, complains of sleep disorders and the absence of peaceful and balanced rest. It presents a frequent and involuntary use of the acting out mechanism. An unknown parameter can also relate to the site of damage: cortical or subcortical [38].

It is challenging to distinguish Alzheimer's disease from other dementias. Some assessment tools (e.g., Hachinski Ischemic Score, modified Hachinski Scale) may be helpful in distinguishing vascular dementia from Alzheimer's disease. Fluctuations in the cognitive state, parkinsonian signs and symptoms, well-structured visual hallucinations and relative short-term memory conservation are indicative of dementia with Lewy bodies rather than Alzheimer's disease [39] (Table 1).

The Neural Correlates in Alzheimer's Disease

The specific mechanisms of Alzheimer's disease include pathological agglomerates, in the brain tissue, of two types of proteins: beta-amyloid, which accumulates in plaques, and tau, which forms the so-called neuro-fibrillar tangles. It is not clear whether their accumulation is one of the causes, or rather the effect, of this condition, but for many researchers, the action of these waste substances is at the basis of the loss of nerve cells and therefore of the decline of typical cognitive

Table 1: The differential diagnosis.

Disease	First Symptom	Mental Status	Neuropsychiatry	Neurology	Imaging
AD	Memory loss	Episodic memory loss	Initially normal	Initially normal	Entorhinal cortex and hippocampal atrophy
FTD	Apathy; Poor judgment/ insight, speech/language; hyperorality	Frontal/executive, language; spares drawing	Apathy disinhibition, hyperorality, euphorbia, depression	May have vertical gaze palsy, axial rigidity, dystonia, alien hand, or MND	Frontal, insular, and/or temporal atrophy; spares posterior parietal lobe
LBD	Visual hallucinations, REM sleep disorder, delirium, capgra's syndrome, parkinsonism	Drawing and frontal/ executive, Spares memory, delirium prone	Visual hallucinations, depression, sleep disorder, delusions	Parkinsonism	Posterior parietal atrophy, hippocampi lager than in AD
CJD	Dementia, mood, anxiety, movement disorders	Drawing and frontal/ executive focal cortical memory	Depression, anxiety	Myoclonus, rigidity, parkinsonism	Cortical ribbing and basal ganglia or thalamus hyper intensity on diffusion/FLAIR MRI
Vascular	Often but not always sudden; variable; apathy, falls, focal weakness	Frontal/executive, cognitive slowing; can spare memory	Apathy, delusions, anxiety	Usually motor slowing, spasticity; can be normal	Cortical and/or sub cortical infractions, confluent white matter disease

Abbreviations: AD: Alzheimer's Disease; CBD: Basal Cortical Degeneration; CJD: Creutzfeldt-Jakob disease; DLB: Lewy Body Dementia; FTD: Frontotemporal Dementia; MND: Motor Neuron Disease; PSP: Progressive Supranuclear Palsy.

functions of the disease. However, in all patients the presence of these protein structures is not associated with the symptoms of dementia: amyloid plaques have also been found in the brains of "super-agers", adults who arrived at 90 with the memory of a fifty-year-old. A recent study showed that a mix of 15 proteins (including the antagonist of Apolipoprotein - ApoE) could protect synapses, such as a chemical shield, from tau and beta-amyloid damage [40].

Diagnosis and Clinical Strategies for The Management of The Pathological Conditions

Diagnosis

Alzheimer's disease is usually clinically diagnosed by the patient's history, clinical observations, the presence of particular neurological and neuropsychological features and the absence of alternative conditions [41,42]. Advanced biomedical imaging systems, such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Single-Photon Emission Tomography (SPECT) or Positron Emission Tomography (cerebral PET) may be used to help rule out other brain diseases or other types of dementia [43]. Furthermore, it is possible to predict the transition from prodromal phases (mild cognitive impairment) to Alzheimer's disease [43,44].

Neuropsychological and cognitive assessments, including memory and executive tests, can further characterize the state of the disease. Several medical organizations have established diagnostic criteria to facilitate and standardize the diagnostic process. The clinical diagnosis is confirmed on a pathological level only by histological analysis of the post-mortem brain [45].

Several neuropsychological screening tests are used for diagnosis in Alzheimer's cases. The tests evaluate different cognitive functions and skills, such as knowing how to copy drawings similar to those shown in the photo, remembering words, reading and subtracting numbers in series. Neuropsychological tests, such as the Mini-Mental State Examination (MMSE), are widely used to assess the cognitive disorders that are considered for the formulation of the diagnosis. However, a full test battery is required to ensure maximum reliability of the results, particularly in the early stages of the disease [46,47].

Another objective indicator of the early stages of the disease is the analysis of cerebrospinal fluid for the search for beta-amyloid or tau proteins. The search for these proteins is able to predict the onset of Alzheimer's disease with a sensitivity between 94% and 100% [48]. Again, perfusion brain SPECT and Positron Emission Tomography (PET) can be used to confirm an Alzheimer's diagnosis in association with mental status assessments.

SPECT seems to be a still superior method of PET, precisely in differentiating Alzheimer's disease from other possible causes, always with respect to the analysis of family history and the observation of the patient [49,50]. A new technique known as PiB-PET was then developed to directly and clearly visualize images of beta-amyloid deposits *in vivo*, using a radiotracer that selectively binds to A-beta deposits. PiB-PET uses carbon-11 for PET scanning [49,51]. Recent studies suggest that PiB-PET is 86% accurate in predicting which people, already suffering from mild cognitive impairment, will develop Alzheimer's disease within two years, and 92% able to rule out the likelihood of developing the disease, Alzheimer [52-55]. Furthermore, a radiopharmaceutical for PET called (E) -4- (2- (6- (2- (2- (2 - (18F) -fluoroethoxy) ethoxy) ethoxy) pyridine-3-yl) vinyl) -N- methyl benzenamine, or 18F AV-45, or florbetapir-fluorine-18, or simply florbetapir, containing the most durable fluoride-18 radionuclide, has been recently developed and tested as a possible diagnostic support in Alzheimer's disease, binds to beta-amyloid, but thanks to the use of fluorine-18 has a half-life of 110 minutes, compared to the radioactive half-life PiB which is 20 minutes, the longer duration allows to accumulate more tracer in the brain of people with Alzheimer's disease, particularly in regions known to be associated with beta-amyloid deposits. Finally, volumetric magnetic resonance can detect changes in the size of brain regions: the atrophy of these regions is showing how a diagnostic indicator of the disease [56-60].

Therapies and clinical strategies

Although there is currently no effective cure, various therapeutic strategies have been proposed to attempt to positively influence the chronic and progressive course of Alzheimer's disease; these strategies aim at pharmacologically modulating some of the underlying

pathological mechanisms. However, it is always advisable to integrate the various interventions proposed in order to have full and satisfactory effectiveness.

Pharmacological intervention: First, based on the fact that in Alzheimer's, there is a decrease in the levels of acetylcholine, a therapeutic hypothesis has been to try to restore its physiological levels. However, pure acetylcholine cannot be used as it is too unstable and has a limited effect. Cholinergic agonists, on the other hand, would have systemic effects and produce too many side effects and are therefore not usable. Instead, it is possible to use cholinesterase inhibitors or the enzyme that catabolizes acetylcholine: by inhibiting this enzyme, the amount of acetylcholine present in the intersynaptic space is increased [61]. Reversible drugs of acetylcholinesterase are available, which have a low affinity for the enzyme present in the periphery, and which are sufficiently lipophilic to overcome the Blood-Brain Barrier (BBB), and therefore preferably act on the central nervous system. Among these, tacrine, donepezil, physostigmine, galantamine and neostigmine were the founders, but the pharmacological interest is currently more concentrated on rivastigmine and galantamine, the former because it has no important drug interactions, the latter because it is very bioavailable and with a half-life of only seven hours, such as not to cause side effects easily. Another recent discovery concerns the use of drugs that act directly on the glutamatergic system, such as memantine; the therapeutic use of this NMDA receptor antagonist has shown a moderate but positive therapeutic activity in the partial reduction of cognitive deterioration in patients with moderate to severe Alzheimer's disease. Tacrine is no longer used instead because it is hepatotoxic, whereas donepezil, a non-competitive acetylcholinesterase inhibitor, would seem more effective because, with a half-life of about 70 hours, it allows only one administration a day (as opposed to galantamine, which has a half-life of only 7 hours). Obviously, however, donepezil is more prone to manifest side effects due to an increase in cholinergic tone (such as insomnia, arrhythmias, bradycardia, nausea, diarrhoea). In contrast, galantamine and rivastigmine can cause the same effects, but to a much lesser extent [62].

Psychosocial and cognitive intervention: The non-pharmacological forms of treatment consist mainly of behavioural interventions, psychosocial support and cognitive training [63]. These measures are usually supplemented in a complementary manner with pharmacological treatment and have shown their positive effects on the overall clinical management of the patient [64]. The neuropsychological evaluation uses a battery of tests for measuring the cognitive framework and the status of the main cognitive functions [65]. The first test that is administered is, generally, the Mini-Mental State Examination, a test that, in a few minutes, can give interesting diagnostic information on the cognitive state of the patient [66]. Through the MMSE, it is possible to evaluate the spatial and temporal orientation of the patient, the cognitive level, the praxis, mnestic, graphic functions; the MMSE is, therefore, an important starting point [67]. Neuropsychological screening includes a series of tests aimed at evaluating various functions: short-term memory (of figures, words, sentences), long-term memory (voluntary and incidental), attentional functions, verbal functions, perceptive and praxis functions, general cognitive functions [68]. The presence of space-time disorientation, memory deficit, acalculia, anomie or agnosia (especially for animated objects) makes the clinical picture compatible with the diagnosis of dementia of the Alzheimer type [69]. Cognitive training (e.g. Reality-Orientation Therapy, Validation Therapy, Reminiscence Therapy, various cognitive stimulation programs-Cognitive Stimulation Therapy, etc.), have shown positive results both in the stimulation and reinforcement of neurocognitive abilities and in the improvement of the performing daily life tasks. The different types of cognitive intervention (e.g. Cognitive Stimulation Therapy) and behavioral (Gentlecare, motor activity programs), as well as social and emotional-motivational (e.g. Reminiscence Therapy, Validation Therapy, etc.), instead, pose 'emphasis on slowing the decline by working on the psychic and environmental sphere of the subject suffering from the pathology: this is because working on the functions means favouring rehabilitation if they have been lost or compromised. Specific forms of music therapy and art therapy, implemented by qualified personnel, can be used to support mood and socialization in the intermediate-advanced stages of the pathology, based on non-verbal communication channels. The effect of moderate physical and motor activity seems to be positive, especially in the intermediate phases of the disease, on mood, on physical well-being and on the regularization of behavioural, sleep and eating disorders, through the use of vitamin E and B12, folate, zinc, Omega 3-6-9 and a food style based on the Mediterranean and/or oriental Japanese diet, excluding seasoned meats and cheeses (rich by their nature of Advanced Glycation End-products-AGEs, products of an aberrant glycosylation of proteins capable of producing inflammation, vascular damage, neuronal and oxidative stress). Therefore, a food style rich in cereals, fruit and vegetables [70-73].

Recent Discoveries, Future Perspectives and Conclusions

Although today no evidence emerges of the existence of a definitive therapy that treats the pathologies, recent discoveries are oriented towards this direction, in the hope of finding the mechanism that restores the lost functionalities [74].

From Oslo comes the miraculous pill that should clean up the damage caused by mitophagy, a process that recycles the defective mitochondria (the power plant of the cell), while from Toronto comes the pill that can slow down the devastating effects of Alzheimer's, facilitating memory processes (precisely because it is a benzodiazepine derivative with a specific Gaba target on the hippocampus) and also acting on depression and schizophrenia. However, again, these pharmacological products have only been tested on animals, albeit with exciting results. Another study, this time American, of the University of Virginia, focused on the "genetic mosaic", in order to explain why the first neurons to die would be those of the temporal lobe: a selective vulnerability that according to researchers seems to be of the genetic matrix. Finally, an American and Israeli genetic study that would focus attention on the need to intervene in the ApoE4 gene, responsible for 60% of Alzheimer's cases [75].

Still on the subject of ApoE4, two recent very interesting researches expand the knowledge on the subject.

- The first research [76] addresses the problem of the correlation between the absorption of glucose in specific brain areas and Alzheimer's starting from the assumption by now in the literature that the presence of the ApoE ε4 allele is a known risk factor for Mild Cognitive Impairment (MCI) and Alzheimer's disease. In the present study, the researchers showed that the frontal, parietal, lateral temporal, medial temporal, caudate, thalamus, post-cingulate and amygdala region had a more significant longitudinal reduction in glucose uptake in ApoE ε4 carriers compared to non-carriers of the allele. Similar results also in the cerebellum and limbic areas. This finding, therefore, suggests that the ApoE Îµ4 genotype is associated with a longitudinal decline in glucose uptake in 8 brain regions.

- The second research [77], instead, focuses on the correlation with respect to sex, confirming that the most influential genetic risk

factor for Alzheimer's Disease (AD) is the Apolipoprotein type 4 allele (ApoE ε4) and demonstrating that women are more sensitive to the accumulation of neurofibrillary tangles and both CSF tau (p-tau, t-tau) and brain PET tau are stable quantitative biomarkers for the ApoE ε4 study based on sexual effects on brain tau deposition in MCI participants.

A further fascinating study hypothesis is to consider the possibility of re-proposing the use of computational drugs. This is because the computational resetting of drugs has the ability to significantly reduce the time and cost of drug development in an era when these factors are prohibitively high; there are numerous examples of drugs successfully re-proposed in pathologies such as neoplastic, infectious, autoimmune and endocrinological diseases; however, the carry-over of computational drugs in neurodegenerative disease has presented several unique challenges arising from the lack of validation methods and difficulties in the study of heterogeneous ageing diseases [78].

In the writer's opinion, such a hypothesis I fear should be discarded entirely, directing the investigation more on the preventive profiles than on the restoring ones: the central element should be the need to keep the psycho-physical apparatus in good condition and not remedy decades of food errors and behavior. Admittedly, finding the drug able to remedy the damage is the general expectation; however, more attention to preventive medicine would be most desirable.

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