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Review

Alzheimer's disease, autoimmunity and inflammation. The good, the bad and the ugly

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ABSTRACT

Alzheimer's disease (AD) has been recognized as the most common cause of sporadic dementia. It represents both a medical and social problem, as it affects 10% of over-65 population. Even if the elderly are the most involved population, aging alone cannot be considered as the only cause of this disease. In this review we wanted to focus on the last hypotheses on the possible causes of this neuronal affection. We focused in particular on the role of inflammation and alteration of the inflammatory status that is typical of the elderly and may lead to chronic inflammation. The inflammation seems to be a cause of neuronal impairment and loss. Some studies have proposed a protective role of antiinflammatory drugs. Then we analyzed the role of genetic polymorphisms of some pro-inflammatory substances that seem to be linked to some cases of dementia. The complement system seems to have a role too, as some factors have been found in senile plaques, representing a possible involvement of classical complement pathway. One of the latest hypotheses is about the role of blood–brain barrier (BBB), as its loss of integrity may lead to a passage of proteins in cerebro spinal fluid (CSF), causing a compromised role of BBB in preserving the brain as an "immune sanctuary".

Contents

1. Introduction

Dementia is a term used to describe various different brain disorders that have in common a loss of brain function that is usually progressive and eventually severe. It can also be considered as a paradigm of lot of situations common in an elderly patient with

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polypathology and different degrees of disability. Alzheimer's Disease (AD) has been recognized as the most common cause of sporadic dementia, involving about 13 million people worldwide. It is the most common cause of cognitive decline in the elderly, as it affects nearly 10% of over-65 population and, if combined with other diseases, represents more than 50% of all demented patients. The neuropathology of AD is characterized from neurofibrillary tangles, senile plaques and neuron and synapse loss: all these alterations are normally present in normal brain aging, but in AD they are more severe and at the beginning the degeneration involves specific regions of the cerebral cortex (hippocampus, entorhinal and temporoparietal cortex) [1]. A lot of hypotheses have been formulated to explain its ethiopathology, but we are still working looking for an explanation of the variety of phenomena involved in AD [2]. Even if the elderly are the most involved population, maybe because of increasing risk of cardiovascular and cerebrovascular problems, aging alone cannot be considered as the only cause of this disease. Because of the increasing number of involved patients and the impact on population and everyday life, hypotheses and experimentation are developing, looking for new theories and therapies [1].

During the last 10 years a new theory proposed the autoimmune mechanism as a trigger for this disease: the most important structures and molecules involved are blood–brain barrier (BBB), neurons, microglia and astrocytes, IL-1, IL-6, IL-10 [3], and CD14 [4]. In this review we will consider the new acquisition regarding these hypotheses, with particular regard to the link between different studies [5,6].

2. Aging and immune status

Aging is associated with a sort of paradox: a state of increased autoimmunity and inflammation coexistent with a state of immunodeficiency [7–11]. This can be explained with a decline in T-cell function and number of CD8+ naïve, and an increased TNF-α and CD8+ memory because of a different sensibility toward apoptosis. In fact, TNF-α action is stronger on CD8+, causing apoptosis and the consequent storage of cellular debris, increasing the inflammatory state. The same thing happens in other "life-shortening diseases", e.g. Systemic Lupus Erythematosus, in which CD4 cells show a shortening of G0–G1 transition time [12] and the decrease of viable progeny. A weaker inflammatory response has been associated with a longer survival and a slower decline [13]. This process has recently been renamed as "inflammaging": this is a chronic, low-grade inflammatory state [14–16]. Another proposal about the role of T-cells is related to their chronic stimulation by persistent antigen, as CMV one. This persistent stimulation can cause a damage that can lead to neurotoxicity [1,17–19].

3. The proinflammatory status in aging and role of non-steroidal anti-inflammatory drugs (NSAIDs)

The theory about the involvement of a dysregulation in immune response in AD pathogenesis has been widely demonstrated. Even if it is still unclear whether the inflammatory processes are a primary or a subsequent event, it's clear that flogistic process has an important role in disease development [20,21]. As some studies have noticed, inflammaging in the elderly is a low-grade one, controlled and asymptomatic, chronic and systemic, and it can constitute a major determinant of frailty and age-associated diseases [22–24].

Lots of epidemiological studies have demonstrated that, in patients treated with NSAIDs, the incidence of dementia and age-related cognitive decline was lower [25]. Though the pre-treatment with NSAIDs has shown an in vivo decreasing of inflammatory markers, it has also been noticed that Cyclo-oxygenase-2 (target of NSAIDs) was reduced in the cerebrospinal fluid of end-stage AD patients [25]. Patients affected by autoimmune diseases, such as rheumatoid disease, undergo on long-term anti-inflammatory therapy and have a lower prevalence of AD [25]. So, pro-inflammatory molecules have a fundamental role in inducing neurodegeneration, which causes cognitive decline, memory loss, and dementia. Those findings can also lead to hypothesize a role for immunotherapy both as for prevention and therapeutic strategy. Despite of good outcomes in murine model, trials of patients did not lead to the same encouraging results. Nowadays, one of the most promising ways is using peripheral amyloid beta (Aβ) hydrolysis to induce the same in brain, but further experimentation is needed [26].

Some studies have revealed also typical histopathological findings in AD patient's brain, as reactive astrogliosis. Because of flogistic setting, microglia is activated and produces substances that are toxic to neurons bystanders [27–29]. There is also an age-related failure of elimination of Aβ by perivascular lymphatic drainage [30]. Astrocytes has a fundamental role in preventing and reduce spreading of inflammation as they can remove Aβ plaques, so this is the cause of the typical astrogliosis we can see in brain of AD patients.

4. The role of polymorphisms

Some pro-inflammatory substances, like interleukin-1 (IL-1) [29–33], interleukin-6 (IL-6), interleukin-10 (IL-10), alpha-1-antichimotrypsin (α1-ACT), apolipoprotein-E (Apo-E), 3-hydroxy-3-methylglutaryl-Coenzyme A reductase (HMGCR), vascular endothelial growth factor (VEGF) can present peculiar polymorphisms that have been studied and related to clinic and development of dementia [34].

4.1. Interleukin-1beta: the −511 C-T polymorphism

Interleukin-1 gene is situated on chromosome 2, where there are genes codifying for IL-1beta (IL-1B), IL-1alpha (IL-1A) [31] and for their receptor. IL-1 has various activities, as it is involved in the activation of the immune response and inflammation. Il-1B is released in blood circulation and can induce fever, sleeping, anorexia and hypotension. In central nervous system (CNS) is an important mediator of brain immune response and an inappropriate expression of the gene could cause different type of dysfunction. It can activate endothelium, promoting an up-regulation of various factors involved in amplification of inflammation and can alter BEE permeability (see Section 5). In AD, IL-1B is expressed by activated microglia surroundings plaques and it seems to promote production and metabolism of amyloid precursor protein (APP), increasing amyloid deposition and plaques formation. Different studies focused on polymorphism of the IL-1B promoter, a substitution of cytosine with thymine in position −511: this polymorphism has been studied in a wide Italian population affected by AD and in a control group of non-demented subjects, and the TT genotype has been associated with an increased risk of developing AD. Another fact to notice is that IL-1 soluble receptors (sIL-1 R type II) are increased in CSF of AD patients, maybe related to an increased release of IL-1 in a state of chronic inflammation [35,36].

4.2. Interleukin-10 (IL-10): the G-1028A mutation

IL-10 gene is on Chromosome 1 and codifies for the homonymous protein. The role of IL-10 is the inhibition of pro-inflammatory cytokines releasing during flogistic processes. It is produced by T-cells, monocytes and macrophages, and it is also synthesized in central nervous system for limiting flogistic response and helping neuronal survival during infections. The G-1028A mutation is particularly interesting as it involves the promoter of IL-10 gene. An adenine takes place instead of a guanine, and its presence cause a reduction in production and secretion of the IL-10, causing a reduced regulation of inflammation. A particular genotype related to this mutation, the AA one, is related to an increased risk of developing AD and causes a faster decline in affected patients [37].

4.3. α-1-antichimotrypsin (α-1-ACT): the −51 G-T mutation

α-1-ACT gene is on chromosome 14 and codifies for α-1-antichimotrypsin, an enzyme inhibitor [38]. It's one of the most important proteins related to inflammation and it is released by the liver during the early phases of flogistic process. Normally its concentration is low, but it can increase dramatically and really fast. It is also produced by macrophages, endothelial and epithelial cells. The importance in Alzheimer's disease is related to its presence in plaques and debris of amyloid. α-1-ACT is in fact produced by reactive astrocytes surrounding the plaques. α-1-ACT can be detected both in cerebrospinal fluid and in blood samples; the most studied polymorphism, related to the substitution of a guanine with a thymine, shows an increasing production of the mutated molecule by astrocytes and it has been found mostly in AD patient than in the control group. It is often related to a early onset of AD and to a faster cognitive decline, especially in patient with the TT genotype [38].

4.4. Apolipoprotein E (APO-E): different alleles

The APO-E gene is situated on chromosome 19 and codifies for apolipoprotein E, a plasmatic protein involved in cholesterol metabolism and transport; it can bind amyloid protein [39]. APO-E exists in three isoforms (different structural conformation of the same protein), that derives from 3 different allelic forms: Apoε2, Apoε3, Apoε4 from allele ε2, ε3, ε4. These differences derives from the change of a single amino acid in two different positions: variant Cys112Arg and Arg158Cys. In the brain, APO-E is synthesized by astrocytes and is able to transport cholesterol both in the cerebral tissue and in the CSF. When linked to cholesterol, APO-E can bind a neuronal receptor, stimulating the growth of neurites and synapses. In AD, APO-E has been found in senile plaques, in neurofibrillary tangles and in amyloid deposition. It has also been the first genetic risk factor studied, in particular for the Apoε4 variety, that also in heterozygous form is related to an increased risk (three times) of developing AD. It depends on the capacity of Apoε4 of binding stronger amyloidogenic fibrils, causing their faster precipitation and deposition [39].

4.5. Hydroxy-3-methylglutaryl-Coenzyme A reductase (HMGCR): the −911 C-A polymorphism

HMGCR is a gene that codifies for the homonymous protein, an enzyme involved in cholesterol production and also target of statins [40]. Epidemiological studies have noticed an association between statins and risk of developing AD: the rate of AD was lower in patients treated with this drugs and a possible association between high cholesterol in serum and AD developing. This can be related to a polymorphism of the promoter region of the gene in −911 position, with an adenine instead of a cytosine. As noticed for other polymorphisms, −911 C-A has been associated with an increased risk of developing AD in a fast-decline form [40].

4.6. Vascular endothelial growth factor (VEGF): the −2578 C-A polymorphism

The gene for VEGF is on chromosome 6 and codifies for an angiogenic protein [41]. In angiogenesis, endothelial cells are activated by a lack of oxygen, releasing different mediators. VEGF is important in regulation of both physiological and pathological angiogenesis, as it is synthesized also by neoplastic cells. It can increase vascular permeability and releasing of proteases. Recent acquisitions demonstrate how VEGF could be involved in AD development, as an abnormal endothelial activation could cause neuronal loss and amyloid deposition. The VEGF concentration is also higher in cortex of affected brains. On the other hand, some studies have noticed that VEGF could have a protective role as a stimulus for neuronal growth. A promoter polymorphisms (the −2578 C-A one) has been found related to an increased risk of developing AD a to a higher conversion rate from Mild Cognitive Impairment (MCI) to AD [41].

5. New actors: the blood–brain barrier (BBB) and T lymphocytes

Recent acquisitions show the role of BBB as a link between immune system and AD. The brain is an immunologically privileged site (a “sanctuary”) protected and isolated from organism's immune reaction by the BBB, that has the function of blocking the entry of macromolecules, like immunoglobulins (Ig), and cells, included the immunocompetent ones. If the integrity of BBB is compromised by multiple microtrauma, microvascular pathology (as cerebrovascular pathology is often associated to AD) and inflammation, that can increase permeability of BBB, the result is a compromised BBB that can lead to the abolition of the immunological privilege of the CNS. A consequence of this impairment is the anomalous presence of serum proteins in CSF and in brain. Recent acquisition [42] have shown increases of Ig-positive neurons in areas with greater Ig reactivity that are also really involved areas if we consider neuronal loss, degeneration and apoptotic features. This happens because of a binding between serum Ig and auto antigens present on specific neurons, in particular on neurons involved in mnemonic functions. The integrity loss of BBB can also lead to a penetration of circulating Aβ in brain, where it can bind astrocytes, starting a degenerative and inflammatory process. Another link could be the fact that autoantibodies bounded with neurons can start or helping Aβ42 internalization and deposition, increasing brain damage. Aβ42 is also a mitochondrial poison: it impairs electron transport, involving ATP production and membrane potential.

We can now consider T lymphocytes role: normally they are able to pass BBB, but physiologically they are not numerous in normal brain. In AD patients, anyway, their number is increased, especially in hippocampus and temporal cortex. Their migration is followed by an increased expression of MHC I and II, produced by activated microglia, especially in areas showing neuronal degeneration, typical of AD. So we can hypothesize that the link between T-cells and AD “passes” through BBB, meaning that their migration is a result of BBB dysregulation and impairment [43,44].

6. The role of complement

The evidence of a possible role of complement has been proposed since 20 years ago, when complement proteins were detected in senile plaques. Then it became clear that the presence of complement proteins was related to the process of activation of the plaques, as level of complement regulatory proteins are up-regulated in AD. There is also an order of appearance of these proteins: in fact, C1q, C3 and C4 have been detected in early plaques. During recent years, data showed that C1q and C5b-9 were detected in Ig-positive neurons [45,46]; so it can be considered a sign of the presence of an antibody-induced classical complement pathway. As seen above, the passage of proteins through a damaged BBB could be the leading mechanism that is responsible of the binding of antibodies to neurons. This process may lead to the activation of the complement pathway, which became involved in neuronal death.

7. The memory involvement

Another theory [5] proposed for the origins of antigens involved in autoimmune response against brain carries on from protein synthesis that occurs in brain when consolidation of long-term memory takes place. It can depend on the fact that lots of synaptic connections are formed after the acquisition of the immune privilege, so proteins used to establish new connections cannot be recognized as “self” by immune system cells. So, when this cells penetrate the brain because

of a BBB impairment, the meeting with these "unknown" proteins can start the autoimmune response [5].

8. Autoimmunity and inflammation: new actors in AD

According to recent studies, both inflammatory component and autoimmune component must be considered in pathogenesis of AD [47–49]. The importance of autoimmunity involvement is confirmed by the presence of auto antibodies and the apparently good outcome after immunotherapy as seen both in the animal model and in a few patients tested [50]. Also inflammatory aspect has been examined and the presence of a chronic inflammatory status has been found in a large number of patients affected by AD [51–53]. Alterations in biomarkers of inflammation or in cells involved in inflammation (e.g., leukocytes, augmentation of ferritinemia, alterations of complement system, high levels of C-reactive protein and IL-6) are typical findings in patients affected, together with a compromised immune status typical in elderly but worse in affected subjects [20].

The role of inflammation in AD has been extensively studied, even if its consequences are not completely clear [54]. We know that in these patients' brains and CFS contain various pro-inflammatory substances, such as cytokines, acute phase proteins and complement proteins. The level of these pro-inflammatory markers is related to the dimensions of plaques [55]. Microglia has an important role as an immune effector on brain cells; it has a dynamic structure that allows a continuous control on cells nearby in order to recognize any foreign substance that can trigger an immune response [56]. In proximity of plaques, microglia shows more surface proteins, like major histocompatibility complex II (MHC II), and proliferates, maybe helping the removal of plaques. This kind of mechanism, even if useful in order to reduce neurotoxic amyloid, can worsen brain damage, leading to the development of the disease. Neuro-inflammation is a common finding in aging brain, as a higher expression of innate immune receptors [57]; in particular, high levels of CD14 are typical in AD patients [58]. A new target to study is the role of toll-like receptors (TLRs), as recent studies have hypothesized its involvement in microglial activation [59]. We know that its ligands are typically endogenous (e.g., microbial origin), but TLR2 or TLR4 may interact with endogenous substances with a hydrophobic domain such as AD plaques, as a results of hydrophobic aggregates of Aβ42 [60,61]. Future studies have the task to investigate this double-edged sword: in fact, inflammation and immune response act both as defensive mechanism and as another harmful process; so, one of the numerous challenges will be to determine whether the trigger is inflammation or autoimmunity, as their connections are so deep and still not completely clear [62], in order to find a possible new therapeutic target.

9. Conclusions

Numerous hypotheses have been proposed for etiology of Alzheimer's disease. During recent years, the immunological theory has been formulated and developed: in fact, in literature there are a lot of findings regarding this area. We are now aware of new involvements to study, as this disease continues to present new different aspects, involving different systems and physiopathological acquirements. Today, we can hypothesize that the link between AD autoimmune theory and acquired knowledge is that cardiovascular diseases can have a more important role in AD development, as they are considered the cause (maybe the most important one) of BBB damage. So, what we need to know now is how to prevent this event, in order to reduce AD incidence. Anyway, there is still a lack regarding practical application: we know polymorphisms linked to AD but until now we are still not able to use them for early diagnosis and genetic screening diagnosis; we have deep acquisition regarding inflammation as a fundamental mechanism of AD but no way to propose guidelines for prevention using NSAIDs and no useful biomarkers for diagnosis and monitoring disease progression [63].

New therapeutical perspectives are considering the role of natural human antibodies to Aβ peptide [64,65]. While active immunization is now abandoned as it caused serious side effects such as sterile encephalitis, passive immunization seems to be a useful therapeutical goal. Natural antibodies, that are anti-Aβ antibodies present in the serum from healthy humans [66,67], can cause decreased levels of Aβ in cerebrospinal fluid because it is mobilized to blood stream, with an improvement of cognitive performances not only in murine model but also in AD patients, according to recent studies [68–70]. These acquisition confirms the importance of approaching AD as an immune disease, trying to focus on its pathogenesis and not only on its symptoms; at the same time, discoveries regarding an increasing importance of inflammation in pathogenesis and development of the disease can be a new stimulus in finding biomarkers or using known biomarkers of inflammation in studying onset and course of AD.

The hope is that these new acquisitions could lead to new research pathways for drugs and way of prevention and early diagnosis of a disease which is estimated to involve nearly the 10% of over-65 population.

Take-home messages

- Aging is associated with a sort of paradox: a state of increased autoimmunity and inflammation coexistent with a state of immunodeficiency
- The importance of autoimmunity involvement is confirmed by the presence of auto antibodies and the apparently good outcome after immunotherapy as seen both in animal model and in a few patients tested
- The role of inflammation in AD has been extensively demonstrated. We know that AD brain and CFS contain various pro-inflammatory substances, such as cytokines, acute phase proteins and complement proteins.
- Neuro-inflammation is a common finding in aging brain; high levels of CD14 are typical in AD patients
- Natural anti-Aβ antibodies present in the serum from healthy humans can cause decreased levels of Aβ in cerebrospinal fluid because in murine model and in AD patients, according to recent studies
- There is evidence of a possible role of complement in autoimmune pathogenesis of Alzheimer Disease because complement proteins were detected in senile plaques and the level of complement regulatory proteins are up-regulated in AD.

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Anti-cytrulinated proteins antibodies and seropositive arthralgia

Anti-cytrulinated protein antibodies (ACPA) may precede the rheumatoid arthritis onset. In an interesting article, van de Stadt et al. (Ann Rheum Dis 2011;70:128-33) have evaluated the role of these antibodies in 244 patients with arthralgia and positibity for ACPA and/or IgM rheumatoid factor. The authors found that 28% of these patients developed arthritis in a median of 11 months. Patients who were positive for at least two ACPA developed arthritis more commonly. In summary, this study demonstrated that in patients with arthalgia and positivity for ACPA, one third of them will evolve with arthritis, maninly those with positivity for at least to antibodies.

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