1. Introduction

Alzheimer’s disease (AD, OMIM #104300) is a chronic progressive neurodegenerative disease and by far the most common irreversible cause of dementia syndrome in elderly people. It accounts for over 60% of all dementia cases, and it presently affects over 24 million people worldwide. It is expected to increase as a greater proportion of the population ages [1].

The disease is divided into two subtypes based on the age of onset: early-onset AD (EOAD) and late-onset AD (LOAD). Early-onset AD accounts for approximately 1% to 6% of all cases and ranges roughly from 30 years to 65 years. Both EOAD and LOAD may occur in people with a positive family history of AD (familial AD, FAD). Approximately 60% of EOAD cases have multiple cases of AD within their families, and of these familial EOAD cases, 13% are inherited in an autosomal dominant manner with at least three generations affected [2].

Early-onset disease can also occur in families with late-onset disease [3]. With the exception of a few autosomal dominant families that seem to be single-gene disorders (and accounting for less than 1% of cases), most AD cases appear to be a complex disorder that is likely to involve multiple susceptibility genes and environmental factors [2]. Although the first-degree relatives of patients with LOAD have approximately twice the expected lifetime risk of the disease, the pattern of transmission is rarely consistent with Mendelian inheritance [4].

Clinical symptoms of both EOAD and LOAD include gradual decline in memory (typical initial presentation is an inability to retain recently acquired information), language, abstract reasoning and decision making. Changes in mood and affect often accompany or precede the memory decline. Death commonly occurs from general wasting, malnutrition, and pneumonia [3].

Clinical diagnosis of AD is currently based on core diagnostic criteria that include objective evidence of gradual and progressive decline in episodic memory, which may be associated with other cognitive changes concerning executive function, language, complex visual processing and gnosis. These criteria can be accompanied by supportive features that include atrophy of medial temporal structures (e.g., entorhinal cortex, hippocampal formation, parahippocampal gyrus) on MRI, abnormal cerebrospinal fluid biomarkers (low amyloid beta (Aβ1-42), or increased total-tau or phospho-tau concentrations), specific metabolic patterns evident with molecular neuroimaging methods, in particular reduced glucose metabolism in bilateral temporo-parietal regions and in the posterior cingulate cortex on positron emission tomography, and familial genetic mutations in amyloid precursor protein gene (APP), presenilin 1 (PS1) and presenilin 2 (PS2) genes [5]. The European...
Federation of Neurological Societies guidelines suggest several additional criteria for AD diagnosis: defining the impact of cognitive decline on activities of daily living, inclusion of information on past medical history, assessing comorbidity (e.g., depression, cardiovascular and pulmonary diseases, infections, sleep disturbances), and electroencephalography measurements [6].

The primary lesions of AD pathology are senile plaques (SP) composed of 39-43 amino acid fragments of the Aβ protein that accumulate in the extracellular space and neurofibrillary tangles (NFT) made of hyperphosphorylated microtubule-associated protein tau (MAPT) in the neurons. The causes of FAD are known and include mutations in the APP gene, as well as in PS1 and PS2 genes, which code for subunits of the APP cleaving enzyme γ-secretase. The dominant view on AD pathology is based on the amyloid cascade hypothesis [7] that is based on the discovery that a mutation in APP gene was able to induce AD in familial cases of the disease [8]. This led to a somewhat premature conclusion that Aβ is the main trigger of the disease. However, neuropsychopathological data actually did not fit well with the amyloid hypothesis [11]. For example, Braak and colleagues have shown that tau pathology in the entorhinal and hippocampal regions precedes Aβ accumulation by as much as 27 years [12] and recent data suggest that this delay may be much longer. Tau-positive materials labeled by the AT8 monoclonal antibody (that shows early neurofibrillary degeneration), were observed in high proportion (38/42) of children and young adults in the absence of Aβ accumulation [13]. As AD is traditionally viewed as a disorder associated with aging (more specifically, with old age) early tau pathology seen in children and young adults, if confirmed, could completely alter our view on brain aging [14]. Taking all of these findings into account it is not surprising that over twenty recent clinical trials of potential disease-modifying drugs based on manipulation of Aβ (including active immunization) have failed [15]. Moreover, in the recently abandoned semagacestat trial, some patients on the drug got worse - the drug that was designed to inhibit formation of Aβ sped up cognitive decline. One plausible explanation is that the formation of Aβ might be in fact the brain’s protective mechanism against the disease process, whereas the progression of the pathological changes of the neuronal cytoskeleton, rather than Aβ burden, is crucial in determining the severity of the dementia syndrome in AD [16-19].

Under the assumption that the pathological lesions developing during the course of AD are directly or indirectly attributable to the aging process, a central position in the pathogenesis of AD has been variously assigned to all factors that are known to be capable of damaging postmitotic cells (a risk that increases during aging and old age), such as greater oxidative stress, chronic inflammation, mitochondrial dysfunction and failure of the ubiquitin-proteasome system [20].

One of the underestimated potential causes of all of these changes is reactivation of a latent infection with herpes simplex virus type 1 (HSV1). As inflammatory responses and oxidative changes have been amply documented in AD brains [21,22] and most people are latently infected by HSV1 (worldwide rates are between 65-90%, [23]), several authors recently suggested that both aggregation of Aβ and formation of NFT could represent inflammatory responses to infection and oxidative stress caused by HSV [for review see 24]. During latent HSV1 infection of neurons in mice there is evidence of ongoing inflammation and oxidative damage not only to infected neurons but also, by measuring the amount of oxidative damage, in nearby uninfected cells [24]. Itzhaki and Wozniak further suggest that aggregation of Aβ and tau could be responses to oxidative stress.

1.1 Herpes Simplex Virus Type 1
HSV1 is a dsDNA virus which causes several diseases in humans, including herpes labialis and herpes simplex encephalitis (HSE). It is composed of four concentric compartments. The central DNA core is coding for at least 74 genes.

The HSV1 life cycle follows two paths: lytic and latent. During the lytic cycle, new viral particles are produced. The virus promotes expression of immediate early or α proteins, and subsequent expression of intermediate or β, and late or γ proteins, which all leads to the assembly of novel viral particles. During the latent cycle, viral DNA remains circularized inside the nuclear envelope and expresses two known isoforms of a single-gene product, named the latency-associated transcript [25]. The trigeminal ganglion, located only a few millimeters from the entorhinal cortex, is the primary site of HSV1 latency [26], although other sites including the sensory neurons [27], the nodose ganglion of the vagus nerve [28] and other regions of the brain may be involved [29], possibly in relation to very early neurofibrillary AD changes in the dorsal raphe [19], locus coeruleus and other brainstem nuclei [13].

In the case of herpes labialis, after the initial infection of the mucosal membranes of the mouth and eye, the virus travels along nerve cells and becomes latent in the peripheral nervous system. Stimuli such as neuronal injury, steroids, hypothermia, ultraviolet light exposure and fever cause HSV1 to break out of latency and to reactivate. The activated virus re-infects the mucosal epithelium, causing the well-known recurrent herpetic sore. Both symptomatic and asymptomatic infection enables virus spread through saliva. The infection with HSV1 occurs usually in infancy, residing in about 90% of the adult population. It is interesting to note that although most of the population is infected with this virus only 25–40% develop cold sores [30].

Herpes simplex encephalitis is a rare, very serious acute neurological condition. Interestingly, infection afflicts regions most prominently affected in AD, such as the hippocampus and fronto-temporal cortices [31]. Further, those who survive HSE usually suffer from memory loss and cognitive impairment.

The entry of the virus is dependent on interactions of the envelope glycoproteins...