Alzheimer’s disease and infections, where we stand and where we go

Editorial

Alzheimer’s disease (AD) is a progressive neurological disorder, which represents the most common form of dementia, one of the major causes of disability in later life. Age is the greatest risk factor for AD, which typically affects people aged 65 years and over, with an age-standardised prevalence of 4.4 [1]. However, AD is not a normal part of ageing and advanced age alone does not justify the disease. Several pathways have been implicated in AD pathophysiology, the most described is the neurodegenerative one, which lead to the brain accumulation of beta-amyloid and neurofibrillary tangles, aggregations of hyperphosphorylated tau protein, macroscopically resulting in brain atrophy due to neuronal death [2]. These pathological hallmarks of AD have been recently incorporated in the new recommendations on diagnostic guidelines for AD, which describe different stages of the disease, including its preclinical and symptomatic pre-dementia phases [3].

Genetics accounts for less than 3% of AD, familiar AD at early onset, resulting from mutations in three genes, i.e. APP, PS1 and PS2. Furthermore, the Apolipoprotein E4 (ApoE4) genotype is the only, robust, susceptibility gene for AD [2], although meta-analysis and genome scanning have revealed several susceptibility loci with low odds ratios [4,5]. Overall, multiple gene-gene and environment interactions cause AD; however, various risk factors differently act throughout ageing [2,6]. Large data have been collected in the last two decades regarding the putative role of vascular disease, including systemic atherosclerosis, high blood pressure, diabetes, high level of cholesterol, tobacco smoking, as well as other vascular risk factors, as pathogenetic cause of AD [6-8]. However, a central role for systemic inflammation has been claimed also taking into account previously reported data, traumatic brain injury and oxidative stress [9-13]. Indeed, only a small percentage of people aged 80 years or over has a pure neurodegenerative AD, and mixed dementia with vascular and/or inflammatory components are present [14]. Peripheral inflammation is indeed present in early stage of AD and is higher than that observed during non-pathological ageing [13]. Moreover, an altered inflammatory regulation is also present in Mild Cognitive Impairment (MCI), the intermediate stage between the expected cognitive decline of normal ageing and the more serious decline of dementia [15], and correlates with the progression to AD [13].

Accordingly, acute episodes of systemic inflammation with increased levels of inflammatory mediator tumor necrosis factor-alpha, which are associated with AD [5], have been shown to be associated with long-term cognitive decline in a prospective cohort study of subjects with AD [16]. The missing link between central neuro-inflammation and peripheral inflammatory state might be represented by infectious factors [17].

The possibility of an infectious aetiology for AD has been repeatedly proposed over the past three decades, suggesting the role of viral and bacterial chronic infections as causative inflammatory pathway for AD. Concerning bacterial infections, data from a recent meta-analysis demonstrated that Spirochetal or Chlamydophila Pneumoniae infections were strongly associated with AD [18].

More interestingly, the role of chronic inflammation in periodontal disease (PD) has been suggested over the last decade as a potential risk factor for AD [17,19-21]. In particular, researchers from US found that antibody levels to specific oral pathogens were significantly increased at baseline serum draw in subjects who lately developed MCI or AD, thus suggesting that PD could potentially contribute to the risk of AD [21]. In cases of severe PD, pro-inflammatory molecules may induce a systemic inflammation and may, therefore, access the brain via systemic circulation. Pro-inflammatory molecules, derived locally from periodontal tissue, may stimulate trigeminal nerve fibres, leading to an increase in the number of brain cytokines. These cytokines may act on the already...
In a study of deceased and autopsied subjects from a clinical-pathological community cohort, the authors found associations of CMV-related immunologic and virologic characteristics with AD neuropathology and additional trends toward associations with clinical diagnosis [29]. Nonetheless, these findings could equally well be explained by an indirect effect since reactivation of HSV-1 is associated with CMV and age, perhaps via CMV-induced immunosenescence [30,31]. On the other hand, a few data present in literature concerning the serological association between EBV or HHV-6 and AD could be explained by a similar indirect effect. Both HSV-1 reactivation and EBV and HHV-6 antibody stimulation can, in fact, be triggered by T immunosenescence that is stronger in AD than in control elderly [32]. As an alternative, but not mutually exclusive, possibility, EBV and HHV-6 titles might indicate a systemic inflammation responsible for HSV-1 reactivation [33].

Indeed, as and reviewed by Itzhaki [23], there is evidence for direct possible pathophysiological mechanisms in AD only for HSV-1 since reactivated HSV-1 can cause direct and inflammatory damage in CNS. Implicating HSV-1 further in AD is the discovery that HSV-1 DNA is specifically localized in amyloid plaques in AD. In addition, data by several groups show that HSV-1 infection of cells in culture causes formation of β-amiloid, datum initially found by Wozniak et al., [34] and of AD-like tau, datum initially found by Zambrano et al. [35]. Other relevant, harmful effects of infection include the following: dynamic interactions between HSV-1 and amyloid precursor protein (APP), which would affect both viral and APP transport [23].

As previously stated, findings from a genome-wide association study in a large cohort of patients with AD showed that a limited set of genes were associated with the disease. Licastro and co-workers [17,36] and manuscript submitted suggest that the polymorphism association in some of these genes is consistent with a non-conventional interpretation of AD aetiology. These data suggest that differential genetic backgrounds in genes regulating immune defences against herpes viruses are associated with age-related cognitive deterioration and AD. Cycles of virus latency/infections may therefore contribute to neurodegeneration associated with AD in genetically predisposed elderly, leading to neuronal loss, inflammation and amyloid deposition.

However, only a few prospective cohort studies have confirmed the role of viral and bacteria infections in AD. Overall, available data suggest a link between chronic infections and increased risk for AD, possibly through a low-grade, chronic infection and inflammation in individuals who have inherent susceptibility traits. However, the majority of researches conducted have been cross-sectional, observational studies, which
include relatively small hospital-based samples with inherent problems of selection and residual confounding. Accordingly, further prospective, population-based studies conducted in large cohorts investigating the link between infection and AD are warranted, taking into account APOE typing because of its involvement both in AD and chronic infections [2,37,38]. In any case, successful treatment of chronic infections is a challenging but mandatory goal to improve the quality of life in the elderly.

**Competing interests**
The authors declare that they have no competing interests.

**Authors’ contributions**
RM drafted the paper. All authors edited the paper and approved its final version.

**Acknowledgements**
This work was supported by Grants from Palermo University to C.C.

**References**
