20 YEARS OF STUDIES OF AB AND TAU IN DEMENTIA; HAS IT BEEN WORTH IT? –NO

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The late onset dementias, like all other common "complex" disorders, are thought to result from complex (albeit still poorly understood) interactions between a multitude of genetic, gene expression, epigenetic and a variety of life- long exposures and environmental factors. However, the main risk factor is *Age* and its related biological and environmental manifestations. The commonest form of late onset dementias is Alzheimer's disease (AD), followed by Dementia with Lewy bodies (DLB) and Vascular Dementia, each with some common and somewhat distinct clinical and neuropathological features. Of note, with increasing age and certainly over the age of 80 +, pathological changes are seldom specific of one type, thus mixed forms seem common in the "older old".

The Amyloid cascade hypothesis has dominated research in the aetiology of AD, following the identification (in the late 80s) of mutations of the APP gene (in and around the amyloid**-**ß portion of the gene) and the preseniline genes in rare familial early onset AD. Based on this hypothesis, in both the rare familial and the commonest sporadic late-onset forms of AD, an abnormal intracerebral accumulation of Aß 42 that facilitates tangle formation (made of phosphorylated tau) and progressive neurodegeneration results in a pre-clinical disease stage that may preceed by one or two decades the early clinical phase of mild cognitive impairment (MCI), followed (within a median period of three years) by AD. Neuropathology has served, from the initial observations of Alois Alzheimer in 1906, as the main validation of the Amyloid hypothesis, as the presence of brain atrophy with amyloid plaques and neurofliament tangles form the hallmark features of AD. However, more recent studies have demonstrated that both plaques and tangles, and indeed Lewy bodies (typical of DLB), are seen in a significant number of asymtomatic individuals over the age of 60, with increasing prevalence in older age groups.

Several genetic and environmental factors have been established as risk factors of AD and other dementia forms. The APOE-4 allele is the most validated genetic risk factor, whilst more recently, other genetic variants have been identified as conferring susceptibility to AD through GWAS studies (such as variants in the CLU, PICALM, CR1, BIN1 and other genes) and through phylogenetic studies (a poly-T repeat in the TOMM40 gene, which is in linkage dysequilibrium of APOE. Epidemiological studies), Well conducted population based epidemiological prospective longitudinal studies have identified a number of environmental, socioeconomic, diet and life-style parameters as conferring risk or protection towards the development of disease. Furthermore, high blood pressure, insulin resistance and obesity have also been established as risk factors of dementia and AD. Interestingly, recent epidemiological population based studies have shown that the age – specific incidence and prevalence of dementia may follow a diminishing trend, in recent years, possibly as a result of better medical management of these conditions from mid-life, at least in Western Europe and the USA.

As a whole, these observations point towards the notion that the amyloid cascade hypothesis is not the sole player in the aetiology of AD. The overwhelming dominance of research efforts and investment both from public funding agencies and the pharmaceutical companies on amyloid and tau have not permitted a more thorough investigation into the taxonomy (heterogeneity and nosological boundaries) of dementias and a better understanding of pathogenic mecanisms underlying dementia forms that may pave the way for novel targets and discovery efforts for novel effective disease mosifying agents. Epidemiological studies will be instrumental in providing more specific information on risk and the natural history of dementia, from the pre-clinical (thus potentially reversible) stages to early clinical stages and beyond. The recent findings on a diminishing trend of the prevalence of dementia provide the first positive signal that there may be light at the end of the tunnel for the prevention of dementia and are unrelated to the amyloid or the tau cascade events.