Extended Abstract Journal of Alzheimer's & Dementia 2021 Vol.4 No.3

Association of IL-6 and TNF- gene polymorphisms with the risk of Alzheimers disease in Saudi subjects

Reem Moteb Abdulaali Almotairi, Saba Abdi, Amani Alghamedi , Taim Muayqil, Syed Danish Hussain, Mohammed Ghouse Ahmed Ansari , Mohammed Masoud, Nasser Al-Daghri

King Saud University, Saudi Arabia

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most prevalent type of dementia. In Saudi Arabia although the exact percent about the spread of AD has not been estimated, but the experts believe that there are approximately 50,000 patients in Saudi Arabia, most of them being females. Many of studies illustrate the role of the inflammation in development of AD, however no such study has been done on Saudi AD patients. Thus, the aims of this study were to investigate the association of inflammatory mediator's, interleukin-6 (IL-6), Tumour necrosis factor-α (TNF-α) and C-reactive protein (CRP) with increased the risk of Alzheimer's disease (AD). Further, the association between the level of IL-6, TNF-α and CRP with the genetic variation in IL-6 (-174 rs1800795 G/C and -572 rs1800796 C/G), and in TNF-α (-308 rs1800629 A/G and -1031 rs1799724 C/T) and their role in occurrence of AD in among Saudi ethnic population was investigated. A total of 47 Saudi subjects with age (65-90 years) were enrolled for the study, 24 (14 male, 10 female) diagnosed as AD patients and 23 (11 male, 12 female) served as normal controls. The level of biomarkers (IL-6, TNF-α and CRP) were assessed by ELISA (c). Single nucleotide polymorphism (SNP) in selected genes were analyzed by RT-PCR using Taqman assay. This study showed that TNF-α was higher in AD patients with CC and GC genotypes for IL-6 gene SNPs rs1800796 (P=0.062) and rs1800795 (P=0.066) respectively. The level of IL-6 was also found to be significantly low among AD patients with AG genotype comparing to AD patients with GG genotype for -308 A/G (rs1800629) of TNF-α gene (P=0.040). In conclusion; The level of inflammatory cytokines IL-6 and TNF-αmay play role in the progression of AD depending on specific genotypes among Saudi AD patients.

Alzheimer's disease (AD) is the most common cause of dementia worldwide and it affects 3% of the population aged between 65 and 74 years. The most common symptoms of AD include progressive impairment of cognitive abilities such as memory, judgement, communication and ultimately death. Alzheimer's disease not only affects a person's living ability but it also causes a substantial economic burden to the society. Globally, it is estimated that the total economic cost for AD raised from US$279.6 billion to US$948 billion in 2016. Pathologically, AD is characterized by specific neuronal loss in temporo-parietal association cortices and in the medial temporal lobe structures presence of extracellular plaques made up of aggregated amyloid-beta protein (Aβ1-42) and presence of intraneuronal tangles composed of truncated and hyperphosphorylated tau (Lashley et al., 2018). In normal physiological state, there is an equilibrium between production and degradation of excess amyloid beta (Aβ) and tau levels but during disease activity, this harmony is disturbed leading to protein aggregation, neuroinflammation and neurodegeneration. Several other neurodegenerative diseases such as Parkinson's disease dementia (PDD), frontotemporal dementia (FTD) and dementia with lewy bodies (DLB) have symptoms similar to AD. These neurodegenerative diseases often occur with substantial degree of co-morbidity, implying the presence of other pathological proteins co-acting in the same brain causing cognitive loss (Lashley et al., 2008). Though there are numerous studies on AD pathogenesis, the exact neurodegenerative mechanisms are still unclear which makes definitive diagnosis difficult. Until now, treatment of AD using pharmacological interventions (Donepezil, galantamine, memantine, rivastigmine) have been modest and consistent providing symptomatic relief (Yiannopoulou and Papageorgiou, 2013)to the patients but disease-modifying therapies using pharmacological or non-pharmacological approach are considered as a worldwide necessity.

AD has been diagnosed based on National Institute of Neurological and Communicable Disorder and Stroke and the Alzheimer's Disease and Related Disorders association (NINCDS-ADRDA) criteria which intervenes disease state as "possible", "probable" and "definitive" based on clinical as well as neuropathological patterns.

Apart from NINCDS-ADRDA scale, clinical diagnosis of AD is performed using three biomarkers tests, cerebrospinal fluid (CSF) Aβ detection and cerebral PiB-PET representing amyloid metabolism FDG-PET representing the status of cerebral glucose metabolism and CSF Tau detection and structural MRI presenting neurodegeneration. Though these biomarkers can enhance the possibility of AD diagnosis, due to several shortcomings (expensive, difficult to perform) they are not recommended for conventional diagnosis.

Patients with metabolic disorders such as diabetes mellitus, hypertension, and obesity have higher risk of AD. Hence, specific biomarkers from patients with metabolic disorders that can detect or prevent AD progression at earlier stage are imperative. Various studies have demonstrated that insulin resistance (IR) and impaired insulin signaling acts as a major pathological factor in both DM and AD. The influence of IR on plasma and CSF AD biomarkers were evaluated in 28 IR and 30 non-IR Finnish men recruited from Metabolic Syndrome in Men (METSIM) study. CSF AD biomarkers such as total tau, phosphorylated tau at Thr181 epitope, Aβ were quantified with respect to IR. However, no difference were noted in CSF AD biomarkers between IR and non-IR group but plasma insulin correlated with CSF Aβ/tau in the whole cohort with 487 plasma and 200 CSF proteins differentially expressed in the two groups. This study concluded that in cognitively healthy men, IR is not directly related to level of CSF AD pathology.

Similarly, levels of Aβ 42, phospoTau, soluble low density lipoprotein receptor related protein 1 (sLRP1) and macrophage-colony stimulating factor (MSCF) were evaluated in CSF and serum of patients with Type 1 Diabetes Mellitus (T1DM) with determinants of cognitive function and white matter integrity. CSF levels of AD biomarkers such as Aβ-42, pTau and sLRP1 were higher in patients with T1DM with no difference in MCSF. However, CSF-sLRP1 were associated with improved attention, information processing and increased white-matter integrity of right inferior fronto-occipital tract. Whereas, elevated tau levels was associated with white-matter integrity of right inferior fronto-occipital tract. However, these observed profile mismatches with the full risk profile as seen in pre-AD patients.