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### Metabolic syndrome, neuroinflammation and cognitive impairment: State of the art and results from a second level outpatient clinic in Italy

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In 2010 it was estimated that 35.6 million people lived with dementia worldwide; those numbers are expected to increase to 65.7 million in 2030 and 115.4 million in 2050 [HYPERLINK \l "\_ENREF\_1" \o "Prince, 2013 #43107"1]. Alzheimer's disease (AD) is the most prevalent type of dementia, including around 60%-70% of all dementia cases [2]. The presence of neuroinflammation is a common feature of dementia; post mortem studies of different types of dementia revealed activated microglia in many regions of central nervous system (CNS) [HYPERLINK \l "\_ENREF\_10" \o "McGeer, 1999 #8207"3]. Microglial cells could be activated in the M1 status from several inflammatory cytokines (e.g. IL-1, IL-6, TNF) and release cytokines and neurotoxins, or, on the other hand, could be activated by different cytokines (IL-4, IL-10, GM-CSF) in M2 status, characterized by the release of anti-inflammatory cytokines and growth factors with a neuro-protective and regenerative effect [HYPERLINK \l "\_ENREF\_9" \o "Varnum, 2012 #4707"4]. This kind of phenotype switching has been observed also in acute and chronic systemic inflammation models [5, 6, 7]. There are a lot of study, conducted in Rotterdam, United States and England, demonstrating that changes in education and reductions in vascular risk factors could reduce the incidence of dementia in cohort compared with oldest generation; otherwise, the prevalence of obesity and diabetes among middle-aged people could reverse this trend [8]. In a study performed in the Alzheimer Outpatient Clinic of the Hospital of Livorno (Tuscany, Italy) 127 subjects, with a mean age of 78, 2±7, 1 years (76 women and 51 men, aged 78, 5±7, 1 and 77, 6±7, 2 respectively) with mild cognitive impairment (MCI) and AD (MMSE score 20.6±5.1, 20, 2±4, 9 for women and 21, 0±5, 4 for men) has been evaluated. We found a high percentage of patients with increased cardiovascular risk. Indeed, 79.1% of the patients (88.5% women and 64.7% men) had dyslipidemia (defined as serum total cholesterol higher than 240 mg/dl and/or triglycerides higher than 200 mg/dl) 53.1% (54.2% female and 51.4% males) elevated systemic blood pressure. Interestingly, the 41.7% of the patients (48.6% female and 30.4% males) showed increased inflammation indexes: CRP and fibrinogen. It is known that metabolic syndrome (MS) is characterized by chronic peripheral inflammation and that both obesity and MS could be associated to MCI and AD development and progression [9]. Interestingly, although the association between peripheral inflammation and cognitive impairment is generally recognized [10] rheumatoid arthritis (RA), a typical systemic autoimmune disorder, seems negatively associated to AD development [10, 11]. To better understand these conflicting data, we have designed a translational research project aimed to evaluate the effect of different conditions (morbid obesity, RA and periodontitis) of peripheral chronic inflammation on neuroinflammation and cognitive function as well as AD pathophysiology. In particular, the aim of the project is to evaluate whether different cytokine patterns, related to specific systemic diseases, could differently act at CNS level, favoring or preventing pathologic inflammation and oxidative stress, with consequent neuro-dysfunction and AD development.

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