MENOPAUSAL TRANSITION: A POSSIBLE RISK FACTOR FOR NEURODEGENERATIVE EVENTS

Bonomo Sara M.[1], Rigamonti Antonello E.[1], Giunta Marialuisa[1], Galimberti Daniela[2], Guaita Antonio[3], Gagliano Maria G.[4], Müller Eugenio E.[1] and Cella Silvano G.[1]

[1]Department of Medical Pharmacology and [2]Department of Neurological Sciences, Fondazione IRCCS Ospedale Maggiore Policlinico, Milan, Italy; [3]Geriatric Institute "Camillo Golgi", Abbiategrasso, Italy; [4]Department of Transfusion Medicine, "San Carlo Borromeo" Hospital, Milan, and CEND, University of Milan

Incidence and prevalence of Alzheimer Disease (AD) are higher in postmenopausal women than in aged matched men. Since at menopause the endocrine system and other biological paradigms undergo substantial changes, we thought to be of interest studying whether (and how) the balance between some biological parameters allegedly neuroprotective (e.g. related to estrogen, DHEA and CD36 functions) and others considered pro-neurotoxic (e.g. related to glucocorticoids and IL-6 activities) vary during lifespan in either sex in either normalcy or neurodegenerative disorders.

Along with this aim, we evaluated leukocyte expressions of estrogen receptors (ERs), glucocorticoid receptors (HGRs), IL-6 and CD36, a scavenger receptor of class B allegedly playing a key role in the proinflammatory events associated with AD, in a population of 209 healthy subjects (73 M, 106 F, 20-91 yr-old) and 85 AD patients (36 M, 49 F, 65-89 yr-old). Results obtained were related to plasma titers of estrogens, cortisol and DHEAS.

In healthy men all the study parameters were quite stable during lifespan. In women, instead, at menopausal transition, some changes that may predispose to neurodegeneration occurred. In particular, there was: 1) an up-regulation of ERs, and a concomitant increase of IL-6 gene expression, events likely due to the loss of the inhibitory control exerted by estradiol (E_2) ; 2) an increase of HGRα:HGRβ ratio, indicative of an augmented cortisol activity on HGRα not sufficiently counteracted by the inhibitory HGRβ function; 3) a reduced CD36 expression, directly related to the increased cortisol activity and, 4) an augmented plasma cortisol:DHEAS ratio, unanimously recognized as an unfavorable prognostic index for the risk of neurodegeneration. In AD patients of both sexes, the expression of the study parameters was similar to that found in sex- and age-matched healthy subjects, thus indicating their unrelatedness to the disease, and rather a better correlation with biological events.

In conclusions, menopausal transition is a critical phase of women's life where the occurrence of an unfavorable biological *milieu* would predispose to an increased risk of neurodegeneration. Collectively, the higher prevalence of AD in the female population would depend, at least in part, from the presence of favoring biological risk factors, whose contribution to the development of the disease occurs only in the presence of possible age-dependent triggers, such as β-amyloid deposition.