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Acute coronary syndrome, brain and neurocognitive functioning. What's in between?

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The relation between acute coronary syndrome (ACS) and neurocognitive functioning was initially based on the observation that patients with history of ACS would have a five times greater risk of developing dementia [1]. The incidence of neurocognitive dysfunction in ACS patients with no dementia in cardiac rehabilitation ranges between 44,2% and 51,2% [2] [3]. Deficits in executive functioning, decrease in simple attention tasks, psychomotor speed immediate memory, mental flexibility and mental processing speed have been consistently reported [4] [5].

In comparison to healthy controls, ACS patients exhibit loss of grey matter volume in several essential areas for high demanding cognitive tasks: left medial frontal cortex, left cingulate and precuneus, left and right parahippocampal gyri and right and left middle temporal gyri [6]. In functional terms, increased connectivity in middle-orbito-frontal regions seems to be related to executive dysfunction [7].

The factors that may underlie these associations are extensive [5]. The severity of the atherosclerotic disease and subsequent ischemia, hypoperfusion due to reduced systemic cardiac output, a persistent low-grade inflammatory activation, oxidative stress, multiple cardiovascular risk factors such as diabetes, central obesity, hypertension and dyslipidemia, are some of the variables of this complex equation. In addition, psychosocial and behavioral aspects have been frequently reported as being on the basis of these relations [5] [8].

It has been long known that some genetic traits are common both to dementia and cardiovascular diseases. The most studied is the Apolipoprotein (APOE) genotype due to its role in the modulation of lipid transport. The APOE ϵ 4 allele seems to increment vulnerability to neurocognitive impairment in the presence of hypertension [9] and higher levels of interleukin- 6 (IL-6) [10]. The association of this allele with worse lipid profile and to obesity [11], creates further ways to impact on heart functioning, brain and neurocognition.

Obesity, especially abdominal obesity, promotes endocrine

dysfunction mainly related to enhanced sympathetic nervous system activity (eg. hypercortisolemia) and inflammation. In fact, inflammatory markers have been associated to heart disease and cognitive decline. Protein C-reactive (PCR) it is associated to a higher risk for Alzheimer's disease and it is related to impaired collateral circulation in patients with coronary disease [12]. IL-6 is related to a decrease in hippocampus volume and it seems to be a predictor of cognitive decline (non-verbal memory, immediate verbal evocation and orientation) especially when associated to metabolic syndrome [13][14]. Another inflammatory marker is tumor necrosis factor- α (TNF- α), which is a pro-inflammatory cytokine, expressed in many brain pathologies and it has been associated with neuronal loss, Alzheimer's disease and to deleterious cardiovascular effects [15]. However, the link between TNF- α , cardiovascular disease, brain and neurocognitive functioning, has not been sufficiently established in literature.

The metabolism of tryptophan in the kynurenine pathway is implicated in cardiovascular disease mortality [16] and it seems to have an important role in neurodegeneration [17]. This pathway is initiated by two enzymes: indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3 dioxygenase (TDO). The proinflammatory cytokine interferon γ and other immune stimulants activates IDO, while TDO expression is induced by corticosteroids in response to stress. Through this pathway tryptophan is converted to immunomodulating and neuroactive substances. The study of tryptophan decrease and kynurenines production in the context of ACS, brain and neurocognitive functioning offers a wide avenue for research. Furthermore, tryptophan is essential for the synthesis of serotonin. Is it licit to hypothesize that this pathway could have implications on patient's mood? Perhaps it could justify the atypical neurocognitive profile in ACS patients with depression [18].

These are some of the factors that may underlie the relation between ACS, brain and neurocognitive functioning.

The study of the interaction between risk factors,

biomarkers, behavioral and environmental aspects as well as the clinical features of ACS and its treatment on brain and neurocognitive functioning, it is an epical challenge for *Current Neurobiology*. Unveiling these interactions may point to new therapeutic targets aiming to prevent brain dysfunction and neurocognitive impairment.

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