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The Vascular Hypothesis of Affective Disorders in the Elderly: A Review

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Abstract

The vascular role is fundamental in the depression and bipolar disorder pathophysiology in the elderly through different mechanisms: 1) disconnection of certain neural paths and circuits related to affective disorders (seen as white matter hyperintensities under Nuclear Magnetic Resonance); 2) inflammatory hypothesis (which poses that aging and affective disorders interfere with the immune response, thus increasing peripheral immune activity and producing a central pro-inflammatory state); and 3) decreased blood flow in different brain areas.

The vascular component is a risk factor that causes vascular depression (VAD), vascular secondary mania (VM), post stroke depression and vascular dementia. Affective disorders are a vascular risk factor as well. In 1997 VAD and VM were defined as psychiatric disorders, but have yet to be included in the most used psychiatric manuals. VAD does not respond well to antidepressants. Certain new treatments, such as cognitive remediation, have had better responses, but to gather more evidence further studies are required.

Keywords: Vascular; Depression; Mania; Cerebrovascular; Hyperintensities

Introduction

Relationship between the Vascular Factor and Affective Disorders

According to several studies published in the last years, the vascular factor plays an important role in affective disorders in the elderly.

The vascular component is a risk factor for developing affective disorders: it causes frontal-limbic circuit interruption and hypoperfusion; it activates pro-inflammatory tracts; it may trigger vascular depression, vascular secondary mania and post stroke depression; and it may result in vascular dementia.

At the same time, affective disorders have an impact on the vascular role: they are vascular risk factors, provoke careless behavior (possibly associated to metabolic syndrome and substance abuse), activate proinflammatory mechanisms, increase morbidity and mortality due to cardiovascular and cerebrovascular disorders, and microvascular images are visualized in neuroimaging.

The vascular role is fundamental in the depression and bipolar disorder pathophysiology in the elderly through different mechanisms: disconnection of certain neural paths and circuits related to affective disorders; inflammatory hypothesis and decreased blood flow in different brain areas.

In a review on the impact of depression on cardiovascular evolution, several mechanisms related to lifestyle and adverse physiological mechanisms were observed. There is poor compliance to low-fat diet, physical activity, giving up smoking, medication and cardiac rehabilitation. On the other hand, there is an increase of platelet adhesiveness, proinflammatory processes, hypothalamus-pituitary-adrenal axis dysfunction, heart rate variability, catecholamines augmentation, endothelial dysfunction and brain-derived neurotrophic factor (BDNF) reduction [1].

In the last decade, many authors have observed that depression might be considered a vascular risk factor, even a risk factor in acute heart attack prediction and evolution. The Yusuf et al. study, a nine-year follow-up of 15.151 heart attack patients, compared the latter to 14.820 control subjects and observed the following: depression increased heart attack risk by 2.6, almost as high as smoking, diabetes and high-blood pressure, and somewhat less than high cholesterol levels [2].

Cardiovascular abnormalities along with depression affect both the cardiac function and peripheral vasculature. Subcutaneous arteries studies in patients with late-life depression show similarities between resistance arteries in experimental models and in patients with depression. Bouzinova et al. [3] suggest that abnormalities in resistance arteries could contribute to comorbidity.

Untreated bipolar disorders increase morbidity and mortality for several reasons: cancer, cardiovascular and cerebrovascular diseases, suicides and accidents. In a study about the impact of 19 chronic somatic illnesses on bipolar disorder patients monitored between 1995 and 2007, an increase of diabetes, hemiplegia, dementia, cerebrovascular disease, peripheral vascular disease, congestive heart failure and heart attack was observed [4].

A Veterans Administration study proved that bipolar patients (90% male) have a higher incidence of high blood pressure (35%), diabetes (17%), ischemic heart disease (11%), congestive heart failure (3%), peripheral vascular disease (3%) and stroke (2%). Furthermore, a study conducted by the National Epidemiologic Survey on Alcohol and Related Conditions showed 4.95 increase of cardiovascular disease and 2.98 higher risk of high blood pressure in bipolar patients [5].

As regards the impact of the vascular role on affective disorders, a review and meta-analysis about the relationship between the vascular risk factors and late-life depression from 1990 to 2012 found a relationship among compound vascular risk factors, smoking, high-blood pressure, dyslipidemia, diabetes, cardiovascular disease and stroke, and late-life depression. It also found a slight association with smoking and a strong one to diabetes [6].

Vascular Depression

Alexopoulos defined vascular depression in 1997: "The cerebrovascular disease may predispose, trigger or perpetuate depression" [7].

Vascular depression is a late-life depression subtype presented with less depressive ideation than in other types of depressions, loss of motivation, disinterest, psychomotor retardation, decision-making problems, executive dysfunction, attention deficit, disproportionate disability for the medical condition, poor insight, poor antidepressant response, high incidence of relapses and

recurrences, and frequent residual symptoms. Hyperintensities under Nuclear Magnetic Resonance are observed [7–9].

The concept of vascular depression is currently not accepted by some authors and it is not included in the DSM V.

Late-onset depression is associated with neurobiological factors (cardiovascular disease, neurodegeneration, inflammation), cardiovascular risk factors (diabetes mellitus, high cholesterol levels, high blood pressure), and other neurological and general diseases [10,11].

Aizenstein et al. propose these criteria to establish a vascular depression diagnosis:

(1) Evidence of vascular pathology in elderly subjects with or without cognitive impairment.

(2) Absence of previous depressive episodes preceding obvious cerebrovascular disease.

(3) Presence of cerebrovascular risk factors.

(4) Co-incidence of depression with cerebrovascular risk factors.

(5) Clinical symptoms typical of VAD such as executive dysfunction, processing speed decrease and lethargy.

(6) Neuroimaging data confirming cardiovascular disease [12].

Executive dysfunction plays such an essential role in the clinical presentation of vascular depression that some authors have referred to it as "Executive Dysfunction Syndrome". There is difficulty in initiative and maintenance of actions, planning, abstract thinking and complex behaviors [13].

Two vascular depression hypotheses have been proposed:

a. Alexopoulos et al. [7] the hypothesis is based on the presence of vascular risk factors and dysexecutive syndrome. It takes into account functionality and its evolution. The definition is supported by clinical presentation, basically executive dysfunction. It proposes the term "dysexecutive syndrome".

b. Krishnan et al. [14] the hypothesis is based on hyperintensities present in deep white matter and subcortical grey matter under the Nuclear Magnetic Resonance. The definition is supported by the underlying pathophysiology. It proposes the term "subcortical ischemic depression" [7,8,14].

In vascular depression, the frontal-limbic circuits are affected by dorsal-cortical hypometabolism and ventral-limbic hypermetabolism. Because of the frontal-limbic vascular affection and dysfunction, it would be a vulnerable affective state.

According to Taylor et al. [15], there are three hypotheses regarding mechanisms involved in vascular depression: 1. Disconnection hypothesis; 2. Inflammatory hypothesis; and 3. Hypoperfusion hypothesis.

Disconnection hypothesis

It states that the specific focal damage of certain neural paths and circuits, especially of frontostriatal circuits due to microangiopathic injuries, is seen as white matter hyperintesnities under the Nuclear Magnetic Resonance.

White matter hyperintensities represent perivascular demyelination, atherosclerosis, ischemia, gliosis or myelin and axons partial loss. These are associated to aging and cardiovascular risk factors (diabetes, heart disease and high-blood pressure) or diminution of blood pressure variability with deterioration of vasomotor reactivity and self-regulatory deterioration.

They are more severe in cingulate bundle, uncinate fasciculus and superior longitudinal fasciculus. White matter hyperintensities intensity and location distinguish subjects with late-life depression from control subjects with similar vascular risk factors [15].

White matter ischemia disrupts brain mechanisms and damage volume is an important factor in affective dysregulation. This was studied in the Framingham Heart Study [16].

In affective disorders, a higher density of white matter hyperintensities in regions related to cognitive function was observed: executive dysfunction, memory disorders and emotional burden. The location of white matter hyperintensities determines the symptoms [16,17].

Inflammatory hypothesis

Aging and affective disorders interfere with the immune response, increasing peripheral immune activity and producing a central proinflammatory state.

There is peripheral cytokines augmentation: Interleukin-6 (IL-6), IL-1β, IL-8 and tumor necrosis factor-α, and a decrease of anti-inflammatory cytokines like IL-10.

The proinflammatory cytokines reduce tryptophan and serotonin due to the increment of IDO (indolamine 2-3 dioxygenase), an enzyme that degrades serotonin, because of tryptophan consumption augmentation and serotonin transporter activation. This increases tryptophan catabolites, which are neurotoxic and produce a brain-derived neurotrophic factor (BDNF) decrease, and there is an increase of dopamine [18–20].

Slavich and Cole associate gene activation of inflammatory

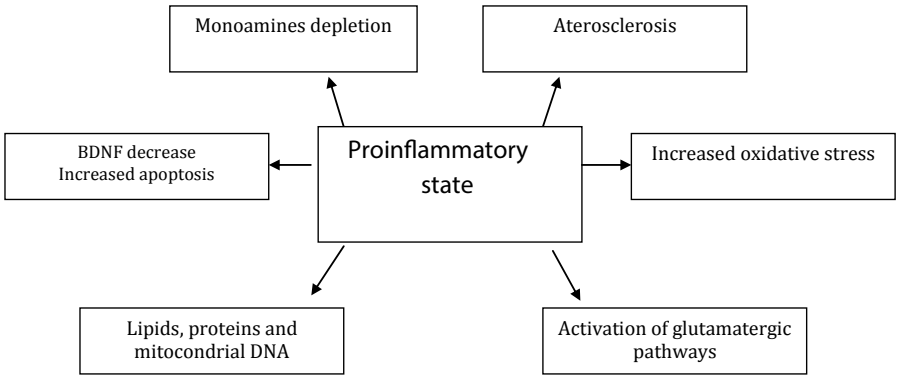

Figure 1: The inflammatory hypothesis.

leukocytes and innate antiviral gene inhibition in response to experiencing social, physical, real, imagined or symbolic environmental threats: conserved transcriptional response to adversity (CTRA). Chronic activation gives rise to several conditions associated to the inflammatory condition, which includes cardiovascular disease, depression, metabolic syndrome, neurodegenerative disorders and cancer [21].

Comorbid systemic diseases contribute to these processes. Some studies, with poor evidence, affirm that anti-inflammatory drugs (minocycline, celecoxib, rofecoxib) may have an antidepressant response in people with high proinflammatory markers. Antidepressants might reduce the inflammatory response [22–28].

Hypoperfusion hypothesis

Decreased blood flow in different brain areas predisposes mood and cognitive symptoms.

In late-life depression there is arterial intima media reduction, augmentation of arterial stiffness and endothelial dysfunction. The subcortical white matter is especially sensitive to perfusion changes [20,29–33].

In addition, the genetic factor should also be considered. There are studies that show the importance of BDNF (val 66val) polymorphisms, apoliprotein E4 (APOE4) and serotonin-transporter-linked polymorphic region (5-HTTLPRs) in late-life depression.

Short-allele serotonin transporter promoter subjects have more anomalies in frontal-limbic areas and lower remission than long-allele homozygotes [34]. They have a flattened neuroendocrine response to serotonin tests, lower platelet serotonin and minor serotonin metabolite (5-hydroxy-indoleacetic acid) concentrations [35]. Short-allele serotonin transporter promoter subjects also have an increased risk of vascular disease: cholesterol and triglyceride augmentation, angina pectoris risk, heart attack and postinfarction unstable angina [36].

Other genetic polymorphisms that increase vascular risk are: renin-angiotensin system (RAS) genetic variation that augments depression risk through monoamine dysregulation, and polymorphism of the 5-10-methylenetetrahydrofolate reductase which metabolizes homocysteine [37–39].

Some researchers question the vascular depression concept, based on vascular events, in clinical studies, in neuroimaging and in neuropathology lesions [40].

Post-stroke depression is a frequent disorder that occurs in one every three patients, even though prevalence is highly variable: 28% (25-79%) according to the used criteria. It may be premature, within the first three months following the stroke, or late [10,41–43].

Depression usually occurs along with anxiety, irritability, agitation, and emotional incontinence, modification of emotional experience, sleep disturbances, disinhibition, inertia and fatigue. The patient experiments loss of self-control, loss of abilities, demotivation, hopelessness, executive dysfunction and other cognitive, motor and language disorders [44].

Injuries may be unique or multiple. Gaps in basal ganglia and thalamus are significantly different in subjects with or without post-stroke depression [45].

Post-stroke depression influences functional and cognitive recovery, social and interpersonal life, and may increase mortality by 10 times [42,10]. Even so, under diagnosis disorder is high.

Vascular-Secondary Mania

A maniac episode first occurring at 60 years-old or older, with no antecedent of previous recurrent depressive episodes, should always make the specialist suspect there is presence of an organic brain disease, like a vascular disease.

Wijeratne et al. [46] studied the vascular mania concept and reviewed studies from 1996 to 2006. They found literature overlaps in the concepts of vascular mania and post-stroke, disinhibition syndrome and secondary mania. They propose some changes in the diagnostic criteria of Steffan and Krishnan in 1998, who classified the maniac episode as a core symptom, together with clinical changes like transient cerebrovascular disorder or stroke, neuropsychological or neuroimaging changes, poor family history of mood disorder and daily activities dysfunction.

Witjeratne et al. [46] criteria include history of transient cerebrovascular disorder, stroke or vascular risk in the central criteria.

Bipolar patients' symptoms of early and late-onset disorder were compared. Cognitive tests and the Framingham Stroke Risk Score were considered. It was observed that in addition to the start peak around 20 of bipolar disorder, there is a start peak around 60 as well as a presentation peak of maniac episodes. The conclusion was that the cerebrovascular factor plays an important role in late-onset bipolar disorder expression [47].

Bipolar disorder has high comorbidity with medical illnesses throughout life. Leboyer et al. [48] propose that bipolar disorder medical comorbidity not only may be seen as a consequence of neglect or drug effect, but also as a manifestation of a multisystem inflammatory disease. Stress, circadian and sleep disorder, the association to autoimmune diseases and retrovirus exposition cause a dysfunction of the immune system and, together with genetic and environmental factors, cause a state of cerebral and peripheral inflammation that promotes vascular disease.

Vascular Depression Treatment

Vascular depression predicts poor response to antidepressants [13,15,49,50]. Endothelial dysfunction [51], executive dysfunction [52–54], verbal fluency decrease, and poor performance in episodic memory, in language processing and in processing speed are poor predictors [55,56]. Other poor predictors are white matter hyperintensities severity and situation, and short allele of the serotonin transporter promoter [57–59].

A study on the relationship between neuropsychological performance and white matter hyperintensities with sertraline treatment remission, on 217 patients older than 60 years, concluded that cognitive deterioration, vascular risk factors and white matter hyperintensities severity predict a lower response to antidepressant treatment [60].

In two further studies something similar was observed: leucoaraiosis disrupted limbic-cortical circuits, which generated a poor response to escitalopram 10 mg/d [61].

Anterior cingulate volume is important in the antidepressant response as well. In 41 major depression elderly patients treated with escitalopram 10 mg/d, those with lower cingulate volume showed a lower remission [62].

BDNF polymorphisms also play a role. BDNF val66met carriers have higher remission rates in depression with antidepressant treatment. No relationship between BDNF polymorphisms and white matter anomalies was found [63].

In the study of suicide prevention in a primary attention

project (PROSPECT), patients were monitored for two years: antidepressants in adequate doses, psychotherapy, side effects and adherence. The research analyzed 20 primary attention places, for patients of 60 to 74 years old (396 with major depression, 203 with minor depression and 627 controls) who had made consultations between 1998 and 2008. Patients with depression had higher mortality caused by cardiovascular disease, cancer, respiratory disease and stroke [64].

Cognitive remediation has significant efficiency in patients with vascular depression, which gets higher if the workload increases [44].

Selective Serotonin Reuptake Inhibitor (SSRI) is a first generation drug for post-stroke depression treatment. They prevent mortality within the year following the stroke and are associated to a higher survival.[65]

Escitalopram treatment disruption increases depressive symptoms compared to placebo and psychotherapy. Escitalopram improves cognitive function within this population [66,67].

Fluoxetine improves life quality after a stroke; improves motor function and it is associated to lower disability [68,69].

There are limited studies that show duloxetine, nortriptyline and venlafaxine efficiency [70–73].

In post-stroke depression it is important to work on psychotherapy focalized on the abilities and the difficulties of patients and their families: problem-solving, treatment compliance, family goals and coordination of patient care [74].

Controlling cardiovascular risks factors and behavioral lifestyle interventions, like cognitive training, cognitive remediation, physical activity and social activity, have many benefits in preventing or treating vascular depression [75,76].

Conclusion

"Vascular depression" and "Vascular mania" are not syndromes, but a subtype of late-onset mood disorders. The most frequent form of cognitive dysfunction is executive dysfunction and it predicts poor evolution and response to antidepressant treatment.

More studies about late-onset affective disorders, vascular risk factors and white matter hyperintensities are needed.

Possibly, when we treat vascular risk factors, we are treating and preventing affective disorders in different life stages, especially in the elderly, due to pathophysiological mechanisms and their consequences.

Conflict of Interest

The author declared there is no conflict of interest.

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