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Depression and cardiovascular disease: a reciprocal relationship

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Abstract

Until relatively recently, depression has been considered a purely "mental" disorder and therefore in the natural domain of psychologists and psychiatrists. However, recent epidemiological studies have revealed that aging, physical and psychological stress, chronic pain, several metabolic disorders such as insulin resistance and established diabetes, alcoholism, inflammatory conditions, and vascular disorders such as arterial hypertension all may be associated with depression. The present review examines some of these depression-associated factors and the mechanisms by which they might give rise to vascular disorders such as atherosclerosis, microcirculation endothelial dysfunction, and interstitial disturbances leading to organ damage. A number of disorders involving the circulation can lead progressively and insidiously to large artery rigidity, remodeling of peripheral arteries, and alterations of the microcirculation of large blood vessels. Perturbations in vasa vasorum blood flow may contribute to atherogenesis, in addition to the influence of numerous cellular events involved in inflammation (tumor necrosis factor α, interleukin 1β, etc). Since Hans Selye first described the neuroendocrine cascade generated by experimentally induced stress half a century ago, phenomena such as the axonal release of neurotransmitters (including serotonin), accumulation of metabolites such as homocysteine, platelet-activating factor, and nitric oxide also have been implicated in the pathogenesis of depression. Moreover, vascular consequences of depression such as heart rate and pulse pressure variations may lead to endothelial dysfunction in critical microcirculation networks (cerebral, myocardial, and renal) and initiate physicochemical alterations in interstitial compartments adjacent to vital organs. The appropriate use of ambulatory monitoring of vascular parameters, such as heart rate and pulse pressure, and eventually, early identification of genetic and metabolic markers may prove helpful in the early detection of events preceding and predicting the clinical manifestations of depression.

1. Introduction

The organic basis of mental disorders has been a major subject of interest, perhaps starting at the end of the 19th century when Philippe Pinel freed the insane from their chains at the Salpêtrière Hospital in Paris. Several years before I started my career as a nephrologist, I had the honor of publishing a paper with 1 of my mentors, Prof Heinz Lehmann from McGill University [1]. He introduced chlorpromazide for the treatment of schizophrenic patients in America more than 50 years ago. The success of this pharmacological approach gave strong support to the concept that a relationship exists between abnormal mental behavior and certain biologic perturbations. Moreover, the brain is no longer thought of as being insulated from events in the periphery that can—and do—affect mental function. Indeed, the identification of more and more biologic messengers involved in vital communication among cells, as well as the genetic profiles that characterize an increasing number of diseases—until now poorly understood in mechanistic terms—encourages us to envision mental disorders such as depression as conditions that arise from underlying biologic disturbances.

2. Morbid conditions associated with depression

Depression can be associated with morbid conditions resulting from the clinical expression of vascular disorders, such as the form of depression that occurs after a heart attack or a stroke. Conversely, a depressive state arising from undue stress in the workplace or at home can give rise to enhanced vascular risk and vital organ damage. It is not surprising that vascular injuries associated with environmental and/or individual behavioral disturbances developed in living organisms with primitive as well as more complex vascular

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systems. Vital interactions between cells first developed in multicellular species, in which metabolic exchanges between organs relied on interstitial compartments. Later, survival of more complex isolated organs involved in the management of energy production required more appropriate systems to integrate delivery of vital substrate and waste product removal. The appropriate solution involved, first, a crude vascular system that included continuously contracting vessels and then, at a later stage, a more complicated arrangement which embodied a multichambered heart.

The existence of a passive fluid circulation, without benefit of a pump, has been observed in primitive organisms, with fluid movements taking place through large and medium-size veins [2]. At a later phase of development, large arteries appeared, through which blood was pushed by the heart at a hydrostatic pressure high enough to deliver oxygenated fluid to central and peripheral organs, in which microcirculation networks containing more than 50% of the total intravascular fluid compartment developed in a variety of organs [3].

In man, depression has been found to be associated with a large variety of vascular disorders, beginning with the simple elevation of mean arterial pressure [4-6]. Subtypes of blood pressure elevation were later reported, such as isolated systolic hypertension, variable hypertension [7,8], and hypertension that developed after an episode of depression [9]. These observations help us understand better the nature of the relationship between depression and vascular disease. First, isolated systolic hypertension is related to the large artery rigidity found in elderly subjects [10,11] and suggests a potential relationship between such rigidity and elevation of peripheral resistance. Second, depression is likely to precede elevation of blood pressure and may therefore be considered a precursor to hypertension in young individuals [12].

Other manifestations of a depression–cardiovascular disease relationship have been described. Ambulatory monitoring of blood pressure has revealed that heart rate variability has been observed in subjects who developed episodes of depression [13-17] These findings suggest a close relationship between baroreceptor abnormalities that may have originated from the cardiac atria and/or carotid area and central nervous structures involved in processing mood in subjects developing depression. Sleep disturbances have also been described in such subjects, again suggesting the existence of neural links between psychological state on the one hand and regulatory cardiovascular mechanisms on the other hand [18,19].

Within the vascular domain, other significant associations have been made with depression. Resistant arterial hypertension has been described in subjects exhibiting panic and hostile behavior [20,21]. Impotence, with or without concurrent alcohol abuse—a problem often difficult to detect in clinical practice—has also been observed in association with depressive states [22,23]. An association between depression and certain metabolic disorders such as diabetes mellitus and dyslipidemia has been reported [24]; however, the precise nature of the relationship between these conditions remains to be established.

Perhaps the most dramatic clinical reports linking depression with cardiovascular events concern target organ damage resulting from arterial hypertension of the various types described above. Acute myocardial infarction and stroke have been reported in large clinical studies as major conditions suspected of giving rise to depression. Conversely, depression was found to precede the development of cardiovascular catastrophes [25-27]. Such reports suggest that mood disorders arising (for example) from a stressful experience in a susceptible individual are capable of producing serious vascular damage that may become irreversible. Further study is clearly needed to clarify the mechanism(s) and pathways by which events that occur in the nervous system can lead to macrovascular and microcirculatory disturbances responsible for target organ damage.

3. Depression and the cardiovascular system

Circadian and seasonal variations in the occurrence of depressive episodes suggest that day and night and/or simply alterations in light exposure (changes in photoperiod) may somehow influence the body's physiology and thereby trigger the onset of depression [28]. Studies of this phenomenon indicate that depression may develop after spontaneous or deliberately elicited conditions in which brain centers that appear to be affected by light (pineal gland and related structures) are activated positively or negatively [29]. Neurohumoral connections that link cerebral centers with the vascular system might explain other phenomena, such as seasonal variations in the behavior of microcirculation networks, the basic component of the vascular system involved in blood/interstitial/cellular substrate exchanges. Recent observations obtained from our laboratory [30] indicate that capillary permeability to albumin varies markedly from season to season, particularly in different segments of the aorta, as well as in organs involved in thermoregulation, such as the trachea and the skin. Such links established between light exposure, specialized brain centers, and microcirculation networks might help explain the target organ damage frequently observed in depression.

Exposure to physical and psychological stress has been associated with depression and coronary heart disease [4]. Because similar stressful conditions have been shown to affect the physical properties of large arteries, including elasticity of aortic segments, it is reasonable to relate these changes to alterations in the macromolecular composition of such arteries [31]. We have demonstrated that aortic proteoglycan contents influence the rigidity of major arteries, leading to increased peripheral resistance, high systemic blood pressure, and consequent target organ damage [32].

Both acute pain and intermittent pain have been reported to precede development of depression. This relationship

between pain and depression has been observed in young subjects exposed to a hostile type of environment [32,33] and brings to mind the type of hyperalgesia recently reported as being premonitory to certain types of vascular disease such as diabetes mellitus [34]. It is conceivable that depression linked to metabolic diseases such as diabetes and dyslipidemia could be connected to the coexistence of hyperalgesia and pain [24]. One could, in fact, propose the possibility of a vascular equivalent to the cutaneous hyperalgesia, described in diabetic rat models [35]. The aortic vasa vasorum system, responsible for nutrition of the vessel wall matrix, is maximally innervated by the autonomic nervous system, being equipped with afferent and efferent branches capable of transmitting information about pulse pressure and/or retrograde wave reflection. The same system—in response to efferent signals—is also capable of adaptive vasoconstriction and vasodilatation [36]. Alterations in the vasa vasorum flow and endothelial permeability could result from albumin, lipoprotein, or even cholesterol accumulation in the intima and media of large arteries, thereby contributing to atherogenesis and the vascular calcification process [37].

Several autacoids and hormones have been implicated as playing an etiologic role in the vascular damage resulting from depression. Potent vasoactive compounds, such as cortisol, catecholamines, and serotonin [38-43], have been identified as possible mediators in the morbid cascade of events leading to depression and are potentially involved in organ damage. Mediators of inflammation, including platelet-activating factor, a potent compound involved in endothelial permeability [44], have also been added to the list of agents capable of causing tissue damage. Finally, homocysteine [45], a compound involved in sulfate homeostasis, has recently attracted the attention of scientists looking at mechanisms responsible for accumulation of this type of end product during chronic renal insufficiency [46].

Target organ damage in a variety of systemic diseases, particularly of the vascular type, results from a sequence of events that includes alterations in microcirculation permeability and of the interstitial space [47]. Primary depression and depressive states secondary to a variety of illnesses are capable of causing organ damage via some of the physiopathological pathways described above. Using proton magnetic resonance spectroscopy, investigators have been able to visualize frontal white matter biochemical abnormalities in elderly patients with major depression [48,49]. Myoinositol/creatine and choline/creatine ratios were found to be significantly higher in the frontal white matter in the depressed subjects, as compared with a control group. In contrast, the gray matter of the depressed subjects and their controls did not differ with respect to these ratios. These findings provide further support for the concept of a metabolic basis of depression in human subjects. In addition, they identify the frontal area of the brain as being involved in the syndrome.

4. Conclusion

Clinical diagnosis of depression requires appropriate knowledge of risk factors for this mood disorder, ranging from environmental and social stresses and strains to organic ailments, including early-stage vascular disease characterized by developing rigidity of large arteries in hypertension to metabolic conditions, such as diabetes mellitus and dyslipidemia. Use of a suitable questionnaire together with a careful clinical examination—including (when indicated) a complete vascular evaluation of patients judged to be susceptible to depression—plays an important role in establishing the diagnosis. Laboratory studies designed to obtain evidence of vascular and inflammatory abnormalities should be used in marginal or obscure clinical cases. The recent development and validation of modern magnetic resonance spectroscopy appear to be helpful in the objective recognition of metabolic abnormalities in key areas of the brain [48].

Management of depression should include recognition of predisposing risk factors—social and environmental—as well as the need for early intervention, if possible, before the disorder and its morbid consequences have become consolidated. Circadian disturbances have also been tackled in therapeutics, especially in the affective disorders area. Pharmacological interventions remain empirical; yet, advances in this domain have been successful over the past decade, particularly by modulating central nervous system melatoninergic and serotoninergic systems.

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