Is poststroke depression a vascular depression?

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Available online 7 October 2004

Abstract

As we learn more about the relationships between depression and cerebrovascular disease (CVD), a complex picture is emerging in which the chain of causality seems to spiral on itself: progressive or focal brain damage, cognitive impairment, depressive symptoms, dementia, and cardiovascular diseases, all seem to be liable to lead to one or another. Stroke may lead to depression, and the inverse may also be true. Depression may lead to cognitive impairment and cardiovascular diseases, which in turn may lead to subtle brain impairment, thereby causing more depression and cognitive impairments, and so on. In this presentation, we provide a rapid glance at the complexities of such issues.

Keywords: Stroke; Poststroke depression; Vascular depression; Risk factors; Mood; Dementia

1. Introduction

Depression is a frequent and important poststroke complication, with a negative influence on quality of life, because it is associated with increased disability, cognitive impairment, and mortality [1–4]. The so-called “poststroke depression” (PSD) has been the focus of many studies in the last decades, and researchers have investigated various potential mechanisms to explain the relationships between stroke and depressive symptoms. These are often presented as direct causal effects, involving the influence of location and lateralization of lesion, the burden of neurological and cognitive impairment, or some form of psychological coping with the stressful event. Indeed, stroke is one of the few conditions listed in the DSM-IV as a direct cause of depression. PSD is such a concern that a multidisciplinary consensus panel, examining more than 1900 clinical research articles on stroke rehabilitation, explicitly proposed as one of their four key recommendations that special surveillance was ascribed to the development of depression [5–7].

Cerebrovascular diseases (CVDs) were thereafter considered more globally as potential factors in the genesis of late onset depression, an approach which has been dubbed “the vascular depression hypothesis” and is now supported by clinical and radiological observations. More recently, in a dramatic reversal of the chain of causality, researchers have begun to publish large studies that highlight the role of depressive symptoms per se as risk factors for the development of subsequent CVD like stroke, an idea we refer to as “prestroke depression”. Taken together, these different approaches give us a complex picture of the relationships between brain function, vascular activity and mood, relationships that appear to be reciprocal rather than sequential. At this state of knowledge, many questions remain open, one of them being the title of this presentation.

2. Poststroke depression

2.1. Definition, diagnosis, and prevalence

PSD has been defined as “depression occurring in the context of a clinically apparent stroke (as opposed to silent CVD)” [3]. It is still a matter of controversy whether depression after stroke should be considered as an equivalent of endogenous depression (ED, also called “functional depression”, that is, depression occurring without acute brain injury), in both its phenotype and neuro-
anatomical bases [8,9]. Nevertheless, researchers generally agree to rely on DSM-IV criteria for major and minor depression, whether endogenous or following stroke [10]. Methodological limitations include difficulties in obtaining reliable self-ratings in acute stroke populations due to aphasia, anosognosia, or intellectual confusion. In addition, multiple diagnostic confounders also following stroke (aphasia, anosognosia, or intellectual confusion). In addition, reliable self-ratings in acute stroke populations due to depression, whether endogenous or following stroke[10]. Methodological limitations include difficulties in obtaining data using a large array of published studies. This is higher than prevalence rates for major depression in the general population, which is estimated at 10% over a 12-month period. Despite a lack of consensus in the literature, it is widely accepted that major depression after stroke is a common occurrence and of sufficient concern to be recognized as a key factor in rehabilitation and outcome after stroke [3,7].

Authors have pointed to a host of factors possibly associated with PSD. In a review of 13 papers, Carota and Bogousslavsky [16] have sorted some of these factors according to their significance (negative or positive), as related to the presence of PSD. Table 1 shows that, except for functional outcome, it has been difficult to find a single good predictor of PSD.

### 2.2. Mechanisms

The etiopathogenesis of PSD has also been hotly debated. Positions on this issue have tended to coalesce around two explanatory poles: authors who insist primarily on a biological mechanism, whereby ischemic insults directly affect neural circuits involved in mood regulation [17]; and authors who rather focus on reactional psychosocial and stress mechanisms [2,18,19].

Among the latter authors, Gainotti et al. [18] have argued that the phenomenology of major PSD, with its high prevalence of reactive diurnal mood variations, anxiety, emotionalism, and catastrophic reaction is distinguishable from the phenomenology of ED, which is characterized by morning prevalence, depressive mood, suicidal thoughts, and guilt feelings. In addition, mood in subjects with PSD appears to be linked more to handicaps and disabilities than to lesion location. They conclude that their data are consistent with a psychological model of PSD, rather than with a neurochemical one, based on a reactive response to a particularly stressful event (Ref. [20], see also Ref. [21]).

In accordance with a psychosocial model, occurrence of a “major life event” before stroke has been shown to be a risk factor for PSD [22]. Other psychosocial risk factors include a previous history of major depression, a neurotic personality style, disability, and social isolation [3]. In addition, others have highlighted the importance of psychological treatment in PSD and thus the need to take into account personality and psychosocial factors [23].

Most of the arguments directed against a strict biological view of PSD mention the contradictory evidence available in this area; for example, there is as yet no consensus on the role of lesion location in PSD [24].

However, hints that PSD may be mediated primarily by biological mechanisms come from a variety of data. First, it is important to underscore the fact that ED itself is underpinned by brain and cognitive abnormalities, specifically basal ganglia and prefrontal dysfunctions. This is well established both from imaging and clinical data [25]. Early studies focused on whether stroke survivors were more likely to suffer from depression than patients with other ailments not involving acute brain injury. For instance, in 1977, Folstein et al. [26] found that depression was more frequent in a stroke population than among orthopedic patients presenting similar levels of physical disability. They concluded that PSD could not be considered a simple emotional reaction to a reduction in autonomy. In a more recent study, depressive symptoms were found to be more severe in stroke patients and patients with symptomatic carotid stenosis, than in patients with peripheral vascular disease [27].

However, other researchers have found no difference in depression scores of stroke patients versus other conditions. For example, in a recent study, Aben et al. [28] have shown that, after controlling adequately for age, sex, and level of handicap, there was no difference in the incidence of depression after stroke or myocardial infarction, thus challenging the idea that specific cerebral factors play a crucial role in the pathogenesis of PSD. Ironically, as will be shown in the next section, comparing stroke patients with
myocardial infarct patients with regard to subsequent depression may precisely be a contestable method, as acknowledged by the authors of the study themselves, for the following reason: “the increased incidence of depression after stroke and myocardial infarction may reflect other factors shared by the two conditions. One possible mechanism is that generalized damage to the vascular system in the brain may subsequently affect mood regulatory processes—the so-called vascular hypothesis [...] This more general vascular mechanism could play a role in both myocardial infarction and stroke (p. 584)”. Hence, “specific cerebral factors” may anyway be involved in depression following myocardial infarction.

Finding a precise brain localization responsible for depression has been elusive and the topic is currently still under debate. Initially, much discussion was derived from the frequent involvement of left anterior lesions in the development of PSD, but recent publications, including one large meta-analysis, have somewhat downplayed this enthusiasm, being unable to find a reliable anatomic correlates of PSD [25,29]. Primarily one research group, led by Robinson [4], has maintained the localizationist approach. He recently fought back with his own meta-analysis, which states that, during the first 2 months after an acute stroke, left frontal and left basal ganglia lesions were indeed significantly more frequent among patients with major depression compared with any other lesion. Even more recently, a team led by this same author confirmed his previous finding of a significant correlation between severity of depression and proximity of the lesion to the left frontal pole, for patients who were less than 6 months poststroke [30]. The mechanism proposed is a disruption of monoaminergic pathways.

Other arguments advanced in favor of a primarily biological mediation in PSD are in sharp contrast with those arguing for a psychological reaction. For example, it has been claimed that clinical symptoms in PSD and ED are similar (as are biological markers such as the dexamethasone suppression test) and that there is no clear correlation between the severity of depression and the degree of the neurological deficit [31].

Depression occurring in patients with anosognosia seems to be a compelling case against a purely psychological mechanism because no “conscious” psychological reaction can account for the depressed mood. This does not necessarily occur in right-sided lesions only, and has been described in left subcortical lacunar infarcts as well [32]. However, anosognosia accompanying PSD is rare [33].

Subcortical lesions have also been reported as favoring the emergence of depressive symptoms, especially when left-sided [34]. Depressive signs following subcortical lesions are thought to be due to disruption of frontal—subcortical circuits, which in turn leads to depletion in cortical biogenic amines [35]. More often than not, subcortical PSD is accompanied by cognitive impairments. This association of PSD and cognitive impairment is well documented. In a 1-year prospective study of 106 first-ever stroke patients, Kauhanen et al. [36] found that severity of depression correlated negatively with performance on neuropsychological measures of nonverbal problem solving, memory, attention, and psychomotor speed at 12 months after stroke. With the same population, this team also showed a strong link between the presence of dysphasia and a higher risk of major depression [37]. Of course, we are left with the question of whether it is depression that causes cognitive and functional impairment or cognitive impairment that leads to depression (although some evidence points to depression as the main factor leading to, or aggravating, cognitive impairment due to stroke. See, for example, Ref. [38]).

It has also been proposed that, while left-sided lesions often lead to PSD, right-sided lesions are mostly associated with poststroke euphoria, mania, or even bipolar disorder [3,4,39].

As will be developed in the next section, more compelling evidence in favor of the importance of biological factors in depression, than for strict localization, is provided by the notion of vascular depression (VaD). Silent infarcts—that is, cerebral lesions of which the patients are unaware because they are largely asymptomatic—can cause depression independently of psychological mechanisms [40,41].

Biological and psychological factors may have a differential impact on PSD depending on the time course of stroke outcome. It is possible that lesion location is strongly associated with the development of early PSD and that psychological factors have more weight in nonacute, later-onset PSD [42]. In the end, it must be said that most authors acknowledge a multifactorial origin of PSD because it always arises from a complex entangled web of prior life events, coping styles, and idiosyncratic neuronal functioning and structure.

2.3. Vascular depression

In contrast with PSD, which occurs by definition after an acute and focal vascular event, vascular depression is considered to be a consequence of chronic ischemic lesions [43]. Here is how it was originally defined: “Depression in the presence of vascular risk factors, accompanying neuro-psychological deficit and distinct localized brain pathology seen on structural imaging” [40,44].

The “vascular depression” hypothesis states that late-onset depression (over 50 years of age) might often be due to vascular damage to frontal-subcortical circuits implicated in mood regulation and cognition [45]. Indeed, patients with late-onset depression have been found to present more cognitive and neuroradiological abnormalities, greater disability, lower familial prevalence of mood disorders, and less personality dysfunction than elderly people with early-onset depression, all pointers to a biological origin of what often appears clinically as a brutal mood transformation in
elderly patients [46]. Numerous imaging studies of late-onset depression have fairly consistently shown abnormalities, referred to as “white matter hyperintensities” (WMHs), especially in the periventricular areas and the striato-frontal circuits, including ischemic damage to the dorsolateral prefrontal cortex. These WMHs are of crucial clinical importance, as they are linked to poor response to treatment, residual cognitive impairment, increased relapse rate, and progression to chronic depression. The specific mechanisms of vascular depression are poorly known and presumably involve an association with age, increase in atheromatous vessels, vascular risk factors, and CVD [47–51].

An important point is that these vascular lesions may or may not be clinically evident before the appearance of depressive symptoms, as is evident from the term “silent cerebral infarct” introduced by Fujikawa et al. [41], in order to refer to the structural brain abnormalities related to major depression in the absence of cognitive or functional deficits. Here, depressive and cognitive symptoms are seen as arising from related neurobiological processes which involve the progressive or sequential disruption of subtle connections important for mood processing and executive functions.

It should come as no surprise that vascular depression has been closely linked to dementia, as researchers have acknowledged since a long time the existence of a relationship between depressive and dementia-like symptoms, as with “pseudodementia” [52] or “reversible dementia” [53]. A recent study by Fuhrer et al. [54] showed that depressive symptoms increase the risk of developing dementia during an 8-year follow-up period, although this effect was noted only in men. Furthermore, the risk for dementia was 50% higher in depressed hypertensive men than in nonhypertensives. In addition, elders who developed vascular dementia had more depressive symptoms than persons without dementia or with AD. The authors conclude that vascular disease may lead to depression and that sometimes this depression can progress into dementia. Importantly, the relationships between vascular disease, depression, and dementia need not be sequential and direct, but rather reciprocal [46].

3. Is depression a risk factor for ischemic stroke?

We now turn to the topic of depression as a risk factor in itself. Well-known cerebrovascular risk factors, from the AHA (American Heart Association) are, hypertension (related primarily to hemorrhagic stroke), smoking, diabetes, asymptomatic carotid stenosis, sickle cell disease, hyperlipidemia, atrial fibrillation, and lifestyle factors. Among these “lifestyle factors”, a depressive mood is known as a risk factor for coronary heart disease in general [55–57], so it appears that a good case could be made for depression per se as a predictor of later stroke. This is indeed what a number of studies have found [58–64]. For example, a recent prospective study by May et al. [59] with a cohort of 2201 men found that the relative risk of fatal stroke was increased by a factor of 3.36 in individuals presenting significant depressive symptoms at baseline. A figure of 2.6 was found in another study [58] that carefully controlled for heart disease, hypertension, diabetes, and current and previous use of tobacco. This finding was not altered by medication used in the treatment of depressive disorder at baseline. In a follow-up of 29 years, Everson et al. [61] reported that individuals presenting five or more symptoms of depression at baseline were 50% more likely to die of a stroke-related cause during this time. A Japanese study found that depressive symptoms were only predictive of ischemic and not hemorrhagic stroke [64]. Therefore, it seems that depression is a serious risk factor for stroke, not necessarily related to other classic risk factors.

Moreover, by exacerbating vascular morbidity and increasing mortality from vascular diseases, depression may contribute to the development of vascular dementia, and perhaps to dementias of other etiologies. Clinicians know well that the first signs of dementia are often preceded by depressive symptoms. This may be indicative that the same underlying vascular impairment is common to both depression and dementia [65]. As Alexopoulos [46] puts it, “depression may be both a risk factor and a prodromal symptom of dementing disorders”.

Hypothetical mechanisms that account for “prestroke depression” have been derived from several findings in the biology of depression involving metabolic changes that may lead to brain impairment [46,55]. Depressive symptoms are related to increased platelet activity (related to increased autonomic sympathetic activity), increased serotonin-mediated platelet activation, and excessive secretion of glucocorticoids. They also predict later hypertension incidence (a possible pathway to a stroke event) and promote subtle lifestyle changes that have an impact on conventional risk factors of stroke. It may also be that the association of depressive symptoms and later onset of ischemic stroke is only an “epiphenomenon”, arising from underlying vascular disturbances cumulating through time. Another line of research focusing on brain plasticity mechanisms suggests that stress-related hormones reduce the production of neurotrophic factors and inhibit neurogenesis, both of which are obviously liable to increase vulnerability to vascular changes [46].

4. Conclusions

At this stage, it seems that the question of whether PSD is of organic or psychological origin has become obsolete. We have seen that organic dysfunctions, even subtle ones that do not produce neurological symptoms, are involved in the development of depressive symptoms. On the other hand, we now have evidence that depressive symptoms per se are involved in the onset of cardiovascular diseases and,
hence, stroke-related disorders. Therefore, depression is both a cause and a consequence of CVD. Bearing all of these elements in mind, we can try to answer the question asked in the title of this presentation: Is poststroke depression a vascular depression? Of course, if we adhere to a strict definition of vascular depression, it seems that PSD does not cover the same idea at all (the former implies silent vascular lesions in depressive elders, and the latter a focal ischemic insult leading to depression). However, in our opinion, “vascular depression” should be viewed from a larger perspective, one that integrates a bidirectional point of view: as there are vascular aspects involved in depressive symptoms, there are mood aspects involved in vascular disorders. Therefore, we can answer yes, in this wider sense, PSD is a vascular depression, but we need to think in a nonlinear fashion and see these problems as the outcome of complex interrelating factors, or as Robinson puts it, “the inextricable relationship between physical and mental disorders” [4].

Acknowledgment

The authors wish to thank Sarah Viollier for kindly reviewing the manuscript.

References


