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Is major depression a neurologic disorder with psychiatric symptoms?

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Abstract

In the last decade, multiple investigator groups have identified structural changes of various neuroanatomic structures in patients with idiopathic major depression and bipolar disorders. Using high-resolution MRI of the brain and functional neuroimaging studies (i.e., PET, SPECT), researchers have described decreases in the volume of hippocampal formation, amygdala, entorhinal cortex, various frontal lobe structures, and basal ganglia, in addition to abnormal cerebral blood flow and metabolic activity in these structures as well as in thalamic nuclei. Similar structural and functional changes have been identified in patients with depression associated with a variety of neurologic disorders (i.e., stroke, Parkinson's disease, epilepsy, Alzheimer's dementia). In addition, recent data have shown that depression is a risk factor for the development of several neurologic disorders, including epilepsy, stroke, and Parkinson's disease and bears a negative impact on the course and outcome of most neurologic disorders. This article reviews these data and provides evidence that major depressive and bipolar disorders may in fact be neurologic disorders with psychiatric symptoms.

Keywords: Magnetic resonance imaging (MRI); Poststroke depression; Hippocampal atrophy; Amygdala; Basal ganglia; Prefrontal cortex; Volumetric measurements

1. Introduction

In 1999 Bejjani et al. [1] reported the case of a 65-year-old woman with advanced Parkinson's disease (PD) who developed transient acute symptoms of depression during high-frequency stimulation of the left substantia nigra. This patient had never suffered from depression or other psychiatric disorders. She had undergone intraparenchymal stereotactic placement of quadripolar electrodes for deep-brain stimulation of subthalamic nuclei for the treatment of her PD, but one of the contacts of the left electrode was erroneously placed in the substantia nigra. After 7 minutes of continuous stimulation of the left substantia nigra with a monopolar 2.4-V rectangular current (pulse width = 60 μs, frequency = 130 Hz), the patient began to cry and voiced feelings of sadness, hopelessness, guilt, self-deprecation, as well as passive suicidal ideation. She denied being in pain and was fully aware of her surroundings. Stimulation failed to cause any changes in the cognitive or motor symptoms of her PD. Ninety seconds after the stimulation stopped, the symptoms of depression remitted; she was able to recall the entire event and for the following 5 minutes she displayed a hypomanic-like affect. The psychiatric symptoms elicited by this stimulation were identical to symptoms identified in patients with major depression, with the exception of the absence of neurovegetative symptoms. This depressive episode was replicated during two additional stimulations.

These symptoms were not elicited with stimulation of any other contact. Positron emission tomography (PET) with oxygen-15-labeled water was performed during one of the depressive episodes, revealing activation of the left orbitofrontal cortex, spreading to the left amygdala, as well as activation of the left globus pallidus, spreading

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to the anterior thalamus, and finally activation of the right parietal lobe.

This case illustrates in a very graphic manner the occurrence of a depressive episode triggered by transient dysfunction of circuitry involving cortical (frontal and temporal) and subcortical (basal ganglia and thalamic nuclei) structures. Yet, can the findings of this case be applied to idiopathic depressive disorders? Do we have evidence to suggest that depression may in fact be a neurologic disorder with psychiatric symptoms?

To prove that depression is a neurologic disorder, it is essential to demonstrate reproducible evidence of structural and/or functional abnormalities in one or more neuroanatomic structures of the central nervous system, as well as neuropathologic changes in postmortem analyses of such structures *in patients with idiopathic depression*. The purpose of this article is to review such evidence.

2. Structural MRI changes in idiopathic depressive disorders

As illustrated in the case presented above, the development of depressive episodes may be mediated by several neuroanatomic structures connected to each other. In a review of the literature, Sheline summarized data revealing morphologic and volumetric changes in neuroanatomic structures that form a "limbic–cortical–striatal–pallidal–thalamic circuit" in patients with major depressive disorders (MDDs) [2]. A limbic–thalamic–cortical branch has been proposed as integrating one of its arms and includes the amygdala, hippocampus, medial-dorsal nucleus of the thalamus, and medial and ventrolateral prefrontal cortex. She also proposed the existence of a second arm running in parallel and linking the caudate, putamen, and globus pallidus with limbic and cortical regions.

2.1. A. MRI changes in temporal lobe structures

The temporal structures affected in patients with MDDs and bipolar disorders (BPDs) include the hippocampal formation, amygdala, prefrontal cortex, thalamic nuclei, and basal ganglia including the caudate and globus pallidum [2]. The most frequent findings have consisted of a decrease in the volume of hippocampus, prefrontal cortex, and basal ganglia and the presence of bilateral areas of increased signal in white matter of frontal lobes [2]. In 1996, Sheline and collaborators [3] found smaller hippocampal volumes, bilaterally, in 10 patients with a history of MDDs in remission when compared with hippocampal volumes of 10 age-, sex-, and height-matched normal controls. They also identified large hippocampal low-signal foci ($\geqslant$4.5 mm in diameter) and their number correlated with the total number of days depressed. A significant inverse correlation between duration of depression and left hippocampal volume was also demonstrated, suggesting that patients with more chronic and active disease were more likely to have hippocampal atrophy. These authors replicated these findings in a larger study of 24 patients and 24 controls matched for age, sex, and height in which they also found that core amygdala nucleus volumes correlated with hippocampal volumes [4]. More recently, Sheline and colleagues [5] demonstrated that pharmacotherapy with antidepressants may protect patients with MDDs from developing hippocampal atrophy. In a study of 38 female patients, they found a significant correlation between reduction in hippocampal volume and the duration of depression that went untreated. On the other hand, there was no correlation between hippocampal volume loss and time depressed while taking antidepressant medication or with lifetime exposure to antidepressants.

Vakili and colleagues [6] also suggested a possible protective role of antidepressant therapy on the development of hippocampal atrophy in depression. In a study of 38 patients with MDDs, they found no difference in hippocampal volumes between patients and controls; yet, they identified a possible relationship between hippocampal volumes and disease severity (left hippocampal volumes correlated with the Hamilton Depression Rating Scale at baseline), as well as with treatment response (female responders to fluoxetine therapy had significantly larger right hippocampal volumes).

Severity of depression may also play an important role in the development of hippocampal atrophy. For example, Shah and colleagues [7] compared hippocampal volumes of 20 patients with treatment-resistant MDDs with those of 20 patients who responded to therapy and 20 healthy controls. Patients with treatment-resistant MDDs were more likely to have hippocampal atrophy.

A functional consequence of hippocampal damage can be reflected in lower verbal memory scores as demonstrated in a study by MacQueen and colleagues [8], who compared hippocampal volumes and hippocampus-dependent memory tests in 20 patients with a first episode that was never treated and normal age-matched controls. The same comparisons were carried out between a second patient group that included 17 patients with recurrent depressive episodes and matched controls and patients with single depressive episode. While patients with single and multiple episodes had verbal memory deficits, only patients with multiple episodes had hippocampal atrophy. As in Sheline's studies, there was a significant correlation between duration of the depressive illness and degree of hippocampal atrophy.

Atrophy has also been identified in other mesial temporal structures. Bell-McGinty and colleagues [9] found an inverse relationship between the volumes of hippocampus and entorhinal cortex and the time since the first lifetime depressive episode in a study of 30 patients with MDDs and 47 matched controls.

In a recent study, Posener and colleagues suggested the need to study the shape of the hippocampus, in addition to measurement of its volume, as the former can identify structural changes even in the absence of volumetric decrements [10]. Using the method of high-dimensional brain mapping, these authors generated 10 variables or components of hippocampal shape in a study that compared high-dimensional mapping of 27 patients with MDDs and 42 healthy controls. In depressed patients, these authors identified hippocampal deformation suggestive of specific involvement of the subiculum while finding no differences in hippocampal volumes between the two groups.

Two potential mechanisms mediating the decrease in hippocampal volume in depressed patients have been suggested: (1) high glucocorticoid exposure and (2) an alteration in neurotrophic factors.

2.1.1. Hippocampal atrophy mediated by glucocorticoid overexposure

Excessive activation of the hypothalamic–pituitary–adrenal axis (HPA) is observed in almost half of individuals with depression and is demonstrated by a decreased ability of dexamethasone to suppress plasma levels of cortisol, ACTH, and β-endorphin. These changes are reversible with treatment with antidepressants [11]. In experimental studies with rats and monkeys, prolonged increased concentrations of glucocorticoids have been found to damage hippocampal neurons, particularly CA3 pyramidal neurons, possibly by reduction of dendritic branching and loss of dendritic spines that are included in glutamatergic synaptic inputs [12]. Hypercortisolemia has also been found to interfere with the development of new granule cell neurons in the adult hippocampal dentate gyrus [13]. Deleterious effects of chronic glucocorticoid exposure may lead initially to a transient and reversible atrophy of the CA3 dendritic tree, to increased vulnerability to a variety of insults, and finally to cell death under extreme and prolonged conditions [14,15].

Unfortunately, there have been very few neuropathologic studies of the hippocampal formation supporting these hypotheses. Lucassen et al. [16] carried out a neuropathologic study of 15 hippocampi of patients with a history of MDDs and compared them with those of 16 matched controls and 9 steroid-treated patients. In 11 of 15 depressed patients, rare but convincing apoptosis was identified in entorhinal cortex, subiculum, dentate gyrus, CA1, and CA4. Apoptosis was also found in three steroid-treated patients and one control. However, no apoptosis of pyramidal cells in CA3 was observed.

2.1.2. Abnormal neurotrophic processes related to the depressive disorder

Involvement of neurotrophic factors has been suggested as a potential pathogenic mechanism of depression and as playing a role in its treatment [17]. Acute and chronic stress decreases levels of brain-derived neurotrophic factor (BDNF) in the dentate gyrus, pyramidal cell layer of hippocampus, amygdala, and neocortex [18]. Thus, a deficiency of BDNF may contribute to structural hippocampal changes. These changes are mediated by glucocorticoids and can be overturned with antidepressant therapy, as chronic administration of antidepressant drugs increase BDNF expression and also prevent a stress-induced decrease in BDNF levels [19]. There is also evidence that antidepressant drugs can increase hippocampal BDNF levels in humans [20]. These data indicate that antidepressant-induced upregulation of BDNF can hypothetically repair damage to hippocampal neurons and protect vulnerable neurons from additional damage. The role played by these potential pathogenic mechanisms may help explain some of the variability in the reported changes in hippocampal volume among studies, as shown above.

2.1.3. Other neuropathologic changes in hippocampal formation

Rosoklija and colleagues have recently reported a decrease in arborization of apical dendrites and a lower density of dendritic spines on subicular pyramidal neurons in six patients with bipolar depression who also had a family history. On the other hand no hippocampal synaptic pathology has been identified in patients with unipolar major depression up to the present time [21].

2.1.4. Changes in amygdala

Volumetric changes of amygdala in patients with MDDs are less consistent than those of hippocampal formation. This is not surprising, as measurement of the volume of the amygdala and its nuclei is technically much more difficult than that of hippocampal structures. Sheline and colleagues [22] found the core volume of amygdala nuclei, but not its total volume, to be decreased bilaterally among 20 patients with a history of MDDs, free of any neurologic disorder, compared with those of 20 matched controls. Conversely, Frodl and colleagues [23] found increased amygdala volumes in 30 inpatients with a first episode of MDD, compared with matched controls. The authors attributed these changes to enhanced blood flow.

In a neuropathologic study of amygdala and entorhinal cortex, Bowley and colleagues [24] carried out a neuronal and glial cell count in brains from seven patients with MDDs, 10 with BPDs, and 12 control cases. The specimens of MDD patients and those of patients with BPD *not treated* with lithium and valproic acid had a significant reduction in glial cells and in the glial/neuron ratio in left amygdala and to a lesser degree in left entorhinal cortex.

2.2. B. MRI structural changes of frontal lobes

Structural changes have been investigated in various structures of the frontal lobes including the prefrontal cortex and cingulate gyrus as well as in their white matter. Bremner and colleagues [25] found that orbitofrontal cortical volumes of 15 patients with MDD in remission were significantly smaller than the volume of orbito-frontal cortex and other frontal cortical regions of 20 controls. Coffey and colleagues [26] also found smaller frontal lobe volumes in 48 inpatients with severe depression who had been referred for electroshock therapy compared with 76 controls.

Neuropathologic studies have also documented structural cortical changes in frontal lobes of depressed patients. Rajkowska and colleagues [27] found decrease in cortical thickness, neuronal size, and neuronal density in layers II, III, and IV of the rostral orbitofrontal region in the brains of depressed patients. In the caudal orbitofrontal cortex there were significant reductions in glial density in cortical layers V and VI that were also associated with decreases in neuronal size. Finally, in the dorsolateral prefrontal cortex, there was a decrease in neuronal and glial density and size in all cortical layers.

Structural changes have been identified in depression occurring in elderly patients and merit a brief review. Lai and colleagues found smaller bilateral orbital frontal cortex volumes in 20 elderly patients with MDDs compared with 20 matched controls [28]. Taylor and colleagues [29] also observed that orbitofrontal cortex volumes in 41 elderly patients with MDDs were smaller than those in 40 controls. Furthermore, these authors found that smaller volumes were independently associated with cognitive impairment. Kumar and colleagues [30] found that the magnitude of prefrontal volume changes was related to the severity of the depression, as elderly patients with minor depression had lesser changes than those with MDDs.

The presence of white matter hyperintensities in frontal lobes has also been associated with depression in the elderly [31]. Kumar and colleagues [32] found that decreased frontal lobe volumes and the number of white matter hyperintensities on MRI represent relatively independent pathways to late-life MDDs. Tupler and colleagues [33] compared the number and volume of white matter hyperintensities on MRI of 69 patients with late-onset depression, 49 with early-onset depression, and 37 controls. Patients with late-onset depression had more severe hyperintensity ratings in deep white matter than those with early-onset depression and controls; both groups of depressed patients had worse ratings than controls. Of note, left-sided white matter lesions were significantly associated with an older age at the onset of depression.

2.3. C. Structural changes of basal ganglia and thalamic nuclei

The volumes of caudate and putamen have been found to be reduced in two studies of patients with MDDs and this is more likely to occur in late-onset depression [34–36], while in one study of patients with BPD, no differences were found with controls [37].

Many fewer data are available on structural changes in thalamic nuclei in idiopathic depression. One study done by Strakowki and collaborators showed a trend toward a larger volume in bipolar patients [38].

3. Findings in functional neuroimaging studies

Functional neuroimaging studies with PET have revealed decreased metabolic activity in frontal and temporal regions, in insula, and in basal ganglia [39–41]. Furthermore, decreased hippocampal metabolism predicts the severity of depression [42]. Abnormal cerebral blood flow patterns may be a trait marker. Liotti and colleagues [43], for example, compared regional blood flow changes before and after a transient sad mood challenge among a group of acutely depressed patients, a second group of euthymic unipolar patients in remission, and a control group of healthy volunteers who had never been depressed. Mood provocation resulted in significant regional cerebral blood flow decrements in medial frontal lobe cortex in both depressed groups. Furthermore, in the group of euthymic unipolar patients, there was a decrease in regional cerebral blood flow in pregenual cingulate cortex.

Disturbances in frontal lobe functions on neuropsychological testing support the abnormalities demonstrated with functional neuroimaging (PET, SPECT). Indeed, executive abnormalities have consistently been found among different studies, and are more apparent in more severe depressive disorders. In two separate studies, investigators demonstrated that these neuropsychological disturbances correlated with reduced blood flow in mesial prefrontal cortex [44,45]. Furthermore, in tests demanding executive function, cingulate cortex and striatum could not be activated in patients with MDDs [46].

4. Depression in neurologic disease: comorbidity or a different clinical manifestation of the neurologic disorder?

4.1. A. Symptoms of depression temporally related to recurrent neurologic events

The depressive episode induced by electrical stimulation of the left substantia nigra in the patient described in our Section 1 is a clear example of depression resulting directly from transient neurologic disturbance. In a

neurology practice, transient depressive episodes clearly associated to neurologic disturbances can be identified among patients with epilepsy who experience ictal, preictal, and postictal symptoms of depression [47].

Ictal symptoms of depression are the clinical expression of a simple partial seizure in which the symptoms of depression consist of its sole (or predominant) semiology. It has been estimated that psychiatric symptoms occur in 25% of "auras"; 15% of these involve affect or mood changes [48–51]. For example, ictal depression ranked second after anxiety/fear as the most common type of ictal affect in one study [52].

Preictal depressive symptoms typically present as a dysphoric mood preceding seizures that may extend for hours or even 1–2 days prior to the onset of a seizure. Blanchet and Frommer [53] carried out a systematic analysis of this type of phenomenon and studied mood changes over 56 days in 27 patients who were asked to rate their mood on a daily basis. Mood ratings pointed to a dysphoric state 3 days prior to a seizure in 22 patients. This change in mood was more accentuated during the 24 hours preceding the seizure.

The prevalence and clinical characteristics of *postictal symptoms of depression* have recently been studied in a systematic manner in 100 consecutive patients with poorly controlled partial seizure disorders who were off all psychotropic drugs [54]. We identified a mean of 4.8 ± 2.4 postictal symptoms of depression (range: 2–9; median = 5) in 43 (43%) patients. These symptoms were a habitual event as they occurred after more than 50% of their seizures and could be identified by patients anytime within the 72 hours after a seizure (or cluster of seizures). The median duration of all but one postictal symptom of depression was of 24 hours (range: 0.1–240 hours). Thirteen of these 43 patients reported a cluster of at least seven symptoms, and 18 patients had six symptoms that lasted 24 hours or longer and mimicked symptoms of major depressive episode, with the exception of the time-frame criterion. Thirteen patients reported habitual *postictal suicidal ideation;* eight experienced passive and active suicidal thoughts; only five reported passive suicidal ideation. No patient ever acted on these symptoms.

4.2. B. Depressive episodes related to specific neuroanatomic structures in secondary depression

Depressive episodes have been associated with specific structural lesions within the CNS, particularly in stroke patients. In 1984, Robinson and colleagues [55] reported a higher occurrence of left hemispheric stroke among patients with poststroke depression (PSD), more often involving left frontal dorsolateral cortical regions. They also found that stroke in left (but not right) basal ganglia was significantly associated with PSD. Robinson and Szetela [56] had a few years earlier observed an inverse relationship between the severity of PSD and proximity of the stroke to the frontal pole. Other authors have replicated these findings in only left hemispheric strokes, while others found the same relationship among patients with left- and right-sided stroke [57].

Some authors have not found a relationship between location of stroke and PSD, however. In a review of the PSD literature, Cummings and Mega [58] found that the relationship between location of stroke and PSD was tied to timing of the onset of depression symptoms after the stroke. Thus, there is a higher frequency of left than right hemisphere lesions associated with PSD if the depressive episode occurs in the early weeks after the stroke, whereas this relationship disappears if the onset of symptoms is 3 months after the stroke. Furthermore, these authors observed that when symptoms appear more than 1 year after the stroke, right-sided lesions are more frequent. In addition, small subcortical lesions of the left hemisphere are associated with a higher frequency of depression than right-sided subcortical lesions [59].

Functional neuroimaging studies with PET have been useful in identifying neuroanatomic areas involved in depressive symptoms of patients with PD. For example, Mayberg and colleagues [60] found decreased metabolic activity bilaterally in the inferior orbitofrontal cortex and caudate in depressed compared with nondepressed, nondemented, PD patients using FDG-PET. The metabolism in the inferior-frontal cortex was inversely proportional to the degree of depression. In a follow-up study, these authors found that in depressed PD patients successfully treated with fluoxetine, metabolic activity increased and normalized in the dorsal fronto-cortical areas with a decrease in the ventral paralimbic areas [61].

Laterality of the seizure focus has been raised as a potential factor mediating depression in epilepsy, but to this day, its role remains controversial. Some investigators have suggested that a left hemispheric focus may be a factor predisposing to depression [62–64]. Functional neuroimaging studies carried out with PET showed that patients with left temporal lobe seizure foci are more likely to exhibit depressive symptoms than those with right temporal lobe lesions, but metabolic activity is decreased in inferior frontal structures bilaterally rather than in the temporal lobe [65].

Given the above data, it is not surprising to find a significantly higher prevalence of depressive disorders in patients with neurologic disease. Indeed, prevalence rates of depression in neurologic patients have consistently been found to be significantly higher than those in medical, nonneurologic patients and in the general population. For example, several cross-sectional studies have identified depression in 30–50% of patients following stroke [57]. Prevalence rates vary depending on the patient population studied. In a recent review article,

Robinson et al. [57] calculated a pooled prevalence rate of all types of depression of 31.8% (range: 30–44%) from four community-based studies. In multiple sclerosis (MS), the lifetime prevalence of a MDDs has been found to range from 10 to 60% [66,67], whereas point prevalence rates have been reported to range between 27 and 54% [68]. Furthermore, Schubert and Foliart [69] found that the prevalence of depression was higher in patients with MS than in patients with chronic diseases associated with debilitating motor deficits such as muscular dystrophy and spinal cord injury of comparable severity. The prevalence of depression in PD has also been relatively high. Gotham and colleagues [70] reviewed 14 studies including 1500 PD patients and Cummings [71] reviewed 26 studies, and both came up with similar rates of depression, i.e., ~46%. These rates are lower in community-based studies [72]. Schrag and colleagues [73] found moderate to severe depression in 19.6% of patients.

In epilepsy, the rate of prevalence of depression is also higher than in a matched population of healthy controls, ranging from 20 to 55% in patients with recurrent seizures and 3–9% in patients with controlled epilepsy [74]. In a community-based study, Jacoby and colleagues [75] found in a large survey that 21% of 168 patients with recurrent seizures were depressed. Blum and colleagues recently reported the results of a population-based survey that investigated the lifetime prevalence of major depression, epilepsy, diabetes, and asthma in close to 181,000 individuals. Among 2281 people with epilepsy, 29% reported having experienced at least one episode of major depression. This contrasted with 8.7% prevalence in healthy respondents and with 17 and 16% in patients with diabetes and asthma, respectively [76]. Finally, in patients with Alzheimer's disease, prevalence rates have been found to range between 30 and 50% [77–79].

4.3. C. Impact of depression on the course of neurologic disease

Depression has been found to have a negative impact on the course and outcome of neurologic disease. For example, in stroke patients, the presence of PSD has been associated with a worse recovery of cognitive impairments and activities of daily living (ADL) and a higher mortality risk. Starkstein and colleagues [80], for example, found that patients with major PSD had significantly more cognitive deficits than nondepressed patients with strokes similar in location and size. This association, however, was demonstrated in left, but not right, hemisphere strokes [81]. In a follow-up study of 140 patients, Robinson and colleagues [82] have shown that the presence of major PSD was associated with greater cognitive impairment 2 years after a stroke.

Parikh and colleagues [83] found that in-hospital PSD was the most important variable that predicted poor recovery in ADL over a 2-year period. Of note, the score of inpatient ADL was not associated with the level of recovery achieved after 2 years. On the other hand, successful treatment of PSD with nortriptyline was significantly associated with recovery of ADL [84].

Of greater concern is the relationship between the presence of PSD and the higher mortality risk following stroke. Wade and colleagues [85] showed that among 976 patients followed for 1 year, those with PSD had 50% higher mortality than those without. Robinson and colleagues [86] found that patients treated with fluoxetine or nortriptyline had an increased survival probability at 6 years (61%) compared with patients given placebo (34%).

Depression may also have a negative impact on postsurgical outcome in patients undergoing a temporal lobectomy for the treatment of refractory epilepsy. In a study of 90 consecutive patients, a lifetime history of a depressive disorder preceding the temporal lobectomy was a predictor for a lesser likelihood of reaching a postsurgical seizure-free outcome [87].

5. Is depression a risk factor of neurologic disease?

Recent studies have demonstrated a bidirectional relationship between depression and some neurologic disorders. That is, while the occurrence of a neurologic insult increases the risk of developing depression, a history of depression is also associated with a greater risk of developing a given neurologic disorder. For example, in a population-based, case–control study of patients with newly diagnosed adult-onset epilepsy carried out in Sweden, Forsgren and Nystrom found that a history of depression *preceding the onset of the seizure disorder* was six times more frequent among patients than controls [88]. In a second population-based, case–control study of the incidence of new-onset epilepsy among adults aged 55 and older, Hesdorffer et al. [89] found that compared with controls, patients were 3.7 times more likely to have had a history of depression preceding their initial seizure (after controlling for the impact on seizures of medical therapies for depression). Interestingly, 26 centuries ago, Hippocrates recognized this bidirectional relationship when he wrote: *''melancholics ordinarily become epileptics, and epileptics melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy''* [90].

By the same token, Larson and colleagues [91] found in a population-based study that patients with depression were 2.6 times more likely to suffer from a stroke than those without, even after controlling for other risk factors of stroke (i.e., diabetes, smoking, heart disease, hypertension).

Nilsson and colleagues [92] carried out a population-based study to determine whether patients with a

diagnosis of depression were at an increased risk of developing PD, compared with medically ill control groups. The investigators identified three cohorts totaling 164,385 patients: one cohort included patients with affective disorders (mania or depression), a second cohort with osteoarthritis, and a third one with diabetes mellitus. Time to the first diagnosis of PD was estimated with the use of survival analyses. Patients with depressive disorder were significantly more likely to develop PD than patients with osteoarthritis ($P < 0.01$) and diabetes ($P < 0.0005$), yielding an odds ratio of 2.2 (95% CI: 1.7–2.9).

In a separate population-based study carried out in The Netherlands, Leentjens and collaborators [93] compared the incidence of depression in patients who were later diagnosed with PD with that of a matched control population. Data were obtained from a population of 105,416 people. At the time of diagnosis of PD, 9.2% of patients had a lifetime history of depression compared with 4% of the control population. The odds ratio for a history of depression was 2.4 (95% CI: 2.1–2.7), similar to that reported by Nilsson.

6. Concluding remarks

Looking at the studies reviewed in this article, clinicians may be able to appreciate that depression is most likely a neurologic disorder with psychiatric symptoms. At the least, these data should be expected to convince clinicians to screen their neurologic patients for the presence of a comorbid depressive disorder to minimize the negative impact that depression has on the course of neurologic disease. The fact is that this is not happening. Indeed, recent studies on the outcome of depressive disorders in neurologic patients suggest that clinicians continue to underrecognize and undertreat depressive disorders. Carson and colleagues [94] illustrated the problem in a study of 226 patients seen at a neurology clinic who were followed for a 2-year period. Depressive disorders were identified in 88 (40%), 54 of whom (26%) had MDDs. Eight months later, 69 (78%) patients continued to display symptoms of depression; 46 (85%) of the 54 patients with major depression continue suffering from major depression. Furthermore, among the 138 patients without depression at the initial evaluation, 20 had developed a new MDD.

Is depression a neurologic disorder with psychiatric symptoms? The data presented in this article appear to suggest it.

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