

Part One

General Considerations

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Depression in Neurologic Disorders: Why Should Neurologists Care?

Andres M. Kanner

Departments of Neurological Sciences and Psychiatry, Rush Medical College at Rush University; Laboratory of EEG and Video-EEG-Telemetry; Section of Epilepsy and Rush Epilepsy Center, Rush University Medical Center, Chicago, IL, USA

Introduction

Depressive disorders are the fourth medical disorder with a significant burden on the individual, the family, and society worldwide. In the general population, their lifetime prevalence has been estimated to be 26% for women and 12% for men [1, 2]. In patients with neurologic disorders, the lifetime prevalence of depressive disorders ranges between 30% and 50%. For example, in patients with epilepsy, a lifetime prevalence of 34.2% (25.0–43.3%) was identified in a Canadian population-based study [3]. In a population-based study of 115,071 subjects aged 18 and older a 12-month prevalence rate of major depression of 25.7% was found among people with multiple sclerosis (compared with only 8.9% of those without) [4]. In a review of the literature, Robinson and Spalletta found an overall prevalence of major depression of 21.7% and minor depression of 19.5% based on pooled data [5]. Reijnders et al. conducted a systematic review of the literature of the prevalence of depressive disorders in Parkinson's disease (PD) and found major depressive disorder in 17%, minor depression in 22%, dysthymia in 13%, and significant symptoms of depression not meeting any *Diagnostic and*

Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria in 35% of patients [6].

Yet, despite their high prevalence rates, depressive disorders remain underrecognized and undertreated in patients with neurologic disorders. For example, in a study of 100 consecutive patients with epilepsy, 69 patients were found to experience symptoms of depression severe enough to warrant referral for treatment; 63% of patients with spontaneous depression and 54% of patients with an iatrogenic depression had been symptomatic for more than 1 year before treatment was initiated [7].

Failure to recognize depression in patients with neurologic disorders is the result of various problems: (1) poor, if not lack of communication between neurologists and psychiatrists; (2) limited training of psychiatric disorders in neurology residency programs and vice versa; and (3) limited access of patients to psychiatric care due to insurance-related obstacles and other economic factors. Thus, can neurologists continue ignoring the comorbid depressive disorders affecting their patients and can they just focus on the management of the neurologic disorder at hand? The aim of this chapter is to set up the

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case for why neurologists must care about the existence of comorbid depressive disorders and ensure of their timely treatment as part of a comprehensive management of their patients.

Neurologists must care about the presence of comorbid depressive disorders for various reasons. These include:

1. Depressive disorders are a risk factor for the development of neurologic disorders.
2. The presence of depressive disorders is associated with a worse course and outcome of the neurologic disorder.

These points are reviewed in some detail in most of the chapters of this book.

Are depressive disorders a risk for the development of neurologic disorders?

Stroke

Since the last decade of the 20th century, various studies were published in the literature suggesting that a history of depression or the mere presence of depressive symptoms were associated with a two- to threefold higher risk of developing a stroke [8–10]. These data were confirmed in a recent meta-analysis of 28 prospective cohort studies that included a total of 317,540 subjects and 8478 stroke cases during a follow-up period ranging from 2 to 29 years [11]. An increased risk was found for total stroke (hazards ratio [HR] = 1.45; 95% confidence interval [CI] = 1.29–1.63), fatal stroke (HR = 1.55; 95% CI = 1.25–1.93), and ischemic stroke (HR = 1.25; 95% CI = 1.11–1.40). The pathogenic mechanisms associated with the increased risk of stroke in people with depression are reviewed in detail in Chapter 10.

Migraine

Patients with depression have been found to be at increased risk of developing migraine and vice versa. For example, in a prospective study of 496 subjects aged 25–55 years with migraine, 151 subjects with other types of headaches of comparable severity and 539 healthy controls were followed for a 2-year period. The presence of major depression at baseline predicted the first onset migraine during the 2-year follow-up period (odds ratio [OR] = 3.4; 95% CI = 1.4, 8.7) but not other severe headaches (OR = 0.6; 95% CI = 0.1,

4.6). Likewise, migraine at baseline predicted the first onset major depression during follow-up (OR = 5.8; 95% CI = 2.7, 12.3) [12]. Of note, this risk was limited to migraines and did not include other types of headache (see also Chapter 9).

Epilepsy

Hippocrates was the first clinician to identify the increased risk of epilepsy associated with depressive disorders when he wrote 26 centuries ago that “epileptics become melancholics and melancholics epileptics.” In the last two decades, three population-based studies have shown that patients with a depressive disorder have a three- to sevenfold higher risk of developing epilepsy [13–15]. The pathogenic mechanisms that may explain the increased risk of epilepsy in subjects with depression are reviewed in detail in Chapters 2 and 11.

Dementia

A history of depression has been associated with an increased risk of developing Alzheimer’s dementia (AD). For example, a meta-analysis of 20 studies that encompassed 102,172 subjects in eight countries revealed a positive relation between a history of depression and a risk for developing AD in 19 of the 20 studies [16]. Symptoms of depression may often be the initial clinical manifestation of AD. Thus, studies that investigate the relation between depressive disorders and the risk of developing AD may be biased by this temporal relation of psychiatric and cognitive symptoms. Yet, in this meta-analysis, the interval between the diagnosis of depression and that of AD was positively and significantly related to the odds of developing AD. In other words, the longer the timing between depressive episodes and the onset of AD was significantly associated with the risk of developing this type of dementia. Furthermore, in a study of 1003 elderly subjects (all with a Mini-Mental State score of more than 26), the presence of significant depressive symptoms at baseline predicted a higher risk of cognitive decline 4 years later [17]. The severity of a mood disorder was also associated with the risk of developing dementia. Also, data from a case register study of almost 23,000 patients with an affective disorder suggested that increasing severity, expressed as the number of major

depressive episodes leading to an inpatient admission, increased the risk of developing dementia [18]. Thus, patients with three admissions had close to a threefold increased risk of dementia (95% CI: 0.64–13.2), compared with patients with only one admission.

Whether a history of depression in individuals with mild cognitive impairment is predictive of an increased risk of developing AD or is only an expression of the temporal association between depressive symptomatology and the onset of the dementing process remains to be established. This dilemma is illustrated in a study of 114 patients with amnesic mild cognitive impairment who were followed for a 3-year period; 41 patients (36%) displayed a depressive disorder at baseline. After 3 years, 35 (85%) of these patients had developed AD, in comparison with 32% of the nondepressed subjects, yielding a relative risk of developing AD of 2.6 (95% CI: 1.8–3.6) [19].

Parkinson's disease

As in the case of dementia, depressive episodes may be the initial clinical manifestations of PD. However, there are data suggestive that depressive disorders may increase the risk of developing PD. These data are illustrated in two population-based studies. In the first one, conducted in The Netherlands, all subjects diagnosed with depression between 1975 and 1990 were included and matched with subjects with the same birth year who were never diagnosed with depression. Follow-up ended at April 30, 2000. Among the 1358 depressed subjects, 19 developed PD, and among the 67,570 nondepressed subjects, 259 developed PD, yielding an HR of 3.13 (95% CI: 1.95–5.01) for depressed versus nondepressed in multivariable analysis [20]. In the second study that included 105,416 subjects, investigators compared the lifetime incidence of depressive disorders in patients later diagnosed with PD with that of a matched control population. At the time of their diagnosis of PD, 9.2% of the patients had a history of depression, compared with 4.0% of the control population; the OR for a history of depression for these patients was 2.4 (95% CI: 2.1–2.7) [21].

The data outlined in the previous two sections illustrate a bidirectional relation between depressive disorders and these neurologic conditions.

These data do not establish causality, however, but rather suggest the existence of common pathogenic mechanisms operant in depressive and neurologic disorders. These mechanisms are reviewed in great detail in the respective chapters of this book.

A comorbid depression is associated with a worse course of the neurologic disorder

If there is one reason for neurologists to care about recognizing and ensuring the treatment of comorbid depression in patients with neurologic disorders, this is it. Here are some concrete examples:

Stroke

Poststroke depression (PSD) has been found to have a negative impact on the recovery of cognitive deficits, on the ability to perform activities of daily living (ADL), and in the mortality risks in patients with stroke. For example, one study demonstrated that patients with major PSD had significantly more cognitive deficits than patients without depression who experienced a similar location and size of left-hemisphere (but not right-hemisphere) stroke [22]. In another study of 140 patients, the presence of major PSD was associated with greater cognitive impairment 2 years after a stroke [23]. Likewise, one study found that in-hospital PSD was the most important variable predicting poor recovery in ADL over a 2-year period. In fact, the score of in-hospital ADL was not associated with the 2-year recovery [24].

There is also an increased mortality risk in patients with stroke associated with the presence of comorbid depressive disorders [25–27]. For example, in a population-based study, 10,025 subjects were followed over 8 years; 1925 deaths were recorded. Mortality rate per 1000 person-years of follow-up was highest in the group with both a history of stroke and depression (HR: 1.88; 95% CI: 1.27, 2.79) versus only depression present (HR: 1.23; 95% CI: 1.08, 1.40) versus only stroke (HR: 1.74; 95% CI: 1.06, 2.85) [25]. However, the combined effect of depression and stroke is less than additive. Furthermore, in another study, patients with PSD had a 3.4-fold higher risk of dying during a 10-year follow-up period than patients without depression independently of

other stroke risk factors [26]. Finally, a higher mortality risk was found over a 3-year follow-up period in patients with PSD even though these patients were younger and suffered from fewer chronic conditions [27].

Epilepsy

A history of depression preceding the onset of epilepsy or identified at the time of diagnosis of the seizure disorder has been associated with a worse response to pharmacotherapy. For example, in a study of 780 patients with newly diagnosed epilepsy who were followed over a median period of 79 months, seizures were controlled in 462 patients, while in 318 patients epilepsy remained refractory to antiepileptic drug (AED) therapy [28]. Univariate and multivariate logistic regression analyses demonstrated that a psychiatric history, and in particular a history of depression preceding the diagnosis of epilepsy, was associated with a twofold higher risk of pharmacoresistance. In a more recent study of 138 patients with new onset epilepsy, those with symptoms of depression at the time of diagnosis were significantly less likely to be seizure free after a 12-month follow-up period [29]. Likewise, in a study of 100 consecutive patients with treatment-resistant temporal lobe epilepsy who underwent an anterotemporal lobectomy, a lifetime history of depression was found to be associated with a worse postsurgical seizure outcome [30]. Indeed, a history of depression was recorded in only 12% of patients who became free of auras and disabling seizures in contrast to 79% of patients with persistent disabling seizures.

Parkinson's disease

The presence of depression in patients with PD has been associated with a more rapid deterioration of motor and cognitive functions, especially executive function [31]. In a study that compared cognitive functions between 45 patients with PD with current depression and 45 patients without depression matched for age, education, gender, age at disease onset, disease duration, and disease severity, patients with depression were significantly more impaired cognitively. While cognitive functions were impaired in both groups, impaired memory was found only in patients with PD with depression [32]. Another

study compared neuropsychological functions among patients with PD and major depression, patients with PD without depression, patients with major depression but without PD, and age-comparable healthy controls. More severe cognitive deficits were identified in patients with major depression, with or without PD, than both healthy controls and patients with PD without depression on tests of verbal fluency and auditory attention [33]. In addition, more severe deficits on tasks of abstract reasoning and set alternation were found in patients with PD and major depression than the other three groups.

Alzheimer's dementia

As in the case of epilepsy, there are data suggesting that a history of depression may be associated with a worse course of AD. For example, in a study of 43 patients with AD who had a mild to moderate cognitive impairment, 22 were found to have a history of a major depressive disorder before the onset of any cognitive impairment. None of these patients were suffering from a depressive episode at time of cognitive assessment. After controlling for age, education, duration of illness, gender, and medication status, subjects with a history of major depressive disorder had significantly lower scores on neuropsychological tests, which included the Mini-Mental State Exam, Wechsler Adult Intelligence Scale (WAIS) Full-Scale and Verbal Scale IQ, and the Initiation/Perseveration subscale of the Mattis Dementia Rating Scale [34]. These subjects also developed symptoms of dementia at a significantly earlier age than the subjects without a prior history of a depressive disorder.

The presence of comorbid depressive disorders in patients with AD is associated with a faster cognitive deterioration, worse deterioration in ADL [35], an earlier placement in a nursing facility [36], and it is also associated with a faster decline in cognitive functions [37].

Is depression a neurologic disorder with psychiatric symptoms?

The pathogenic mechanisms that explain the bidirectional relation between depression and various neurologic disorders and the mechanisms mediating the negative impact of comorbid depression on their course are multiple and complex and are reviewed in great detail in the

corresponding chapter of this book. Accordingly, they do not need to be discussed here. Yet neuroimaging and neuropathologic abnormalities in primary depressive disorders suggest that depression is in fact a neurologic disorder. Here is a very brief summary of the evidence: Neuroimaging studies with volumetric measurements of various neuroanatomical brain structures conducted in patients with primary major depressive disorders have revealed the presence of atrophy of hippocampal formations and frontal lobes, including cingulate gyrus and orbitofrontal and dorsolateral cortex [38–41]. The presence of neuropathologic abnormalities further supports our contention that depressive disorders are a neurologic disorder. These are manifested by: (1) decreased glial densities and neuronal size in the cingulate gyrus; (2) decreased neuronal sizes and neuronal densities in layers II, III, and IV in the rostral orbitofrontal cortex, resulting in a decrease of cortical thickness; (3) a significant decrease of glial densities in cortical layers V and VI, associated with decreases in neuronal sizes in the caudal orbitofrontal cortex; and (4) a decrease of neuronal and glial density and size in all cortical layers of the dorsolateral prefrontal cortex [42–46].

Concluding remarks

The data reviewed in this chapter clearly illustrate the negative impact of comorbid depressive disorders on the course and response to treatment of neurologic disorders. If for no other reasons, these are the ones which should make neurologists care about the early recognition and treatment of depressive disorders. This topic is discussed in great detail in the chapters of this book. Yet, if we are to believe in these data, we must start thinking on how to overcome the obstacles that have been responsible for the indifference of neurologists toward psychiatric comorbidities, beginning by expanding the training of medical students and neurology and psychiatry residents on the psychiatric comorbidities of neurologic disorders and the neurologic comorbidities of psychiatric disorders. Finally, if a bidirectional relation between psychiatric and neurologic disorders appears to be well established, isn't it time for neurologists and psychiatrist to establish a bidirectional relation?



PEARLS TO TAKE HOME

- A history of depression is associated with a two- to threefold higher risk of developing a stroke.
- Poststroke depression has been found to have a negative impact on the recovery of cognitive deficits, ability to perform activities of daily living, and in the mortality risks of patients with stroke.
- Patients with depression have been found to be at increased risk of developing migraines and vice versa.
- Patients with a depressive disorder have a three- to sevenfold higher risk of developing epilepsy.
- A history of depression preceding the onset of epilepsy or identified at the time of diagnosis of the seizure disorder has been associated with a worse response to pharmacotherapy, while a lifetime history of depression is associated with a worst postsurgical seizure outcome in temporal lobe epilepsy.
- A history of depression has been associated with an increased risk of developing AD.
- A history of depression is associated with a worse course of AD.
- Depressive disorders may increase the risk of developing PD.
- The presence of depression in patients with PD has been associated with a more rapid deterioration of motor and cognitive functions.

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