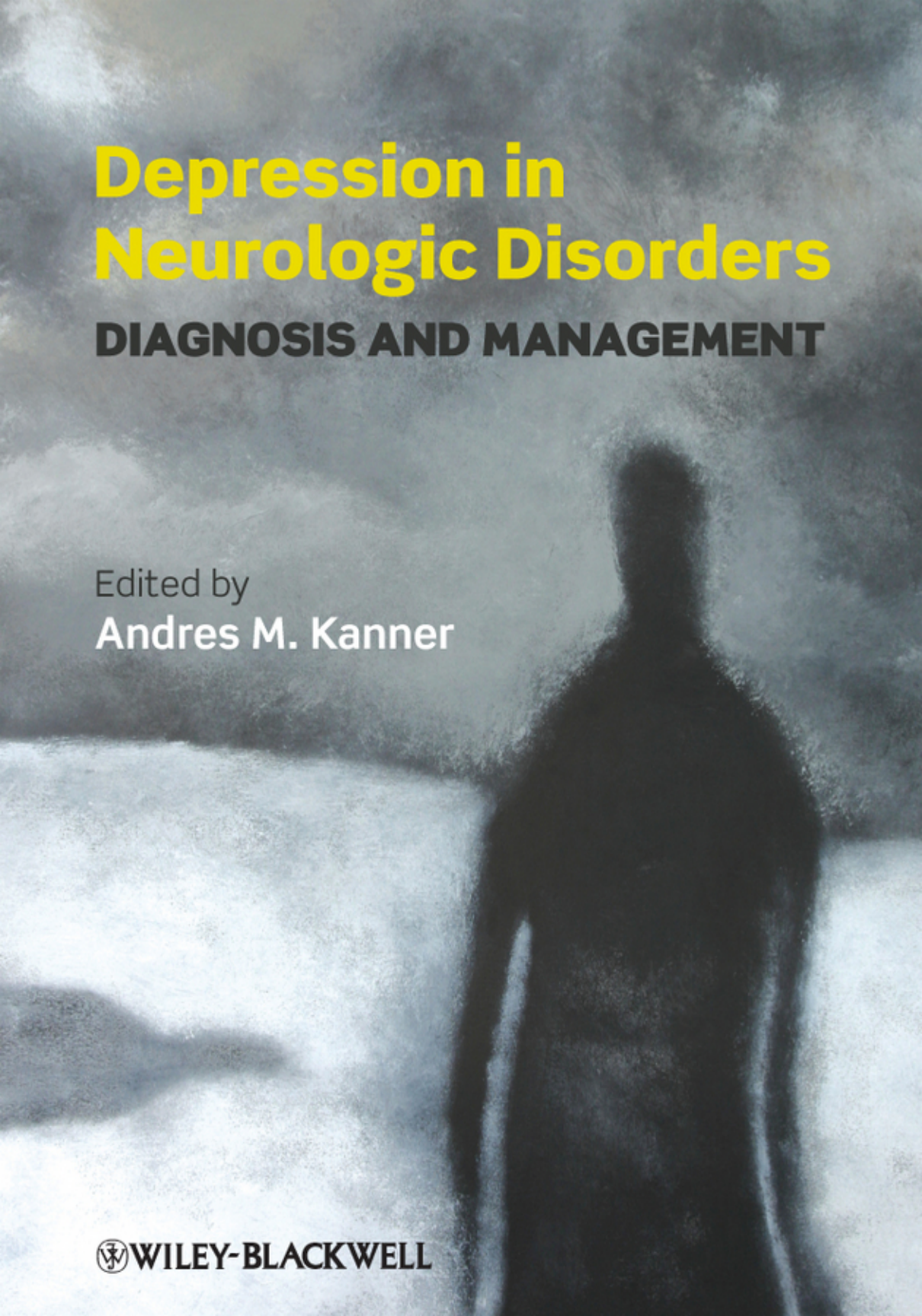
Depression in Neurologic Disorders
DIAGNOSIS AND MANAGEMENT
Edited by
Andres M. Kanner
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Depression in Neurologic Disorders: Diagnosis and Management

I wish to dedicate this book to all the academicians of the Universities in Israel, who through their creativity and accomplishments have been a constant inspiration to me throughout my professional career.

I also wish to dedicate this book to my wife Hilary and my daughters Lesley Anne and Lauren Amanda who through their unconditional love and support have filled my life with joy.

Depression in Neurologic Disorders: Diagnosis and Management

EDITED BY

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Foreword

There is a new buzzword in neurologic circles, which is *comorbidity*. Sometimes mistaken for denoting any separate medical problem found to be increased in frequency with an index disorder, and defined as the co-occurrence of two disorders at above chance levels, the term usefully should relate to where there is a direct or a heuristic proposition of a biological or sociological link between the conditions. In other words, where the substrate of condition *x* presupposes condition *y* or vice versa. There needs to be some dependent endogenous link between two disorders, such that the causal link between them can be explored.

There is little to be pursued in trying to understand why people with tetraplegia develop sacral ulcers or have urinary infections, or why someone with epilepsy has head injuries. However, where a common organ is involved in two diagnostically separate disorders, then an increased comorbidity between the two will have both biological relevance and may lead to improved patient management. Since psychiatric and neurologic disorders both share the brain as the font of symptomatology, it is hardly surprising that overlapping syndromes are frequently noted in clinical practice.

The description of psychiatric symptoms in neurologic disorders has a long history, dating back to the times of Hippocrates, but such interest accelerated in the European literature of the 19th century, when the distinction between neurology and psychiatry as separate medical disciplines was not countenanced. With the growing rift between an organically based neurology and a psychologically based psychiatry in the first six decades of the 20th century, interest in such comorbidities waned, in spite of such obvious clinical presentations of, for example, postictal psychoses, or the dementias seen in conditions such as Parkinson's disease or multiple sclerosis.

However, we are now in a different era, not only of shifting paradigms, with disciplines such as behavioral neurology and neuropsychiatry ready to embrace a more holistic view of brain–behavior associations, but with an understanding of neurobiology based on sophisticated technology, both for exploring the intricacies of brain structure and function, but also for bringing the live brain to life with differing imaging modalities. This timely book has been edited by Andres M. Kanner, who has not only made the psychiatric comorbidities of epilepsy a central area of research, but who has also the requisite clinical experience to envisage a wider perspective, embracing a spectrum of neurologic disorders and a frequently encountered but often ignored clinical problem, namely depression.

The observation that patients with various neurologic disorders develop depression is nothing new, except that few investigators have expressed much interest in the association until recently. The renewed importance of the comorbidity arises from several factors. Some decade or two ago, measuring quality of life (QOL) in various disorders became fashionable, and not surprisingly most neurologic conditions investigated compromised this important variable. However, closer inspection of QOL assessments revealed that much of the variance could be explained by the presence of depression. The growing understanding of the neuroanatomical and neurochemical substrates of depression, revealing interlinks between neural circuits and neurotransmitters common to both neurologic and psychiatric disorders, led the curious minded to reexplore the clinical situation, and the thera-

peutically minded to pursue treatments for the psychiatric comorbidity, thus going beyond that required for the index condition. Even more recently, the acknowledged link between certain neurologic disorders and their treatment and suicidal behaviors, including completed suicide, has placed all neurologists in the challenging position to explore the affective state of their patients, and if depression is suggested, to either manage it themselves or to refer to a competent associate.

Andres M. Kanner sets the scene by asking, "Why should neurologists care?" The rest of the book develops this theme, and helps with an even more important question: "How should neurologists care?"

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January 2012

Preface

The lack of communication between psychiatrists and neurologists is one of the most incomprehensible phenomena in modern medicine, as most (if not all) neurologic disorders affecting the central nervous system are associated with a psychiatric comorbidity, of which depression is the most common. And yet, in a majority of patients, depression remains unrecognized and untreated, as most neurologists focus only on the identification of neurologic signs and symptoms and their treatment.

Nevertheless, the impact of a comorbid depressive disorder in the life of these patients can be as devastating as and often more disabling than the actual neurologic disorder. When investigated, a lifetime history of depression can be identified in one out of every three to four patients suffering from any of the major neurologic conditions including epilepsy, stroke, migraine, multiple sclerosis, dementia, movement disorders and traumatic brain injury.

Contrary to old assumptions, depression is not simply a "reactive process" to the limitations and obstacles caused by the underlying neurologic disorder. In fact, there is a complex relation between depression and several neurologic disorders, as evidenced by the existence of a bidirectional relation between depression and conditions like epilepsy, stroke, migraine, Parkinson's disease and possibly also dementia. In other words, not only are patients with these neurologic conditions at higher risk of developing depression, but patients with depression are at a higher risk of developing one of these neurologic disorders. This bidirectional relation does not establish causality but suggests the existence of common pathogenic mechanisms operant in the psychiatric and neurologic conditions.

The complex relation between depression and neurologic disorders has significant clinical implications that should be of great concern to neurologists, as the existence of a comorbid depressive disorder is associated with a worse course and poorer response to treatment of the neurologic disorder. Furthermore, comorbid depression has been found to be an independent risk factor for a poor quality of life and increased suicidal risk. It accounts for higher medical costs (not related to the psychiatric treatment) and lesser compliance with the neurologic treatment. Accordingly, one would expect to find a plethora of data on the impact of the treatment of depression on the course of the neurologic disorder. Alas, nothing is further from the truth! In fact, a review of the literature reveals a paucity of studies on the treatment of depression in most neurologic disorders. This problem is compounded by the limited access of patients to psychiatric treatment because of financial reasons, reluctance on the part of patients and their family to seek psychiatric evaluations, and a discomfort on the part of psychiatrists to treat patients with neurologic disorders.

The aim of this book is to start overcoming these serious shortcomings in the management of patients with neurologic disorders and facilitate the dialogue among neurologists, psychiatrists, neuropsychologists and other mental health providers. I was extremely fortunate to count with a group of international experts in the field to make this book a reality. The task given to each author was to review the available data in the literature and to provide practical strategies for the identification and treatment of comorbid depressive disorders in the major neurologic conditions.

The book is introduced by a chapter that makes the case of why neurologists should care about depression in neurologic patients by reviewing its impact on the course and treatment response of the neurologic disorder. In the other chapters of the book's first section, we review the neurobiologic aspects of primary depression (Chapter 2), its clinical characteristics and treatment strategies (Chapter 3), and the use of screening instruments of depression in various neurologic disorders (Chapter 4). Suicide is more frequent in neurologic patients than in the general population. This important topic is reviewed with a focus on the prevalence and variables associated with its occurrence in the major neurologic conditions (Chapter 5). Cognitive disturbances are key clinical manifestations of depression, but they may result as well from the underlying neurologic condition. Distinguishing one from the other poses a significant diagnostic dilemma, which can be resolved with neuropsychological testing. The indications, diagnostic yield and limitations of this diagnostic modality are discussed in patients with primary depression as well as in neurologic patients with comorbid depression (Chapter 6). The diagnosis and management of depression in pediatric patients poses particular challenges which frequently limit its recognition and its management. Accordingly, a chapter is dedicated to review the principal aspects of this topic (Chapter 7). The last chapter of the first section (Chapter 8) provides a review of the basic principles in the management of depression in neurologic disorders.

The second section of the book focuses on the specific aspects of depression in the major neurologic disorders, including migraine (Chapter 9), stroke (Chapter 10), epilepsy (Chapter 11), movement disorders (Chapter 12), multiple sclerosis (Chapter 13), Alzheimer's disease (Chapter 14) and traumatic brain injury (Chapter 15). Each one of these seven chapters reviews the epidemiologic aspects of depression in the respective neurologic condition, the potential pathogenic mechanisms that may explain the high comorbid prevalence and bidirectional relation, the clinical manifestations, with special emphasis on the clinical differences of depression in each particular neurologic disorder (relative to primary depression) and, finally, the treatment strategies that can be considered.

My hope is that this book will provide clinicians the necessary data to understand the need to identify and treat comorbid depression in neurologic disorders, and make available the necessary tools to achieve those goals. While I do not expect or believe that neurologists should treat the depressive disorders in all their patients, they should ensure that their existence is investigated in every evaluation and, when possible and appropriate, treated by them or referred to a mental health professional.

Andres M. Kanner, MD

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Part One

General Considerations

1

Depression in Neurologic Disorders: Why Should Neurologists Care?

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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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