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REVIEW

Depressive syndromes in neurological disorders

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Abstract Depressive syndromes represent a common and often characteristic feature in a number of neurological disorders. One prominent example is the development of post-stroke depression, which can be observed in more than one-third of stroke survivors in the aftermath of an ischemic stroke. Thus, post-stroke depression represents one of the most prevalent, disabling, and potentially devastating psychiatric post-stroke complications. On the other hand, depressive syndromes may also be considered as a risk factor for certain neurological disorders, as recently revealed by a meta-analysis of prospective cohort studies, which demonstrated an increased risk for ischemic events in depressed patients. Moreover, depressive syndromes represent common comorbidities in a number of other neurological disorders such as Parkinson's disease, multiple sclerosis, or epilepsy, in which depression has a strong impact on both quality of life and outcome of the primary neurological disorder.

Keywords Depression · Neuropsychiatry · Psychosomatic medicine · Neurological disorders

Introduction

Psychiatric symptoms, particularly depressive syndromes, represent characteristic and frequently observed comorbid conditions in a variety of neurological conditions. Major depressive disorder (MDD) represents a risk factor for the development of neurological disorders (e.g., stroke) and often impairs recovery precipitating worse prognosis of a primary neurological disorder. MDD is one of the most prevalent psychiatric disorders with a point prevalence of 5.6 % and a 12-months prevalence of 10.7 % for people between age 18 and 65 in the general population of Germany [67, 77, 159]. This underscores the considerable likelihood of observing depressive syndromes as a comorbidity of a neurological disorder and should be kept in mind when appraising the prevalence of depression in neurological disorders. On the other hand, the high prevalence of MDD in the general population underlines its relevance as an exacerbating risk factor in neurological disorders.

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This article aims to review current knowledge on MDD as a risk factor and depressive syndromes in the context of selected neurological disorders and will focus on the following topics:

- Post-stroke depression
- Major depressive disorder as a risk factor for stroke
- Parkinson's disease and depression
- Depressive syndromes in multiple sclerosis
- Depressive syndromes in epilepsy

Both epidemiological, pathophysiological, and therapeutic aspects of these issues will be addressed, and potential consequences for clinical practice will be discussed.

This article represents an update to a previously published review on depressive syndromes in neurological conditions that is available in German only [123]. Contents and references were updated wherever relevant material was found. A PubMed search was conducted during July and August 2013 using previously established search terms [123]. Moreover, snowball searches of reference lists of identified articles were conducted to find additionally relevant literature.

Post-stroke depression

Ischemic stroke represents one of the most challenging neurological disorders and one of the leading causes of morbidity and mortality worldwide, resulting in significant, often permanent disability [56]. In Germany, ischemic stroke represents a common medical condition with an incidence of approximately 250,000 new stroke patients per year [70]. A depressive syndrome occurring in the aftermath of an ischemic stroke is termed post-stroke depression (PSD) and may be considered the most important, and most frequently observed psychiatric complication following cerebral ischemic events [93]. PSD is defined as a depressive syndrome occurring in the aftermath of a clinically apparent stroke and must not be confused with depressive symptoms occurring as a consequence of "silent" ischemic vascular events as observed in silent cerebrovascular disease ("vascular depression") [86, 157].

It is estimated that at least one-third of all stroke survivors will eventually develop PSD [86]. Despite these high rates of PSD in stroke patients, the precise pathophysiologic mechanisms linking stroke and depression are still largely unknown [85]. However, it is widely accepted that the development of PSD may not only represent a secondary consequence of psychological distress, cognitive, or motor impairments, but is in addition the result of specific, stroke-associated neurobiological changes. This notion is further supported by significantly lower rates of depression in equally impaired orthopedic patients [48]. Finally, as confirmed by a recent meta-analysis, PSD may have significant burden not only on the patients' mood, but also on functional recovery and long-term outcomes. This underlines the medical need for the identification of risk factors, underlying pathophysiology, secondary preventive interventions, and efficient treatments [16].

Epidemiology

The literature on post-stroke depression suggests prevalence of PSD to range between 3 and 37 % for major depression and 8–44 % for minor depression according to DSM or research diagnostic criteria [93, 131]. Figures vary significantly depending on rating instruments employed, time frame chosen for screening, and population characteristics such as in- versus out-patients, hospitals, or rehabilitation settings. Based on pooled data from a recent review, an overall prevalence of post-stroke minor and major depression is estimated at 19.5 and 21.7 %, respectively [131]. A recently published systematic review and meta-analysis to estimate the natural history, predictors, and outcomes of depression after stroke included a total of 50 studies and revealed prevalence rates at 29 % (95 % CI 25–32), remaining stable up to 10 years after stroke, and a cumulative incidence of 39–52 % within 5 years following stroke with recovery rates ranging from 15 to 57 % 1 year after stroke [11]. With respect to the dynamics of the disorder, a large retrospective evaluation of data from a stroke register on a 15-year time course following stroke revealed a cumulative PSD incidence of 55 % over 15 years, prevalence rates ranging between 29 and 39 %, and high rates of recurrence throughout the time course [10]. These findings indicate that the development (recurrence) of PSD must also be considered at later time points, even after primary neurological deficits and initial PSD symptoms may have long been settled.

Risk factors and etiology

Although neuropsychological and motor deficits are often treated as separate entities, there is a growing body of knowledge suggesting substantial, bidirectional interactions between neuropsychological and motor function [25]. A reliable and early identification of patients at risk of PSD represents a prerequisite for providing prophylactic interventions and adequate treatment of PSD, a condition known to increase mortality and morbidity and thus negatively impact overall stroke outcome [16, 107, 131]. Therefore, the identification of reliable predictors for PSD as well as potentially underlying pathomechanisms is essential [74].

A growing body of studies has aimed at elucidating potential links between the location of a cerebrovascular lesion and the development of PSD, for the chance to gain additional insight into pathophysiological mechanisms underlying not only PSD, but also MDD. While a meta-analysis published in 2000 was not able to point out any striking associations between stroke location and PSD development [23], preclinical evidence has revealed associations between lesion characteristics and depressive-like behavioral consequences: In an animal model of PSD based on an established unilateral 30-min middle cerebral artery occlusion (MCAo) and reperfusion technique, only left MCAo resulted in depressive-like behavior, which was furthermore accompanied by a delayed exofocal degeneration of midbrain dopaminergic neurons [85]. Despite limitations of animal models for depression, these findings clearly suggest an important role for the dopaminergic system in the development of PSD. Furthermore, a study in 243 stroke patients revealed that the dimension of PSD symptoms (apathetic vs. affective) may differ depending on anatomical stroke correlates. As revealed by this study, damage to the basal ganglia was associated with apathetic PSD, while damage to the left frontal lobe was associated with affective PSD [64].

In a systematic review of 20 studies on a total of 17,000 patients, Hackett et al. [63] point out three main risk factors positively associated with the development of PSD, which are physical disability, cognitive impairment, and severity of stroke. Moreover, female sex, social isolation, and the prevalence of prior depressive episodes have been suggested as risk factors for PSD development [20]. Another systematic review published in 2013 by Ayerbe et al. suggests major predictors of depression as disability, pre-stroke depression, cognitive impairment, stroke severity, and anxiety. Lower quality of life, mortality, and disability were identified as independent outcomes of depression after stroke, highlighting the need for targeted interventions [11].

Treatment

Both the treatment of manifest PSD and prophylactic strategies to prevent the development of PSD, but also to potentially improve recovery after stroke, even in patients that are not depressed, has been investigated. A 2008 meta-analysis by Hackett et al. [62] evaluating interventions for treating already manifest PSD came to the conclusion that pharmacotherapy was twice as effective in inducing remission compared to placebo (OR 0.47, 95 %-CI 0.22–0.98). However, there were also more side effects in pharmacotherapy versus placebo (OR 1.96, 95 %-CI 1.19–3.24). While electroconvulsive therapy was not investigated in these studies, no effects were identified for psychotherapy [62]. Conversely, a study within the "living well with stroke" trial on 101 depressed stroke survivors investigated the effects of an 8-weeks brief psychosocial–behavioral intervention adjunct to antidepressant treatment versus antidepressant treatment only and identified a strong and early effect of the psychotherapeutic intervention compared with control subjects [104]. Another recently published study revealed positive effects of a cognitive therapy augmented with graded activity training on post-stroke fatigue, a common symptom following stroke [161].

The German national guidelines on the evidence-based treatment of depression conclude that antidepressant pharmacotherapy should be offered to patients suffering from depression after stroke, with a preference for fluoxetine, citalopram, or nortriptyline, evidence level B [67]. With respect to citalopram and tricyclic antidepressants (TCA), their potential to cause prolongation of the QT interval [96], as well as their potential to inhibit platelet function and increase the risk of GI bleedings, especially when administered together with anticoagulants, must be taken into account [60, 90, 111]. Finally, a case-crossover study has recently even claimed a potential association between the use of antidepressants and increased risk of stroke. With depression itself already being a strong risk factor for stroke, however, these findings must be cautiously interpreted, bearing in mind the risk of confounding by indication [160].

Finally, any early intervention always requires an early and reliable identification of patients at risk. Thus, more efficient screening strategies for an early identification of PSD patients represent a practical need and are currently under development [35].

With respect to the prevention of PSD, there are also a number of trials that have investigated both pharmacological and psychotherapeutic interventions. The above-mentioned meta-analysis also aimed to identify whether pharmaceutical or psychological interventions can prevent depression and improve outcomes in patients after stroke. The authors concluded that only psychotherapy had a small, but significant effect on improving mood and preventing depression following stroke [61, 62]. However, lack of suitable control interventions and blinding represent common methodological problems of psychotherapy trials that should always be taken into account for the interpretation of such results.

An open study of mirtazapine including a nontreatment group demonstrated reduced incidence of PSD and also efficacy of mirtazapine in the treatment of PSD that developed in patients that were randomized to the non-treatment group [113].

A randomized placebo-controlled trial by Robinson et al. [130] investigated the outcome of stroke patients under a 12-month treatment period with escitalopram/

placebo or psychotherapy ("problem-solving therapy"). Interestingly, both escitalopram treatment and psychotherapy resulted in a lower incidence of PSD. However, effects of psychotherapy were not significant in the intent-to-treat analysis, but only in the per-protocol analysis [130].

In a more recent meta-analysis published in 2012 by Salter et al., 8 RCTs testing antidepressant intervention in nondepressed stroke patients for the prevention of PSD were identified. Pooled analyses also revealed effective PSD prevention by SSRI; however, the authors conclude that timing and treatment duration as well as identification of appropriate recipients of preventive medication required additional optimization [132].

The recently published results of the "FLAME Study" by Chollet and others revealed improved motor function in stroke patients treated with fluoxetine compared to placebo after 3 months [27]. These findings are further supported by other trials [32, 120, 162] and are compatible with a neuroprotective mechanism of action for fluoxetine in these conditions and beneficial effects of antidepressants on early rehabilitation.

Moreover, a recently published Cochrane review by Mead et al. followed up on the question, whether SSRIs might improve recovery in stroke patients independent of PSD development by performing a meta-analysis of data from 52 RCTs with a total of 4,059 patients, revealing statistically significant effects of SSRIs not only on depression-related scores, but improvement in dependence, disability, and neurological impairment as well [99].

Despite these promising results, it is a long-known phenomenon that SSRIs may increase the risk of gastrointestinal bleedings and brain hemorrhage [90, 111, 60]. While the risk of brain hemorrhage appears to be statistically increased, the overall rarity of the event suggests a rather low absolute risk, which cannot be said for upper gastrointestinal hemorrhage (UGIH). Particularly, concomitant antiplatelet and anticoagulant therapy or treatment with nonsteroidal anti-inflammatory substances, substances often used in the secondary prevention of stroke, may result in an additively increased risk of UGIH [6]. Reduction of this risk may be achieved by proton-pump-inhibitor treatment [5, 34, 146]. Therefore, a careful risk–benefit assessment is essential, especially in elderly patients and those with a history of UGIH [89, 144].

Remaining questions and challenges

It remains a controversial issue whether antidepressants should be routinely prescribed after stroke in a preventive manner. Despite persuasive data of SSRI efficacy on PSD symptoms and the chance to simultaneously improve other domains such as motor deficits as revealed by Chollet et al. and others [27, 99, 130], the use of SSRI antidepressants may still cause a heightened risk of gastrointestinal bleedings and possibly intracerebral hemorrhage in anticoagulated subjects [160]. Therefore, identifying the precise mechanisms underlying both antidepressant efficacy and potential neuroprotective effects of, e.g., fluoxetine, represents an urgent need and a necessary prerequisite for developing targeted interventions in the treatment of both PSD and stroke-related morbidity.

Key points and recommendations

Post-stroke depression (PSD) is a common psychiatric complication in the aftermath of ischemic stroke that negatively impacts stroke recovery. More than one-third of all stroke survivors are expected to develop PSD during their rehabilitation. Evidence-based treatment guidelines suggest best evidence for a treatment with the SSRIs fluoxetine and citalopram. Despite the efficacy of some TCAs, their side effect profiles, e.g., anti-cholinergic effects, should always be kept in mind. This partially also applies to citalopram, where both enantiomers may dose-dependently prolong the QT interval, requiring regular ECG checks in patients at risk. Finally, antidepressant treatment could even improve stroke-related deficits in nondepressed patients to enhance overall stroke recovery. However, further evidence on safety, efficacy, and mechanisms of a secondary preventive antidepressant intervention is required before a general recommendation can be made.

Depression as a risk factor for ischemic stroke

The former notion of a rather unidirectional association between stroke and the subsequent development of depression has changed considerably with increasing evidence from prospective epidemiological studies, which clearly point toward an increased risk for MDD patients to develop ischemic events. Although an association may not yet imply causality, such findings nevertheless allow the hypothesis of a bidirectional association between depressive syndromes and cerebrovascular events [112]. This hypothesis is further supported by the large body of evidence on an association between depression and coronary heart disease, a medical condition sharing many common features with cerebrovascular disease and stroke.

Epidemiology

Major depressive disorder (MDD) represents an often severely debilitating disease with a great and growing impact not only on the individual patient and its relatives,

but also on society. MDD has become a global public health concern, and by 2020, according to projections by the World Health Organization, unipolar depression is expected to become the number one cause of disease burden in developed countries (as measured by disability adjusted life years), and the second leading cause of disability worldwide [98]. Against the background of a comparably high prevalence of depression and the serious impact and consequences of ischemic stroke, a potential association between these two disorders is of utmost importance. Two recently published meta-analyses with the objective to substantiate a potential association between major depression and the risk for developing ischemic cerebral events evaluated a number of prospective cohort studies and were able to confirm a positive association [38, 119].

Pan et al. analyzed 28 prospective cohort studies that reported depression status at baseline with a total of 315,000 patients of which 8,478 patients suffered a stroke during a follow-up period of 2–29 years. The authors found an adjusted hazard ratio of 1.45 (95 % CI 1.29–1.63) for total stroke and a hazard ratio of 1.55 (95 % CI, 1.25–1.93) for stroke with lethal outcome among depressed subjects. Thus, depression is associated with a significantly increased risk of stroke.

These conclusions were further underlined by yet another meta-analysis with slightly different inclusion and exclusion criteria of 17 prospective cohort studies and a total of >200,000 cases including >6,000 stroke events during a 3–29 years follow-up period, which revealed a significant positive association between depression and the subsequent risk of stroke, as revealed by a pooled relative risk of 1.34 (95 % CI, 1.17–1.54) with similar associations for men and women [38].

In a large, multi-national case–control study that was published in 2010 (Interstroke Trial), 3,000 stroke cases were compared to a healthy control population of 3000 subjects. Depression (odds ratio 1.35, CI 99 %, 1.10–1.66), arterial hypertension, alcohol, and tobacco use as well as diabetes emerged as significant risk factors for the development of stroke [116].

Pathophysiological mechanisms

Stroke and cerebrovascular disease share many pathophysiological features and risk factors with cardiovascular disease, for which a substantial body of evidence has revealed an association with depression. The many variables revealed as relevant and discussed as critical for the association between depression and cardiovascular disease may mainly be categorized to biological and behavioral variables. Biological variables mainly include alterations in, e.g., the hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system, blood clotting—or immunological parameters [155], for all of which alterations in depressed patients are well documented [39, 71, 88, 102, 112, 117, 118, 135]. On the other hand, behavioral variables such as low physical activity [156, 158], low adherence [51], and tobacco use [150] have been identified as factors mediating an association between depression and cardiovascular disease. Given the shared pathophysiology of cerebro- and cardiovascular disease, these findings should be transferable to an association between depression and stroke.

Treatment (of depression in vascular disease)

Currently available evidence suggests the preferential use of SSRI antidepressants in patients with comorbid vascular disease and comorbid depression [52, 87]. The German national guideline on the treatment of unipolar depression [67] discourages the use of tricyclic antidepressants and recommends the preferential use of sertraline or citalopram, but limits the suggestion for citalopram at doses greater than 20 mg/day due to its potential to dose-dependently increase the QT interval.

An effect of antidepressants on mortality, however, is still a matter of debate. While some studies have identified either no effect or even positive, mortality-reducing effects of SSRI treatment [115, 147], there are also studies suggesting a negative impact of antidepressants on mortality [60, 65, 72, 140]. Since depression per se has been demonstrated to be positively associated with stroke and cardiovascular disease, potential "confounding by indication" must always be carefully considered before drawing premature conclusions. Interestingly, effects of antidepressants on stroke risk in patients already suffering from significant cardiovascular disease have not been systematically studied to date.

Remaining questions and challenges

A large body of evidence indicates that depression represents a risk factor for both cardiovascular and cerebrovascular disease. Further implementation of the recommendations by the AHA guidelines on depression in cardiovascular disease may represent an important step toward better addressing—and potentially reducing—the stroke risk of depressed patients with cardiovascular disease [92]. For an evidence-based confirmation, however, further studies are needed.

Finally, when it comes to the selection of specific antidepressants for the treatment of patients with cardiovascular disease and comorbid depression, there are even more open questions and more research to be done on both safety and efficacy issues in this vulnerable patient population.

Key points and recommendations

Depression represents a risk factor for stroke and cardiovascular disease. Best evidence for the use of antidepressants in patients with cardiovascular disease is currently available for the SSRI antidepressants sertraline and citalopram. For the reasons of cardiac side effects, any use of tricyclic antidepressants is strongly discouraged in this patient population. While behavioral psychotherapeutic techniques were effective in reducing mortality in nondepressed patients with cardiovascular disease [58], results in depressed patients with cardiovascular disease were rather disappointing [18]. Since reduced physical activity in depressed patients represents a major contributor to cardiovascular disease, increased physical activity should always be encouraged in depressed patients with comorbid cardiovascular disease [156].

Parkinson's disease

Parkinson's disease (PD) represents the second most common neurodegenerative disorder with an overall prevalence of 1 % in the elderly population worldwide [49]. Despite PD being dominated by motor impairments such as slowness of movement, tremor, rigidity, and postural instability, the characteristic symptomatology of PD also includes a number of so-called non-motor symptoms, affecting the majority of all patients and precipitating a significant amount of disease burden [3, 82]. Among those non-motor symptoms, there are changes in taste and smell, choking difficulties, bladder dysfunction, weight changes, sleep and cognitive impairment, and psychotic symptoms including hallucinations, circadian abnormalities, and not least affective symptoms including depression and anxiety [2, 3, 136].

Epidemiology

About one-third of all PD patients will at some point exhibit a clinically significant depressive syndrome [4, 14, 126, 129]. Depressive symptoms significantly impact the quality of life of PD patients, and they are associated with reduced functioning and cognitive impairment, leading to great burden for patients but also for caregivers [4]. Again, a bidirectional association is discussed for depression and PD: While depressive syndromes are disproportionately increased in PD patients, there appears to be also an increased risk for depressed patients to develop PD [76]. However, it remains to be elucidated whether a depressive episode preceding PD actually represents an individual depressive episode or rather an early, prodromal state of a developing PD [4].

Underlying pathophysiological mechanisms

The interplay between depression and PD, including potentially underlying pathophysiological aspects, is still not fully understood [134]. As revealed by positron emission tomography (PET), alterations in monoaminergic neurotransmitter systems appear to be of high relevance [127]. Moreover, a number of studies following different methodological approaches identified an association between dysfunctional mesolimbic, frontostriatal dopaminergic and limbic noradrenergic structures, and the occurrence of depression in PD [4], with data on serotonergic systems being still inconclusive [4, 134]. Furthermore, degeneration of cholinergic neurons and a reduced capacity of nACh receptors have been suggested as a potential neurobiological correlate of depression in PD patients [134]. Finally, alterations in homeostastic neurotropic mechanisms, including changes resulting in so-called Lewy-body-pathology in limbic structures, will likely be involved in the pathophysiological processes underlying depression in PD patients [4, 110].

Treatment

Most data are currently available on the use of TCAs, which compared to SSRIs appear to be slightly more effective, but importantly also more prone to side effects [49].

Consensus statements also underline a good response of PD-related depression to the dopamine agonist pramipexole [134, 136]; however, a large randomized controlled trial of pramipexole in 323 depressed PD patients only revealed small effects with a doubtful clinical significance (mean difference in the Beck's Depression Inventory of 1.9 (95 % CI 0.5–3.4; $p = 0.01$)) [60]. Despite efficacy of desipramine and nortriptyline on depressive symptoms in clinical trials, case numbers were rather small and further confirmation in larger trials would be beneficial [136]. On the other hand, a recent meta-analysis suggested that the use of TCAs might delay the need for a dopaminergic therapy independent of an antidepressant effect [122].

However, again, since most TCAs exhibit cardiac side effects to some degree and a potential to cause sedation, psychotic symptoms, or worsening of cognitive function, caution should always be applied when prescribing TCAs to PD patients [136].

Until recently, there was a general notion of insufficient evidence for the use of SSRI antidepressants in the treatment of PD-related depression [134, 136, 139]. This was changed by a recently published and so far largest multicenter trial, which was able to prove superiority of venlafaxine and paroxetine to placebo with effect sizes exceeding those of pramipexole [128]. Conversely, atomoxetine, a selective norepinephrine reuptake inhibitor, was not superior to placebo [154].

Limited data are available for an evaluation of an efficacy of psychotherapeutic interventions in PD patients with comorbid depression. The results of the few uncontrolled trials available suggest potential efficacy of cognitive behavioral therapy in depressed PD patients; however, lack of an adequate control group remains an issue [37, 41].

Remaining questions and challenges

Promising preliminary findings indicating a putative neuroprotective mechanism for TCAs by modifying disease progression should be substantiated, and underlying mechanisms should be identified in preclinical settings. In order to identify the most efficient and best tolerable antidepressant interventions in PD, adequately powered trials including direct comparisons of SSRIs and SNRIs are needed. While most intervention studies were conducted in rather mildly to moderately depressed PD patients, more severe depressive syndromes should also be included in clinical trials. Evidence for efficacy of psychotherapeutic interventions in PD-related depression is largely lacking.

Key points and recommendations

PD-related depression represents a frequently observed comorbid psychiatric condition that is often underestimated in clinical practice. Alterations in noradrenergic and cholinergic, but less likely in serotonergic systems, appear to be involved in the development of PD-related depression; yet, underlying pathophysiological mechanisms remain incompletely understood.

For the pharmacological antidepressant treatment of PD-related depression, pramipexole, desipramine, and nortriptyline are recommended by consensus statement [136]. However, venlafaxine and paroxetine may also be considered as alternatives to TCAs [62].

Multiple sclerosis and depression

Depressive syndromes are frequently observed in patients with multiple sclerosis (MS) and can severely impact cognitive functioning and quality of life [44]. Moreover, comorbid depression in MS is associated with lower adherence to treatment [21] and represents one of the strongest predictors for suicidal intent [43]. Despite the clinical relevance of MS-associated depression, depressive syndromes are often underdiagnosed and undertreated in clinical practice [1].

Epidemiology

Estimates regarding the lifetime prevalence for major depressive disorder (MDD) in MS patients vary between 25 and 50 % [137]. In a large US population-based survey, the 12-month prevalence for MDD in MS was found to be as high as 25 % (95 % CI, 15.6–35.7) [121]. Moreover, not only the risk of unipolar, but also the risk of developing bipolar disorder has been reported to be elevated in MS patients [133].

Pathophysiological mechanisms

Depression in MS is not related to the severity of neurological impairment [106] or disorder-specific coping deficits [59] and can occur at any stage of the disease [145]. The mechanisms underlying the high prevalence of depressive symptoms in MS are still incompletely understood but likely include neurobiological as well as psychological factors [44]. Several studies have addressed a potential role for psychological factors in the pathogenesis of MS-related depression and point toward inadequate coping strategies, feelings of helplessness, a lack of support, and fatigue symptoms as core factors associated with MS-associated depression [9].

Depression in MS has also been attributed to side effects of immunomodulatory therapies since early studies had suggested that depression may be induced by disease-modifying drugs such as interferon (IFN)-β [148]. However, the occurrence of depression after IFN-β therapy was later found to be better explained by a previous history of depression [43]. Therefore, biological aspects of the disease itself may at least in part be responsible for the high prevalence of depression in MS.

In line with a biological link between neuroinflammation and depressive symptomatology, the animal model experimental autoimmune encephalomyelitis (EAE), a widely used model for MS, also exhibits behavioral changes preceding neurological deficits, which are termed "EAE-associated behavioral syndrome" [124, 125]. Moreover, several lines of research have investigated the correlation of MS-associated pathology and depression in clinical studies. While the location of lesions in depressed MS patients did not reveal any consistent topological patterns with an effect on mood [12, 13, 46, 163, 164], there appears to be a more robust association of MS-related depression with regional cortical atrophy in the frontal and temporal lobe [46, 163, 164]. White and gray matter abnormalities in frontal and temporal regions as measured by diffusion tensor imaging have also been linked to depression in MS [45]. Within the temporal lobe, reduced volumes of the hippocampal formation, especially the glucocorticoid-sensitive subregions CA2–3 and dentate gyrus [53, 55, 83], have been associated with depressive symptoms. Moreover, some studies observed an association between HPA hyperactivity and MS-associated depression [42, 53, 54, 81], suggesting a

pathogenesis in analogy to the glucocorticoid hypothesis of depression.

Some evidence also exists for associations with differential cytokine (e.g., TNF-a or IFNg) expression in MS-related depression [54]. Increased cytokine secretion despite hypercortisolemia may be mediated by glucocorticoid resistance of T cell responses [47].

Treatment

Consensus statements indicate adequate response of MS-related depression to both pharmacological and psychotherapeutic interventions [84]. A recent Cochrane review of two available RCTs revealed a trend toward efficacy of antidepressant therapy (desipramine and paroxetine) in the short term but also a significantly higher risk for adverse events. Therefore, further clinical research is clearly needed. Several behavioral interventions including cognitive behavioral psychotherapy [105] and other psychotherapeutic interventions such as meditation [57] have shown some promise in the treatment of MS-related depression. Intriguingly, two small trials have suggested that antidepressant intervention (fluoxetine) may have anti-inflammatory and potentially even "neuroprotective" effects [108, 138] in MS. This possibility requires further study.

Remaining questions and challenges

Fatigue and cognitive impairment are frequently observed in MS, especially attention and memory deficits [26], which may hamper the diagnosis of depression. Clinical discrimination of affective and vegetative symptoms remains a challenge, and more research on determining neurobiological underpinnings of MS-related depression is urgently needed. RCTs of treatments for MS-related depression are largely lacking for both pharmacological and psychotherapeutic approaches, and the potential impact of comorbid depression on the long-term outcome of MS remains to be elucidated.

Key points and recommendations

Depression may significantly decrease the quality of life in MS patients. MS-related depression is underdiagnosed and undertreated, a fact that may be of great importance in the light of the established association between MS-related depression and suicide in MS [43, 142, 143]. Combinations of conventional treatments such as SSRI antidepressants and behavioral psychotherapy are deemed effective interventions by experts in the field; however, solid evidence from RCTs is largely lacking.

Epilepsy and depression

Epidemiology

Regardless of defining depression in epilepsy as a comorbid condition of the epilepsy spectrum, or rather as a concomitant psychiatric disorder, it is widely recognized that depressive syndromes represent a clinically relevant comorbid condition in patients suffering from epilepsy [15, 78]. Data on the prevalence of depressive syndromes in patients with epilepsy vary considerably, depending on the methodology of assessment and the sample size. In a large, population-based survey on 130,000 persons, the prevalence of depression was identified as 13 % in patients suffering from epilepsy versus 7 % in persons from the normal population [50]. In other studies of similar size, the prevalence of depression in epileptic patients was as high as 20 % [100]. Highest rates of depression (50 %) were identified for those epileptic patients treated in an in-patient setting [22]. A number of studies have indicated increased mortality in patients with epilepsy due to suicide even independent of the prevalence of depressive syndromes [17, 28, 66, 114].

Risk factors and etiology

A link between epilepsy and depression has already been described by the Greek physician Hippocrates around 400 BC [91]. Both neurobiological and psychosocial factors are nowadays thought to underlie this link.

With respect to psychosocial factors, the pathophysiological mechanisms of depression in epilepsy can be explained by the diathesis–stress model: Chronic stress exposure due to the burden of the primary disease and learned helplessness as a consequence of unpredictable stress by seizures may be considered as pivotal risk factors for the development of depression [73]. In analogy to other chronic medical conditions, an overall elevated level of psychosocial stress due to life-threatening aspects of the disorder, irreversibility, uncertain future prospects, reduced performance, social decline, and loss of familiar surroundings may represent aggravating factors for the development of depressive syndromes. Due to their aversive and unpredictable nature, seizures may be considered a key contributing factor for the development of "learned helplessness" and thus inducing and sustaining a state of depression in epilepsy patients [68] [152]. Further, epilepsy-associated fatigue, cognitive deficits, and low socioeconomic status may represent stress-precipitating factors that lead to increased allostatic load and thus increase a well-known risk factor for depression [69].

Finally, with respect to neurobiological aspects, there are theories suggesting alterations of basic neurobiological

mechanisms to play a role in the pathogenesis of depressive syndromes in epilepsy. On the one hand, assumptions of underlying neurobiological mechanisms are based on the frequent clinical observation of preictal, but also postictal depressive episodes [141] [80]. On the other hand, subclinical hypersynchronous neuronal discharge [75] as well as depressiogenic side effects of some antiepileptic drugs (AEDs) is discussed as potential contributing factors [103, 109].

Interestingly, there is also the notion of specific common neurobiological and neuroendocrine determinants that have been described for both depression and epilepsy, including HPA axis dysregulation or altered hippocampal neurogenesis. Neurogenesis has been found to be functionally decreased in epilepsy, which could on the one hand facilitate new seizures and increase the vulnerability to depression on the other hand [33]. Being either cause or consequence of both depression and epilepsy, these mechanisms are discussed as common denominators for the bidirectional relationship between depression and epilepsy.

Treatment

Reducing the likelihood of seizures, regardless of pharmacological or surgical treatment, has been found to reduce the risk of depression [101]. While evidence from large randomized and controlled trials is still lacking, based on clinical experience, experts in the field currently recommend the use of SSRI antidepressants as the treatment of choice [15, 19, 40].

Over the past years, a number of new, cognitive behavioral therapy (CBT)-based psychotherapeutic approaches have been developed, including the "*Using Practice and Learning to Increase Favorable Thoughts*" [*UPLIFT*] [149, 153], "*Program to Encourage Active Rewarding Lives for Seniors*" [*PEARLS*] [29], "*Coping Openly and Personally with Epilepsy*" [*COPE*] [151], and the "*Epilepsy Awareness, Support and Education*" [*EASE*] program [36].

A randomized controlled trial comparing *PEARLS* against *treatment-as-usual* demonstrated a significant decline in depressive symptoms and suicidality after 12 months [121], an effect that remained stable even after 18 months [24]. ACT (acceptance and commitment therapy) was investigated in two RCTs and found to exhibit a positive effect on depression, health-related quality of life, and even on seizure frequency [94, 95]. Moreover, preliminary evidence suggests a potential for CBT-based psychotherapeutic interventions to prevent the development of depressive symptoms in adolescents with epilepsy [97]. Finally, psychotherapeutic interventions achieving activation, e.g., physical exercise, demand less self-reflection and may therefore be beneficial especially in patients with cognitive impairment [7, 8].

Novel interventions using intracranial electroencephalographic recordings for the prediction of seizure likelihood are under way and may represent a milestone toward addressing the issue of unpredictability of seizures in drug-resistant epilepsy [30].

Remaining questions and challenges

The precise mechanisms that might underlie and mediate an association between depression and epilepsy remain to be elucidated. In analogy to the associations between stroke and depression, a bidirectional relationship is also expected between depression and epilepsy [79].

In clinical practice, the implementation of efficient therapeutic strategies is of foremost importance [31]. In order to achieve this goal, more randomized controlled trials on the efficacy of both psychotherapeutic and psychopharmacologic interventions will be required.

Key points and recommendations

Depression represents a common and long-known comorbidity of epilepsy. Almost every fifth patient with epilepsy also suffers from comorbid depression. Both epilepsy alone and especially comorbid depression precipitate a significant suicide risk. Etiological aspects may be explained by the diathesis–stress model at the psychosocial level, while at the neurobiological level, subclinical hypersynchronous discharges, impaired neurogenesis, and depressiogenic side effects of AEDs are discussed. Both antidepressant pharmacotherapy and psychotherapeutic approaches appear to be effective in targeting depressive symptoms and in some cases might exhibit even positive effects on seizure frequency. Evidence on therapeutic efficacy from large, randomized controlled trials is still missing and will be required to substantiate preliminary findings for clinical practice.

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