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Post-stroke Neuropsychiatric Problems

İnme Sonrası Nöropsikiyatrik Durumlar

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Abstract

Stroke is the most frequent and significant reason of disability in society. The underlying basic pathophysiological mechanisms of stroke are infarct and hemorrhage. 20% of patients that had a stroke became dependent. Dementia, depression, anxiety disorder, mania, psychosis, pathological emotions, apathy and catastrophic reactions constitute challenging clinical presentations that occur after stroke. In this review, current data about epidemiology, etiology, clinic and treatment of psychopathologies that occur in poststroke period will be discussed.

Keywords*:* Stroke, clinical presentation, treatment, neuropsychiatry.

Öz

İnme toplumdaki en sık yeti yitimi nedeni olarak göze çarpan bir hastalıktır. İnmenin altında yatan temel patofizyolojik süreçler enfarkt ve hemorajidir. İnme geçiren hastaların %20'si bağımlı hale gelmektedir. Demans, depresyon, anksiyete bozukluğu, mani, psikoz, patolojik emosyonlar, apati ve katastrofik reaksiyon, inme sonrasında klinisyenlerin karşılaştıkları zorlu psikiyatrik tabloları oluşturmaktadır. Bu derlemede, inme sonrası dönemde görülen psikopatolojilerin epidemiyoloji, etyoloji, klinik ve tedavileri konusunda güncel gelişmeler perspektifinde elde edilen veriler paylaşılacaktır.

Anahtar sözcükler: İnme, klinik görünüm, tedavi, nöropsikiyatri.

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STROKE, which is defined as a sudden cessation of the brain blood flow, contributes to psychiatric disability at a great deal, and is the third most common cause of mortality following heart disease and cancer (David et al. 2012). The incidence of stroke, which is common especially in the elderly population, is 2/1000 on an annual scale (Bamford et al. 1988). A total of 750000 stroke cases are reported in the USA every year (Thom et al. 2006). Although the annual incidence is 1-2/1000 between 55-64 years of age, this rate rises up to 2% over 85 years of age (Sadock and Sadock 2007). The prevalence of stroke is 176/100000 in our country. The reported mortality rate, on the other hand, is 24% (Özdemir et al. 2000). However, since the registration system is not reliable in our country, the data on incidence and prevalence rates are not clear. According to Hurwitz and Adams (1972), in an area where 250.000 people live, approximately 150 stroke cases that require continuous care appear on an annual scale. All these data show that stroke is the most common reason of disability in the society (David et al. 2012).

The two main underlying pathological processes of stroke are infarct (ischemia) and hemorrhage. Infarct occurs because of thrombosis or embolism. Although the most common reason of thrombosis is atherosclerosis, the most common reason of cerebral embolism is heart diseases. Infarct is seen 4 times more compared to hemorrhage. Although the survival rate in patients with infarct is 75%; a total of 65% of hemorrhagic patients die within one year's time following hemorrhage (Bamford et al. 1990). Atherosclerosis, hypertension, heart diseases, diabetes and smoking are among the reasons of stroke (House et al. 1990, Tamam et al. 2008). It was reported in previous studies that there is a stronger relation between hypertension and hemorrhage (Song et al. 2004).

Following stroke, neuropsychiatric conditions appear in most of the cases with different clinical manifestations. It is important to know these neuropsychiatric conditions, which frequently cause that clinicians face challenges in diagnosing and treating the disease. Because, early diagnosis and treatment may be life-saving.

In the present study, the purpose was to review the relation between stroke and neuropsychological conditions, which might appear following stroke, and which are one of the most important health problems in recent years affecting the life quality and the progression of the disease in a negative way, in the light of current literature findings.

Intracerebral Hemorrhage (IH)

The mortality rate of IH, which constitutes 10-20% of all the stroke cases, varies between 25% and 60% (Sacco et al. 2009). IH, which is seen more commonly between 60-80 years of age, generally occurs during effort; and headache, vomiting and loss of consciousness are seen more commonly compared to infarct (David et al. 2013). Hypertension (HT), vascular malformations, intracranial tumors, bleeding disorders, anticoagulant therapies, cerebral amyloid angiopathy, vasculitis, hemorrhagic infarcts, traumas and sympathomimetic agents are among the reasons of IH (Bradley et al. 2008). How IH will end up depends on the place, amount and spread of it in the ventricles (Hemphill et al. 2001). It progresses more fatally when compared with the infarct-caused strokes, and disability is more common (An et al. 2017). Definitive diagnosis is made with magnetic resonance ımaging (MRI) or computerized brain tomography (CBT) that includes T2 sequences. If stroke emanates from hemorrhage, thrombolytic therapy is contraindicated.

Infarct

A total of 80% of all strokes are caused by infarct; and 50% of ischemic infarcts occur because of large artery atherosclerosis; 25% because of lacunar infarcts, 20% cardiac embolism, and 5% because of more rare causes (Davenport and Dennis 2000). Elderly, male gender, being African American, positive family history, arterial hypertension (AH), transient ischemic attack (TIA), cardiac disease, diabetes mellitus, dyslipidemia, smoking, alcohol use, obesity, use of oral contraceptives, increased fibrinogen/homocysteine levels are among the risk factors for infarct that have been reported in previous studies (Bradley et al. 2008).

In infarcts caused by thrombosis, neurological symptoms generally start in sleep, and proceed in hours-days. The conditions caused by embolism mostly appear during an action, and develop in acute way. Deficits are severe when they first appear; however, they diminish in time. Infarcts have better prognosis compared to bleeding (Keep et al. 2012). Although 20% of the patients recover completely, 20% die in the acute phase, and the rest of them live with disability. Following the embolus, recovery may be faster, and may occur completely -due to the collaterals (David et al. 2013).

Prognosis

No matter whether the reason is hemorrhage or infarct, following the stroke, the mortality rate varies between 18 and 50% (Wolfe 2000). Intracerebral hemorrhage and subarachnoid hemorrhage have mortality at higher rates compared to infarct. More than 20% of these patients become dependent on other people at a level that can only meet most of their basic personal needs with help (Wilkinson et al. 1997). Epileptic seizures develop in 3-6% of patients in the early phase, and in 2-4% of patients in the long term. Stroke alone is the most common reason of late-onset epilepsy (Ryvlin et al. 2006). Many psychiatric clinical manifestations appear in addition to neurological deficits following stroke. Each of these manifestations will be reviewed below.

Stroke and Dementia

Stroke is a precursor risk factor for dementia (Pendlebury and Rothwell, 2009). Nowadays, this issue is examined under the name of dementia after stroke or post-stroke dementia (PSD), and consists of vascular dementia (VD), Alzheimer-type dementia (AD), and mixed-form dementia (Cordonnier et al. 2005, Leys et al. 2005). Demographic changes, increasing life expectancy and increasing survival after strokes caused an increase in the number of PSD patients (Leys et al. 2005). Today, the probability of having dementia or stroke at the age of 65 is 1/3 in males, and 1/2 in females (Mijajlovic et al. 2017).

The risk factors for PSD are being over 65 years of age, low education level, being female, having physical diseases and/or cognitive disorders before stroke, the stroke being in hemorrhagic type, the stroke being in the supratentorial region, involving the dominant hemisphere, recurrent stroke development, infection after stroke, delirium, early-stage epileptic seizure development, cortical atrophy in neuroimaging, medial temporal lobe atrophy, and having cerebral small vessel disease (Pasquier et al. 1999, Pendlebury 2009). Age and education level are also important predictor factors (Zhou et al. 2004, Klimkowicz et al. 2006). It was also reported that the number of lesions is

predictive as well (Tamam et al. 2008). Although it was reported in many previous studies that gender is not a predictor, there are several studies reporting that PSD is more frequent in males (Tatemichi et al. 1992, Skoog 2000). The relation between silent brain infarcts, which are frequent in the elderly, and the PSD development has not yet been determined. Ischemic cerebral small vessel diseases, on the other hand, are considered as prodromal pathologies for PSD (Mijajlovic et al. 2017). A total of 30% of stroke patients complain about cognitive impairment following the stroke, and develop dementia within 1 year (Cullen et al. 2007, Öncel et al. 2009). A total of 47.3% of patients who have stroke for the first time experience memory loss within 3 months following the stroke (Jacquin et al. 2014). Stroke increases the risk of developing dementia 4 times more; and the average prevalence is reported as 30% (Barba et al. 2000, Zhou et al. 2004, Tamam et al. 2008). Recurrent strokes increase the PSD risk (Pendlebury 2009).

The data reported in the literature about the relation between the location of the stroke lesion and the development of PSD are not clear. There are several studies reporting that the risk of developing PSD in the lesions that involve the left hemisphere is high (Pohjasvaara et al. 1998, Desmond et al. 2000); and there are also some authors reporting that PSD might be detected more frequently in bilateral lesions (Tang et al. 2004).

Clinical Features

The most common symptoms seen in patients who have PSD are irritability, apathy, insomnia, agitation, intolerance, impatience and emotional lability. Except for these symptoms, emotional incontinence, somatic complaints, restlessness and wandering at nights are also common in these patients. It was emphasized in previous studies that apathy and irritability are important for PSD. It was also reported that depressive symptoms are more frequent compared to AD and it is differential (Cummings et al. 1987).

Multi infarct dementia is characterized by sudden onset. Intellectual functions become worse step-by-step, neurological deficits increase in a fast manner, and some cognitive functions become more disrupted compared to others. Agitation, depression or apathy, visual orientation disorders, and agnosia, which are detected in the early periods following the stroke, may cause misdiagnosis of dementia by clinicians. Especially, amnestic syndrome that is seen in the early phase of posterior cerebral infarcts, recessive-type aphasia that occur following the stroke in the left angular gyrus, and cognitive impairment syndromes accompanied by configuration deficits must be considered by clinicians before diagnosis (Benson and Cummings 1982). Gait disorders may accompany dementia in bilateral thalamic strokes. In addition to dementia symptoms, apathy progressing with excessive sleepiness and vertical vision disorders are observed in bilateral medial thalamic infarctions (Kumral et al. 2001). In anterior thalamic infarcts, on the other hand, a clinical manifestation appears that is characterized with adding irrelevant data to each other together with apathy, amnesia, and perseveration. After paramedian infarcts; however, amnesia, loss of self-activating ability, personality changes, and disinhibited behaviors are also observed. In the inferolateral lesions, impairments are seen in executive functions as well as neglect and aphasia syndromes in posterior lesions (David et al. 2013).

Biomarkers

Biomarker studies are carried out for PSD. In cerebrospinal fluid (CSF), the A 42 peptide and tau proteins were examined, and it was determined that these markers were not sensitive for VD although they were sensitive for AD (Battistin and Cagnin 2010). Gelatinases are proteins that are associated with myelin destruction. The ischemia that occurs following a stroke induces the A and B Gelatinase. Recent studies show that gelatinase B levels are higher in VD patients at a significant level compared to healthy individuals and AD patients (Adair et al. 2004). There are 1 antitrypsin, plasminogen activator inhibitor-1 and apolipoprotein H among the CSF markers that are reported to be associated with VD and PSD (Wallin et al. 2012).

Inflammatory Mediators

Among the inflammatory mediators that are considered to be associated with PSD, there are erythrocyte sedimentation rate (ESR), C - reactive protein (CRP), IL-6 and IL-12 (Narasimhalu et al. 2015). Recent studies show that there is a relation between ESR and cognitive performance in the period following the stroke. It was determined that patients whose ESRs were high had worse cognitive success (Kliper et al. 2013).

Neuroimaging

It was reported that hippocampal atrophy is a strong predictor for PSD (Mehrabian et al. 2015), and especially thalamus, angular gyrus, deep areas of the frontal lobe and left hemisphere lesions are associated with PSD (Grysiewicz and Gorelick 2012).

Treatment

The most important way to avoid PSD is to prevent stroke recurrence. In this respect, acetylsalicylic acid provides a decrease at a rate of 21.7-25.1% in nonfatal stroke, MI or mortality. There are studies reporting that blood pressure control with perindopril reduces cognitive decline following the stroke (PROGRESS CollaborativeGroup 2002). Acetycholine esterase (Ach) inhibitors and memantine still continue to be the strongest agents to treat dementia and slow down the cellular degeneration (Mijajlovic et al. 2017).

Mead et al. (2013) reported that fluoxetine brought positive cognitive results following the stroke. In addition to all these data, it was also reported that statin use, smoking cessation and good diabetes control are important in the management of the clinical manifestations of PSD (Sadock and Sadock 2007).

Stroke and Depression

The lifetime major depression prevalence is 15% (Burvill et al. 1995). It was reported that the rate of depression is between 20-50% in the period following the stroke; and it affects the functional recovery in a negative manner (Aström et al. 1993a). The most common emotional disorder in cerebrovascular diseases is depression (Soyuer and Soyuer 2007). It is determined more frequently in females (Paradiso and Robinson 1998). Although the first three months is the period when the risk of developing depression after stroke (DS) is highest, it was reported that the risk continued for two years more (Robinson and Starkstein 1990). No relation was determined between the type of

stroke and depression (Shimoda and Robinson 1999). The depression occurring in the early period following the stroke increases mortality (Williams et al. 2004).

Although the etiology is not known, possible reasons of DS are the emotional response of the individual to sudden disability and related changes, the change in biochemical balance because of the brain damage, predisposition to depression, and history of depression (Royal College of Physicians 2005). In addition to these, several other factors like the burden brought by coping with physical obstacles, uncertainties about the solutions of problems, becoming dependent on other people, lack of the validity of some previous roles in which the individual felt important and valuable at work and family life, decreasing economic power, and feeling that the individual is worthless also contribute to the development of DS (David et al. 2013).

It is considered that premorbid personality traits are important in DS development, and that struggling, self-sufficient people who do not give up easily can cope with the limitations of stroke better; and anxious people who show depressive reactions in stressful situations are more likely to experience DS (David et al. 2013). It was determined that being socially isolated and being deprived of family support increase the susceptibility to depression (Hackett and Anderson 2005).

There are many studies conducted on the relation between the clinical manifestation and the localization of the lesion to determine the relation between the lesions in the left frontal and right posterior-localized lesions (Starkstein et al. 1987, Shimoda and Robinson 1999). In a study that was conducted with 163 patients and in the meta-analysis of 13 studies, it was determined that there was a reverse correlation between the distance of the lesion from the left frontal pole and the severity of depression (Narushima and Robinson 2003). Today, authors name the pathways that are associated with DS as "frontal-subcortical circuit" or "limbic-cortical-striatal-pallidal-thalamic circuit" (Tang et al. 2011). Another parameter that is associated with the presence and severity of depression is the size of the infarct. Vataja et al. (2004) conducted a study with 70 patients, and Nys et al. (2005) conducted another study with 126 patients, and showed that the size of the infarct was significantly greater in the patients who had DS compared to others.

Studies reporting that hyperintensities and silent cerebral infarcts seen in the white matter are associated with late onset DS made us consider that vascular structures might play roles in DS. It was reported that especially the silent lesions that cause damage in the cortico-striato-pallido-thalamo-cortical pathways in time might cause depressive symptoms (Caeiro et al. 2006). One of the mechanisms, which are considered to be responsible for the DS development, is to reduce the bioavailability of serotonin, dopamine and norepinephrine by the lesions that occur as a result of the stroke by preventing the ascending projections that reach frontal cortex by passing through the thalamus and basal ganglia from the midbrain and brain stem. Gao et al. (2008) examined the blood and CSF serotonin levels of 60 DS patients and found that the serotonin levels were low in all samples. Currently, the fact that the selective serotonin reuptake inhibitors (SSRI) and the serotonin noradrenaline reuptake inhibitors (SNRIs) used in DS treatment having clinical efficacy supports this opinion.

The relation between DS and proinflammatory cytokines was also examined by researchers, and it was shown that there is a relation between stroke and interleukin (IL), tumor necrosis factor (TNF) and interferon (IF) (Iadecola and Anrather 2011). In

animal models, the fact that the proinflammatory cytokines like IL-1 and TNF increase infarct and edema in hippocampus and striatum was shown in previous studies support the viewpoint that increased inflammatory response following the stroke causes DS (Caso et al. 2006, Fan et al. 2012). It is known that these cytokines are involved in the control of the synthesis and metabolism of neurotransmitters, and are effective on apoptosis and necrosis mechanisms. IF increases the synthesis and uptake of serotonin (Feng et al. 2014). Aström et al. (1993b) conducted a study with 70 patients, and examined the relation between DS and cortisol. They reported that high cortisol levels after dexamethasone in the 3rd month following the stroke could predict major depression that might occur within three years. Neurogenesis is another topic that is examined by researchers who investigate DS. It was shown in previous studies that hippocampal volume and neurogenesis decreased in depressed patients and animal models, and the antidepressants had effects that caused increases in the hippocampal neurogenesis (Eisch and Petrik 2012). There is also a relation between hippocampal volume and cytokines. Eyre and Baune (2012) reported that systemic TNF-α administration decreased hippocampal cell proliferation and shortened its life. It was shown in previous studies that brain-derived neurotrophic factor (BDNF) played significant roles to maintain neurogenesis and plasticity; and low BDNF levels were associated with DS (Yang et al. 2011, Zhou et al. 2011).

Clinical Features

Clinical manifestations of DS are depressive mood, apathy, gaining or losing weight, changes in sleep patterns, fatigue, decreased self-esteem and anhedonia. Depressive mood and apathy are considered to be the core symptoms. In addition to these findings, DS is also related with disrupted learning, disrupted executive and motor functions; and increases mortality and morbidity by affecting stroke rehabilitation adversely (Loubinoux et al. 2012, Quaranta et al. 2012). Spaletta et al. (2005) conducted a study and reported that depressive mood, loss of desire-interest, fatigue, insomnia, psychomotor retardation and agitation were more prevalent in DS patients. The symptoms that are in the foreground may change over time in DS. Although autonomic and vegetative symptoms might appear in earlier stages, vegetative and psychological symptoms might be detected together in further stages (Paradiso and Robinson 1998). If DS is with early onset, it was reported that lesion volume is larger and vegetative symptoms are more prevalent (Tateno et al. 2002). Unlike what is considered, no relations were determined between the depressive mood severity and motor deficits (Andersen and Vestergoard 1994). It was reported that subcortical basal ganglion and brain stem lesion depressions lasted shorter than the depressions that stem from cortical lesion (Starkstein et al. 1988).

DS is differentiated from the depression that develops after myocardial infarct or spinal cord trauma with anxiety symptoms being detected more (Castillo et al. 1993, Dilbaz et al. 1994). In addition, more reduction is observed in cognitive functions. It should not be forgotten that DS increases mortality (Morris et al. 1990).

Treatment

In the publications that were released in the first period about the DS treatment, conflicting results were obtained on the efficacy of the drugs. The reason for this might be

the inability to complete the study by patients due to tricyclic agents that had more anticholinergic side effects because the patient were old. With the use of SSRI and SNRI group drugs, the success in the treatment in DS increased, and this group was used more often. SSRIs still continue to be the first choice in the treatment (Gainotti et al. 2001).

In a double-blind placebo study conducted with 66 patients, although the citalopram response rate was reported as 59%, this rate was 28% in placebo (Andersen et al. 1994a). In addition, Wang et al. (2008) showed that the proliferation and survival of neurons increased with citalopram in rat DS models. Bilge et al. (2008) reported that 20 mg/day citalopram that was administered in depression patients following stroke provided a clinical recovery in patients, and increased the functional recovery rates of the patients. Robinson et al. (2000) conducted a placebo-controlled study and compared the efficacy of nortriptyline and fluoxetine in DS, and reported that nortriptyline ensured more reduction in Hamilton Depression Scale (HAM-D) scores at the end of 12 weeks, and there were no differences between fluoxetine and placebo.

Escitalopram is preferred more because it is an effective molecule and has less drug-drug interaction and low side effects. Havle et al. (2010) conducted a study with 35 DS patients, and obtained a significant reduction in depressive symptoms with escitalopram (10mg/day) at the end of the 3rd month. In a study in which the results of 16 randomized controlled studies were examined, it was determined that the response rate to antidepressants was 65%, and the response rate to the placebo was 44% (Chen et al. 2006). In a study that was conducted with 20 patients who were diagnosed with DS, it was reported that sertraline was effective and tolerated well (Spalletta and Caltagirone 2003). Zifko et al. (2002) conducted a study with 267 DS patients, and reported that there were decreases in the depression scores of 252 patients with sertraline; however, there were no changes in 10 patients, and 5 patients left the study because their symptoms were deteriorated.

Stroke and Anxiety Disorders

Anxiety is a symptom that is observed frequently in the acute and chronic period of stroke (Lincoln et al. 2013). Studies report that 30% of stroke patients experience anxiety at varying severities (Watanabe 2005, Gilworth et al. 2009). Post-stroke anxiety disorder (PSAD) is observed more frequently in young patients (Broomfield et al. 2015). It is already known that anxiety which is experienced in post-stroke period, is independent from gender and depressive symptoms, and stems from worries like whether stroke will strike again, whether the patient will work again, and whether she/he will maintain his/her social activities; and is related to life quality (Tang et al. 2013). It was determined in previous studies that all anxiety types were observed in the period following the stroke, and these affected the life quality negatively (Knapp et al. 2017).

When the literature is examined, it is seen that there are no adequate studies conducted on PSAD. The reason of this might be that researchers are focused more on depression, and anxiety might be overlooked due to high comorbidity levels. In addition, further age and decreasing speech ability might make it difficult to detect PSAD (Van Rijswijk et al.2009). According to a meta-analysis study which examined 37 studies, PSAD was detected in 29.3% of the patients in the first year following the

stroke, and in 37.7% in the first 2 weeks (Rafsten et al. 2018). Major and minor depression frequently accompany PSAD (Dilbaz 2001). It was determined that depression was more serious and lasted longer when anxiety accompanied as comorbidity (Shimoda and Robinson 1998). In another study, generalized anxiety disorder was determined in 28% of 80 acute stroke patients; major depression was determined in 55% of these patients (Sadock and Sadock 2004).

The number of lesion-location studies conducted for PSAD is relatively small when the studies conducted on DS are considered. There are studies which report that there is a relation with left cortical lesions in DS and PSAD togetherness, and a relation with right hemisphere lesions when there is only PSAD (Castillo et al. 1993, Shimoda and Robinson 1998). It is required that there are at least three of the following criteria in the diagnosis of PSAD; restlessness, early tiredness, difficulty in concentration, irritability, sleep disorder and muscle tension. The alcohol use history is significantly higher in generalized anxiety disorder in acute stroke patients (Sadock and Sadock 2004).

Chun et al. (2018a) conducted a study in which they investigated PSAD, and examined the anxiety under two titles as phobic and generalized; and determined that the phobic type was more dominant in stroke patients. It was determined that stroke patients avoided agoraphobia-related situations (going out alone, going to crowded places, using public transport, spending effort, avoiding sexual activity, experiencing stroke again, falling down); and the most dominant one among these was having another stroke again (Chun et al. 2018b). The likelihood of PSAD being detected in adolescents, women and those who have a history of anxiety is high.

Treatment

Paroxetine and buspirone are the two influential agents that are well-tolerated in PSAD treatment. Paroxetine and psychotherapy combination did not yield a significant difference (Knapp et al. 2017). Mikami et al. (2014) conducted a placebo-controlled study, and determined that both the escitalopram and problem-solving therapy were beneficial in avoiding PSAD. Rao et al. (2012) conducted a 16-week pilot study, and started sertraline for 4 patients who had PSAD. At the end of the study they reported that there were decreases in the complaints of three patients, and one patient left the study because of increased anxiety. Robinson et al. (2000) conducted a study and compared nortriptyline and placebo. They determined that there were significant decreases in the Hamilton Anxiety Scale (HAM-A) scores. Clinicians must be careful in terms of sedation, ataxia, disinhibition and confusion when they are using benzodiazepines in ISAB (Dilbaz 2001).

Stroke and Mania

Post-stroke mania (PSM) is not a common clinical manifestation. Robinson et al. (1988) reported only 2 mania cases in 500 stroke patients. There are no epidemiological studies showing the incidence and prevalence of PSM. The mania, which occurs following a brain injury is called secondary mania, which might be metabolic, pharmacological and neurological (Krauthammer and Klerman 1978). Unlike the post stroke manifestations, manic symptoms develop in the first year in 10% of patients who experience closed-head traumas (Starkstein and Robinson 1997). The reason for the amount

of PSM being low is that the orbitofrontal and basotemporal areas, which are the areas that are frequently damaged in traumas, are rarely affected in a stroke (Dilbaz 2001).

It is considered that PSM is triggered by the damage of right hemisphere structures, which have connections with the limbic system. Especially the loss of the inhibitory impact caused by this region together with orbitofrontal cortex in the basotemporal cortex damages that are associated with secondary sensory and multimodal association regions and the limbic and paralimbic regions cause disinhibition symptoms (Starkstein and Robinson 2000). Although the data on the relation between right hemisphere lesions and mania are dominant in the literature, there are also some mania case reports on left hemisphere lesions (Turecki et al. 1993, Liu et al. 1996). The sudden disruption of the neuronal synaptic functions, blood flow and metabolism following an acute damage to the central nervous system for any reason is called diaschisis. Diaschisis is a process that occurs depending on a focal damage and it is reversible (Meyer et al. 1993). McGilchrist et al. (1993) reported a case with bipolar disorder following thalamic infarct. It was reported that thalamic infarcts might cause secondary mania by leading to metabolic dysfunctions by diaschisis mechanism and in the frontal lobes. The fact that mania does not develop in every patient who has right hemisphere lesion made clinicians consider that there should be some other risk factors in such patients. These are familial genetic load in affective diseases, subcortical atrophy and the damage in right hemisphere limbic region (Santos et al. 2011).

Clinical Features

Secondary mania appear at further ages compared to primary mania. Mania might start immediately after the stroke or after months-years (Das and Khanna 1993). Neurological diseases are seen twice as much in late-onset bipolar disorders (Tohen et al. 1994). Although PSM symptoms show similarities with primary mania, irritability, aggression and agitation are more dominant in the clinical manifestation (Santos et al. 2011).

Treatment

The treatment of PSM is similar to that of the primary mania. However, the treatment is difficult and the response to treatment is slow (Evans et al. 1995). Lithium is the most preferred one among the mood stabilizers. Using lithium in elderly population might cause problems because of the fact that non-steroidal anti-inflammatory drugs that are used often by this patient group might reduce the lithium clearance, and cause neurological side effects, and because lithium can cause hypothyroidism in the elderly more easily. Using valproic acid (if there is no hepatic failure) or carbamazepine (if there is epilepsy) in patients who have secondary mania will be more appropriate. There are not adequate studies conducted on topiramate and lamotrigine. Risperidone, quetiapine, olanzapine and aripiprazole might be used as antipsychotics (Evans 2006, Brooks and Hoblyn 2005). Antipsychotic agents might be used for agitation in elderly patients. In addition to this, lorazepam might be a proper preference as it is metabolized through phase II glucuronidation, and its effects are not long-lasting.

Stroke and Psychosis

Psychosis that develops after stroke has been given different names throughout history like "agitated delirium, acute atypical psychosis, peduncular hallucinosis, oscillation

hallucination, acute organic psychosis" (Dilbaz 2001). The incidence of post-stroke psychosis (PSP) varies between 1% and 5.3%. In a study in which 360 cases were examined, delusions were detected in 15 patients (Kumral and Öztürk 2004). In a large-scale cohort study, the cumulative psychosis incidence was determined as 6.7% in patients who were followed-up for 12 years as of the first stroke attack (Almeida and Xiao 2007).

To explain the reason why PSP is so rare, it is suggested that lesions must exist in more than one area for the delusions to be noticeable in clinical terms (Devine et al. 2014). In addition, it was reported that cerebral atrophy -especially in frontal horns and trunk of the lateral ventricle, i.e. subcortical atrophy- facilitates the occurrence of PSP (Rabins et al. 1991). There are also several other studies reporting that the manifestation of psychosis develops more often in the right inferior frontal gyrus damages. In addition, it was also reported that signal disorders that might appear in right inferior frontal gyrus might also create predisposition to psychosis in healthy people (Corlett et al. 2007). In addition, it was reported that the presence of schizotypal characteristics in the history of patients might cause susceptibility to PSP (Linscott and van Os 2010). When the literature is examined, it is seen that particularly the lesions in the right temporoparietooccipital region have high risks for PSP (Starkstein et al. 1992, Edwards-Lee and Cummings 2000). The right hemisphere lesions are considered as a risk factor for PSP (Rabins et al. 1991).

It was reported in the literature that the seizures stemming from lesions increased the probability of PSP development as well as anatomical localizations (Dilbaz 2001). In a study, it was reported that in 7 of the 8 right temporoparietooccipital stroke or traumatic injury cases there were psychosis and seizures (Levine and Finklestein 1982). The hypothesis claiming that the electrical activity that is caused by the lesion plays roles in psychosis development was suggested after this association was detected (Mishra and Hastak 2008). Symptoms vary according to the location of the lesion in PSP. It was reported that psychotic symptoms usually start in the first week after stroke. There are several studies, which report that PSP starting after the first week might be associated with epilepsy (Barboza et al. 2013).

Treatment

PSP responds well to antipsychotics. There is no treatment protocol that has been established for PSP treatment. Treatment suggestions are limited with case reports. There are case reports in the literature reporting that clozapine and valproic acid (Almeida et al. 2011) risperidone (Ferreira et al. 2017), fluvoxamine and chlorpromazine (Rocha et al. 2014), and fluoxetine and risperidone (Duggal 2005) yielded positive results.

Post-stroke Pathological Emotions

It is a clinical condition that is characterized with uncontrollable laughing/crying episodes, which might appear several times a day, which result from damage to the areas involved in emotional regulation. Laughing/crying episodes occur in an independent manner from mood and social context, and causes social isolation and decreased life quality because of the shame it causes in the individual (Ahmed and Simmons 2013). It is also called under many different names like post-stroke pathological emotions (PE),

emotionalism, pseudobulbar emotions, emotional lability, emotional incontinence, and post-stroke labile emotion (Andersen et al. 1994b). Although this clinical manifestation is not represented by any of these names in DSM-5, it may be defined as "Possible dominant vascular neurocognitive disorder progressing with behavior disorders (F01.51)". PE might appear after dementia, stroke, traumatic brain damage, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, posterior fossa tumors, vascular malformations and Parkinson's disease (Tateno et al. 2004).

Pathophysiological process has not yet been understood fully. Although the response of PE to antidepressants makes clinicians consider that it is associated with depression, studies that were conducted to determine this association could not detect a symptomatic or diagnostic relation between PE and depression (Robinson et al. 1993, Feinstein et al. 1997, Petracca et al. 2009). The hypothesis that is most widely accepted is that the dysfunction of cortico-pontine-cerebellar circuit causes PE (Parvizi et al. 2009). The fact that this syndrome develops following the damage to the hemisphere and to the raphe nucleus itself made clinicians consider that PE was caused by serotonergic system dysfunction (Andersen et al. 1994b). The SSRIs being efficient in treatment strengthens this hypothesis (Brown et al. 1998, Burns et al. 1999). The rate of PE in the first year following the stroke is 15-20%. PE is more frequent in hemorrhagic stroke compared to ischemic stroke (Robinson 1998). Crying is seen more commonly than laughing. In patients who have bilateral pontine lesions, crying periods are more frequent. The PE frequency has increased in patients who experience depression after stroke.

Treatment

Evidence is increasing for the efficacy of SSRIs, which are used frequently in PE treatment. There are a great number of studies conducted on the efficacy of fluoxetine (Brown et al. 1998), citalopram (Andersen et al. 1994b), paroxetine (Derex et al. 1997) and sertraline (Burns et al. 1999) in PE. It is possible to claim that citalopram and escitalopram are the most selective and are one step ahead compared to other SSRIs because of the serotonergic system dysfunction that is emphasized in pathophysiological processes (Hiemke and Hartter 2000). In addition, there are studies reporting that amitriptyline, lamotrigine and mirtazapine are also effective in PE treatment (Schiffer et al. 1985, Ramasubbu 2003, Kim et al. 2005). Dextromethorphan/quinidine, which have antiglutamatergic and serotonergic effects, have been used recently in PE treatment. Randomized controlled trials that were conducted on this combination show that it has significant efficacy compared with placebo (Pioro et al. 2010, Ahmed and Simmons 2013).

Apathy

Apathy is the decrease of targeted actions at significant levels because of motivation loss. The cognitive findings are lack of interest, inadequacy in planning the future. The emotional findings are superficial affect and indifference. Simultaneous decreases are observed in all of the purposeful thought, behavioral and emotional expression (Marin 1991).

The rate of apathy in 80 cases with a single stroke lesion was determined as 11% (Robinson et al. 1984). According to Jorge et al. (2010), the frequency of developing

apathy following a stroke is between 20 and 25%. Apathy is seen more frequently in elderly patients (Dilbaz 2001). Starkstein et al. (1993a) conducted a study with 80 patients who had stroke, and determined the rate of detecting apathy as 22.5%. According to the study results, post-stroke apathy is associated significantly with further age, cognitive disruption, deterioration in daily life activities, major depression and internal capsule back leg lesions. Brodaty et al. (2005) conducted a study with 167 patients who had ischemic stroke and a control group consisting of 109 people, and detected apathy in 26.7% of stroke patients, and in 5.4% in the control group; however, they failed to detect a correlation between apathy and depression. They also failed in detecting any associations between apathy and the type of the stroke, its location, volume and severity. Apathy is seen in 60% of the conditions that affect the cerebral cortex, and in 40% of the events that affect the subcortical regions (Reekum et al. 2005). Apathy is observed especially in the medial frontal cortex lesions, and in dorsolateral frontal cortex, anterior and medial nucleus of the thalamus, and in striatum and amygdala lesions (Dufy and Kant 1997).

Treatment

SSRIs, nortriptyline, apomorphine, amphetamine, methylphenidate and bromocriptine are used in the treatment of apathy. In addition to these treatments, Whyte et al. (2008) reported in their studies, which investigated the efficacy of donepezil and galantamine in stroke patients that the apathy rates of the patients who used donepezil decreased at a significant level. Another agent that promises hope is nefiracetam in apathy treatment. Nefiracetam is a new cyclic GABA compound, which has been shown to increase aminergic, glutamatergic and cholinergic neurotransmission by stimulating the α4β2-type neuronal nicotinic acetylcholine receptors (Jorge et al. 2010). Robinson et al. (2008) reported that nefiracetam was effective at a rate of 900mg/day in apathy that was associated with post-stroke depression.

Catastrophic Reaction

This term, which was first used by Goldstein, is used to describe aggressive behavior, anxiety, crying, swearing, rejection, and sometimes, compensatory boasting conditions (Goldstein 1948). It was claimed that it stemmed from the failure of the organism in coping with the physical and cognitive deficits it faces. This clinical manifestation might be expressed in DSM-5 with the diagnosis "Possible dominant vascular neurocognitive disorder progressing with behavior disorders (F01.51).

Catastrophic reaction (CR) is seen more frequently in the left hemisphere lesions; and the rate of psychiatric disorders in the familial and personal history of patients with CR is more (Gainotti 1972). Depression was diagnosed in 75% of CR patients. Its frequency after acute stroke was determined as 19-20%. Basal ganglion involvement and anterior side lesion located in the subcortical region are more common in such patients. Subcortical damage causes that the emotional expression is released in an unlimited manner by preventing the inhibitor inputs of the limbic areas of the cortex. No differences were detected in terms of CR in aphasic and nonaphasic patients. No effective treatment modalities have been reported (Starkstein et al. 1993b).

Conclusion

It is believed that stroke, which is currently the most important cause of social disability, will remain in this form in the future because of the increasing life expectancy in humans. Although developments have been reported in the treatment of stroke, it is inevitable that the number of patients, who are in need of constant care, will increase - with the effect of continuously increasing population. One of the consequences that are inevitable brought with this condition is the psychiatric symptoms caused by stroke. Dementia, depression, anxiety disorder, mania, psychosis, pathological emotions, apathy and CR are the psychopathology group which clinicians will face in the polyclinic, service or intensive care units after strokes. When the literature was examined, it was seen that there were few studies especially on psychopathologies in the post-stroke period. The increase in our knowledge in terms of epidemiological, etiological, pathogenesis and treatment of these psychopathologies will help us to make necessary regulations in treatment by examining the risk factors specifically for patients, and to administer the correct treatment agents at the correct time. In this way, the life and working qualities of patients, their relatives and clinicians will increase.

References

Adair JC, Charlie J, Dencoff JE, Kaye JA, Quinn JF, Camicioli R et al. (2004) Measurement of gelatinase B (MMP-9) in the cerebrospinal fluid of patients with vascular dementia and Alzheimer disease. Stroke, 35:e159-e162.

Ahmed A, Simmons Z (2013) Pseudobulbar affect: prevalence and management. Ther Clin Risk Manag, 9:483-489.

Almeida OP, Xiao J (2007) Mortality associated with incident mental health disorder after stroke. Aust N Z J Psychiatry, 41:274-281.

Almeida J, Serrao EM,Almeida AT, Afonso JG (2011) Effective treatment with clozapine and valproate for refractoryschizophrenia-like psychosis after cerebellar hemorrhage. Clin Neuropharmacol, 34:131-132.

An SJ, Kim TJ, Yoon BW (2017) Epidemiology, risk factors, and clinical features of ıntracerebral hemorrhage: an update. J Stroke, 19:3-10.

Andersen G, Vestergaard K, Riis JO (1993) Citalopram for post-stroke pathological crying. Lancet, 342:837-839.

Andersen G, Vestergoard K (1994) Incidence of poststroke depression during the first year in a large unselected stroke population determined using a valid standardize rating scala. Acta Psychiatr Scand, 90:190-195.

Andersen G, Vestergaard K, Lauritzen L (1994a) Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. Stroke, 25:1099-1104.

Andersen G, Ingeman-Nielsen M, Vestergaard K, Riis JO (1994b) Pathoanatomic correlation between poststroke pathological crying and damage to brain areas involved in serotonergic neurotransmission. Stroke, 25:1050-1052.

Aström M, Adolfsson R, Asplund K (1993a) Major depression in stroke patients. A three-year longitudinal study. Stroke, 24:976-982.

Aström M, Olsson T, Asplund K (1993b) Different linkage of depression to hypercortisolism early versus late after stroke: A 3-year longitudinal study. Stroke, 24:52-57.

Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K et al. (1988) A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-86. 1. Methodology, demography and incident cases of first ever stroke. J Neurol Neurosurg Psychiatry, 51:1373-1380.

Bamford J, Sandercock P, Dennis M, Burn J, Warlow C (1990) A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project--1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry, 53:16-22.

Barba R, Martinez-Espinosa S, Rodriguez-Garcia E, Pondal M, Vivancos J, Del Ser T (2000) Poststroke dementia clinical features and risk factors. Stroke, 31:1494-1501.

Barboza RB, De Freitas GR, Tovar-Moll F, Fontenelle LF (2013) Delayed onset post-stroke delusional disorder: a case report. Behav Neurol, 27:287-291.

Battistin L, Cagnin A (2010) Vascular cognitive disorder. A biological and clinical overview. Neurochem Res, 35:1933-1938.

Benson DF, Cummings JL (1982) Angular gyrus syndrome simulatind Alzheimer's disease. Arch Neurol, 39:616-620.
Bilge C, Koçer E, Koçer A, Türk Börü Ü (2008) Depression and functional outcomes after stroke: the effect of antidepressant therapy on functional recovery. Eur J Phys Rehabil Med, 44:13-18.
Bradley WG, Daroff RB, Fenichel GM, Jankovic J (2008) Neurology in Clinical Practice (Çev. Ed. E Tan, SE Özdamar). Ankara, Kalkan Matbaacılık.
Brodaty H, Sachdev PS, Withall A, Altendorf A, Valenzuela MJ, Lorentz L. (2005) Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke – the Sydney Stroke Study. Psychol Med, 35:1707-1716.
Brooks JO, Hoblyn JC (2005) Secondary mania in older adults. Am J Psychiatry, 162:2033-2038.
Broomfield NM, Scoular A, Welsh P, Walters M, EvansJJ (2015) Poststroke anxiety is prevalent at the population level, especially among socially deprived and younger age community stroke survivors. Int J Stroke, 10:897-902.
Brown KW, Sloan RL, Pentland B (1998) Fluoxetine as a treatment for post-stroke emotionalism. Acta Psychiatr Scand, 98:455-458.
Burns A, Russell E, Stratton-Powell H, Tyrell P, O'Neill P, Baldwin R (1999) Sertraline in stroke-associated lability of mood. Int J Geriatr Psychiatry, 14:681-685.
Burvill PW, Johnson GA, Jamrozik KD, Anderson CS, Stewart-Wynne EG, Chakera TM (1995) Prevalence of depression after stroke: the Perth Community stroke study. Br J Psychiatry, 166:320-327.
Caeiro L, Ferro JM, Santos CO, Figueira ML (2006) Depression in acute stroke. J Psychiatry Neurosci, 31:377-383.
Caso JR, Lizasoain I, Lorenzo P, Moro MA, Leza JC (2006) The role of tumor necrosis factor-alpha in stress-induced worsening of cerebral ischemia in rats, Neuroscience, 142:59-69.
Castillo CS, Starkestein SE, Federoff JP (1993) Generalized anxiety disorder after stroke. J Nerv Ment Dis, 181:100-106.
Chen Y, Guo JJ, Zhan S, Patel NC (2006) Treatment effects of antidepressants in patients with post-stroke depression: a metaanalysis. Ann Pharmacother, 40:2115-2122.
Chun HYY, Carson AJ, Dennis MS, Mead GE, Whiteley WN (2018a) Treating anxiety after stroke: the feasibility phase of a navel web-enabled randomised controlled trial. Pilot Feasibility Stud, 4:139.
Chun HYY, Whiteley WN, Dennis MS, Mead GE, Carson AJ (2018b) Anxiety after stroke The importance of subtyping. Stroke, 49:556-564.
Cordonnier C, Henon H, Derambure P, Pasquier F, Leys D (2005) Influence of pre-existing dementia on the risk of post-stroke epileptic seizures. J Neurol Neurosurg Psychiatry, 76:1649-1653.
Corlett PR, Murray GK, Honey GD, Aitken MR, Shanks DR, Robbins TW et al. (2007) Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. Brain, 130:2387–2400.
Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA (2007) A review of screening tests for cognitive impairment. J Neurol Neurosurg Psychiatry, 78:790-799.
Cummings JL, Miller B, Hill MA, Neshkes R (1987) Neuropsychometric aspects of multi-infarct dementia and dementia of the Alzheimer type. Arch Neurol, 44:389-393.
Das A, Khanna R (1993) Organic manic syndrome causative factors, phenomenology and immediate outcome. J Affect Disord, 27:147-153.
Davenport R, Dennis M (2000) Neurological emergencies: acute stroke. J Neurol Neurosurg Psychiatry, 68:277-288.
David D, Fleminger S, Kopelman M, Lovestone S, Mellers J (2013) Lishman Organik Psikiyatri (Çeviri Ed. AEA Yağcıoğlu). Ankara, Sözkesen Matbaacılık.
Derex L, Ostrowsky K, Nighoghossian N, Trouillas P (1997) Severe pathological crying after left anterior choroidal artery infarct: reversibility with paroxetine treatment. Stroke, 28:1464-1466.
Desmond DW, Moroney JT, Paik MC, Sano M, Mohr JP, Aboumatar S et al. (2000) Frequency and clinical determinants of dementia after ischemic stroke. Neurology, 54:1124-1131.
Devine MJ, Bentley P, Jones B, Hotton G, Greenwood RJ, Jenkins IH et al. (2014) The role of the right inferior frontal gyrus in the patoghenesis of post-stroke psychosis. J Neurol, 261:600-603.
Dilbaz N (2001) Akut inme sonrası gelişen patofizyolojik ve nöropsikiyatrik sonuçlar. Klinik Psikiyatri Dergisi, 4:166-174.
Dilbaz N, Oğuztürk Ö, Kılıç N, Okyay Y, Çakçı A (1994) Spinal kord yaralanması sonrası bası yarası alan hastalarda depresyon ve kaygı. Romatoloji ve Tıbbi Rehabilitasyon Dergisi, 5:182-186.
Dufy JD, Kant R (1997) Apathy secondary to neurologic disease. Psychiatr Ann, 27:39-43.
Duggal HS (2005) Cognitive affective psychosis syndrome in a patient with sporadic olivopontocerebellar atrophy. J Neuropsychiatry Clin Neurosci, 17:260-262.
Edwards-Lee T, Cummings JL (2000) Focal lesions and psychosis. In Behavior and Mood Disorders in Focal Brain Lesions (Eds J Bogousslavsky, JL Cummings):419-437. Cambridge: Cambridge University Press.

Eisch AJ, Petrik D (2012) Depression and hippocampal neurogenesis: a road to remission? Science, 338: 72–75.
Evans DL (2000) Bipolar disorder: diagnostic challenges and treatment considerations. J Clin Psychiatry, 61:26-31.
Evans DL, Byerly MJ, Greer RA (1995) Secondary mania: diagnosis and treatment. J Clin Psychiatry, 56(Suppl3):31-37.
Eyre H, Baune BT (2012) Neuroplastic changes in depression: a role for the immune system. Psychoneuroendocrinology, 37:1397–1416.
Fan T, Jiang WL, Zhu J, Zhang YF (2012) Arctigenin protects focal cerebral ischemia-reperfusion rats through inhibiting neuroinflammation, Biol Pharm Bull, 35:2004–2009.
Feinstein A, Feinstein K, Gray T, O'Connor P (1997) Prevalence of neurobehavioral correlates of pathological laughing and crying in multiple sclerosis. Arch Neurol, 54:1116-1121.
Feng C, Fang M, Liu XY (2014) The neurobiological pathogenesis of poststroke depression. Scientific World Journal, 2014:521349.
Ferreira MC, Machado C, Santos B, Machado A (2017) Post-stroke psychosis: how long should we treat? Trends Psychiatry Psychother, 39:144-146.
Gainotti G (1972) Emotional behaviour and hemispheric side of lesion. Cortex, 8:41-55.
Gainotti G, Antonucci G, Marra C, Paolucci S (2001) Relation between depression after stroke, antidepressant therapy, and functional recovery. J Neurol Neurosurg Psychiatry, 71:258-261.
Gao H, Zhu H, Zhang Y, Wang L (2008) Reduction of cerebrospinal fluid and plasma serotonin in patients with poststroke depression: a preliminary report. Clin Invest Med, 31:E351-E356.
Gilworth G, Phil M, Cert A, Sansam KA, Kent RM (2009) Personal experiences of returning to work following stroke: an exploratory study. Work, 34:95-103.
Goldstein K (1948) Language and Language Disturbances. New York, Grune & Stratton.
Grysiewicz R, Gorelick PB (2012) Key neuroanatomical structures for post-stroke cognitive impairment. Curr Neurol Neurosci Rep, 12:703-708.
Hackett ML, Andeson CS (2005) Predictors of depression after stroke:a systematic review of observational studies. Stroke, 36:2296-2301.
Havle N, Altunkaynak Y, Dayan C, İlnem MC, Arpacı B (2010) İnme sonrası depresyon tedavisinde essitalopram. Klin Psikofarmakol Bulteni, 20:74-78.
Hemphill JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC (2001) The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke, 32:891-897.
Hiemke C, Hartter S (2000) Pharmacokinetics of selective serotonin reuptake inhibitors. Pharmacol Ther, 85:11-28.
House A, Dennis M, Mogridge L, Hawton K, Warlow C (1990) Life events and difficulties preceding stroke. J Neurol Neurosurg Psychiatry, 53:1024-1028.
Hurwitz LJ, Adams GF (1972) Rehabilitation of hemiplegia: indices of assessment and prognosis. BMJ, 1:94-98.
Iadecola C, Anrather J (2011) The immunology of stroke: from mechanisms to translation. Nat Med, 17:796-808.
Jacquin A, Binquet C, Rouaud O, Graule-Petot A, Daubail B, Osseby GV et al. (2014) Post-stroke cognitive ımpairment: high prevalence and determining factors in a cohort of mild stroke. J Alzheimers Dis, 40:1029-1038.
Jorge RE, Starkstein SE, Robinson RE (2010) Apathy following stroke. Can J Psychiatry, 55:350-354.
Keep RF, Hua Y, Xi G (2012) Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. Lancet Neurol, 11:720-731.
Kim SW, Shin IS, Kim JM, Lim SY, Yang SJ, Yoon JS (2005) Mirtazapine treatment for pathological laughing and crying after stroke. Clin Neuropharmacol, 28:249-251.
Klimkowicz MA, Dziedzic T, Slowik A, Szczudlik A (2006) Predictors of poststroke dementia: Results of a hospital-based study in Poland. Dement Geriatr Cogn Disord, 21:328-334.
Kliper E, Bashat DB, Bornstein NM, Shenhar-Tsarfaty S, Hallevi H, Auriel E et al. (2013) Cognitive decline after stroke: relation to inflammatory biomarkers and hippocampal volume. Stroke, 44:1433-1435.
Knapp P, Campbell Burton CA, Holmes J, Murray J, Gillespie D, Lightbody CE et al.(2017) Interventions for treating anxiety after stroke. Cochrane Database Syst Rev, 5:CD008860.
Krauthammer C, Klerman GL (1978) Secondary mania: Manic syndromes associated with antecedent physical illness or drugs. Arch Gen Psychiatry, 35:1333-1339.
Kumral E, Evyapan D, Balkır K, Kutluhan S (2001) Bilateral thalamic infarction. Acta Neurol Scand, 103:35-42.
Kumral E, Oztürk O (2004) Delusional state following acute stroke. Neurology, 62:110-113.
Levine DN, Finklestein S (1982) Delayed psychosis after right temporoparietal stroke or trauma: relation to epilepsy. Baillieres Clin Neurol, 32:267-273.
Leys D, Henon H, Mackowiak-Cordoliani MA, Pasquier F (2005) Poststroke dementia. Lancet Neurol, 4:752-759.
Lincoln NB, Brinkmann N, Cunningham S, Dejaeger E, De Weerdt W, Jenni W et al. (2013) Anxiety and depression after stroke: a 5

year follow-up. Disabil Rehabil, 35:140-145.
Linscott RJ, van Os J (2010) Systematic reviews of categorical versus continuum models in psychosis: evidence for discontinuous subpopulations underlying a psychometric continuum. Implications for DSM-V, DSM-VI, and DSM-VII. Annu Rev Clin Psychol, 6:391-419.
Liu CY, Wang SJ, Fuh JL, Yang YY, Liu HC (1996) Bipolar disorder following a stroke involving the left hemisphere. Aust N Z J Psychiatry, 5:688-691.
Loubinoux I, Kronenberg G, Endres M, Schumann-Bard P, Freret T, FilipkowskiRK et al. (2012) Post-stroke depression: mechanisms, translation and therapy. J Cell Mol Med, 16:1961–1969.
Marin RS (1991) Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci, 3:243-254.
Meyer JS, Obara K, Muramatsu K (1993) Diaschisis. Neurol Res, 15:362-366.
McGilchrist I, Goldstein LH, Jadresic D, Fenwick P (1993) Thalamo-frontal psychosis: a case report. Br J Psychiatry, 163:113-115.
Mead GE, Hsieh CF, Hackett M (2013) Selective serotonin reuptake inhibitors for stroke recovery. JAMA, 310:1066-1067.
Mehrabian S, Raycheva M, Petrova N, Janyan A, Petrova M, Traykov L (2015) Neuropsychological and neuroimaging markers in prediction of cognitive impairment after ischemic stroke: a prospective follow-up study. Neuropsychiatr Dis Treat, 11:2711-2719.
Mijajlovic MD, Pavlovic A, Brainin M, Heiss WD, Quinn TJ, Ihle-Hansen HB et al. (2017) Post-stroke dementia - a comprehensive review. BMC Medicine, 15:11.
Mikami K, Jorge RE, Moser DJ, Arndt S, Jang M, Solodkin A, et al. (2014) Prevention of post-stroke generalized anxiety disorder, using escitalopram or problem-solving therapy. J Neuropsychiatry Clin Neurosci, 26:323-328.
Mishra NK, Haschak S (2008) Poststroke hallucination delusion syndrome. J Neuropsychiatry Clin Neurosci, 20:116.
Morris PL, Robinson RG, Andrezejwski P (1993) Association of depression with 10 year post stroke mortality. Am J Psychiatry, 150:124-129.
Narasimhalu K, Lee J, Leong YL, Ma L, De Silva DA, Wong MC et al. (2015) Inflammatory markers and their association with post stroke cognitive decline. Int J Stroke, 10:513-518.
Narushima K, Kosier JT, Robinson RG (2003) A reappraisal of post-stroke depression, intra and interhemispheric lesion location using meta-analysis. J Neuropsychiatry Clin Neurosci, 15:422-430.
Nys GMS, van Zandvoort MJE, van derWorp HB, deHaan EHF, de Kort PLM, Kappelle LJ (2005) Early depressive symptoms after stroke: neuropsychological correlates and lesion characteristics. J Neurol Sci, 228:27-33.
Öncel Ç, Kalaycı D, Cura Ç, Can İ, Kalkancı Ö (2009) Akut inmeli hastalarda depresyon ve kognitif bozukluk. Türk Serebrovasküler Hastalıklar Dergisi, 15:7-11.
Özdemir G, Özkan S, Uzuner N, Özdemir Ö, Gücüyener D (2000) Türkiye'de beyin damar hastalıkları için majör risk faktörleri: Türk Çok Merkezli Strok Çalışması. Türk Beyin Damar Hastalıkları Dergisi, 6:31-35.
Paradiso S, Robinson RG (1998) Gender differences in poststroke depression. J Neuropsyc Clin Neurosci, 10:41-47.
Parvizi J, Coburn KL, Shillcutt SD, Coffey CE, Lauterbach EC, Mendez MF (2009) Neuroanatomy of pathological laughing and crying: a report of the American Neuropsychiatric Association Committee on Research. J. Neuropsychiatry Clin Neurosci, 21(1):75-87.
Pasquier F, Henon H, Leys D (1999) Risk factors and mechanisms of post-stroke dementia. Rev Neurol, 155:749-753.
Pendlebury ST, Rothwell PM (2009) Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol, 8:1006-1018.
Petracca GM, Jorge RE, Ación L, Weintraub D, Robinson RG (2009) Frequency and correlates of involuntary emotional expression disorder in Parkinson's disease. J Neuropsychiatry Clin Neurosci, 21:406-412.
Pioro EP, Brooks BR, Cummings J, Schiffer R, Thisted RA, Wynn D et al. (2010) Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. Ann Neurol, 68:693-702.
Pohjasvaara T, Leppavuori A, Siira I, Vataja R, Kaste M, Erkinjutti T (1998) Frequency and clinical determinants of poststroke dementia. Stroke, 29:2311-2317.
PROGRESS Collaborative Group (2001) Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet, 358:1033-1041.
Quaranta D, Marra C, Gainotti G (2012) Post-stroke depression: main phenomenological clusters and their relationships with clinical measures. Behav Neurol, 25:303–310.
Rabins PV, Starkstein SE, Robinson RG (1991) Risk factors for developing atypical (schizophreniform) psychosis following stroke. J Neuropsychiatry Clin Neurosci, 3:6-9.
Rafsten L, Danielsson A, Sunnerhagen KS (2018) Anxiety after stroke: a systematic review and meta-analysis. J Rehabil Med, 50:769-778.

Ramasubbu R (2003) Lamotrigine treatment for post-stroke pathological laughing and crying. Clin Neuropharmacol, 26:233-235.
Rao V, Bergey A, Rosenberg P (2012) Sertraline for treatment of post-stroke anxiety. J Neuropsychiatry Clin Neurosci, 24:E22.
Reekum RV, Stuss DT, Ostrander L (2005) Apathy: Why care? J Neuropsychiatry Clin Neurosci, 17:7-19.
Robinson RG, Boston JD, Starkstein S, Price TR (1988) Comparison of mania and depression after brain injury: causal factors. Am J Psychiatry, 145:172-178.
Robinson RG, Starkstein SE (1990) Current research in affective disorders following stroke. J Neuropsychiatry Clin Neurosci, 2:1-14.
Robinson RG, Parikh RM, Lipsey JR, Starkstein SE, Price TR (1993) Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. Am J Psychiatry, 150:286-293.
Robinson GR (1998) Pathological laughing and crying. In The Clinical Neuropsychiatry of Stroke (Ed GR Robinson):455-471. Cambridge, Cambridge University Press.
Robinson RG, Schultz SK, Castillo C, Kopel T, Kosier JT, Newman RM et al. (2000) Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. Am J Psychiatry, 157:351-359.
Robinson RG, Jorge RE, Clarence-Smith K (2008) Double-blind randomized treatment of poststroke depression using nefiracetam. J Neuropsychiatry Clin Neurosci, 20:178-184.
Rocha S, Pinho J, Ferreira C, Machado A (2014) Othello syndrome after cerebrovascular infarction. J Neuropsychiatry Clin Neurosci, 26(3):E1-E2.
Royal College of Physicians (2005) Use of Antidepressant Medication in Adults Undergoing Recovery and Rehabilitation Following Acquired Brain Injury: National Guidelines. London, Royal College of Physicians of London.
Ryvlin P, Montavont A, Nighoghossian N. (2006) Optimizing therapy of seizures in stroke patients. Neurology, 67(12 suppl 4):S3-S9.
Sacco S, Marini C, Toni D, Olivieri L, Carolei A (2009) Incidence and 10-year survival of intracerebral hemorrhage in a population based registry. Stroke, 40:394-399.
Sadock BJ, Sadock VA (2007) Comprehensive Textbook of Psychiatry, Sekizinci Baskı (Çeviri Ed. H Aydın, A Bozkurt). Ankara, Güneş Yayınevi.
Santos CO, Caeiro L, Ferro JM, Fiqueira ML (2011) Mania and stroke: a systematic review. Cerebrovasc Dis, 32:11-21.
Schiffer RB, Herndon RM, Rudick RA (1985) Ttreatmant of pathologic laughing and weeping with amitriptiline. N Engl J Med, 312:1480-1482.
Shimoda K, Robinson RG (1998) Effect of anxiety disorder on impair-ment and recovery from stroke. J Neuropsychiatry Clin Neurosci, 10:34-40.
Shimoda K, Robinson RG (1999) The relationship between poststroke depression and lesion location in long-term follow-up. Biol Psychiatry, 45:187-192.
Skoog I (2000) Risk factors for dementia after stroke. Fifth Annual Advances in Stroke Symposium Proceedings Highlights. Bermuda, 27-28.
Song YM, Sung J, Lawlor DA, Smith GD, Shin Y, Ebrahim S (2004) Blood pressure, haemorrhagic stroke, and ischaemic stroke: the Korean national prospective occupational cohort study. BMJ, 328:324-325.
Soyuer F, Soyuer A (2007) Kronik dönem inme hastalarında depresyon ve fonksiyonel sonuç arasındaki ilişki. İnönü Üniversitesi Tıp Fakültesi Dergisi, 14(3):167-170.
Spalletta G, Caltagirone C (2003) Sertraline treatment of post stroke major depression: an open study in patients moderate to severe symptoms. Funct Neurol, 18:227-232.
Spalletta G, Ripa A, Caltagirone C (2005) Symptom profile of DSM-IV major and minor depressive disorders in first-ever stroke patients. Am J Geriatr Psychiatry, 13:108-115.
Starkstein SE, Robinson RG, Price TR (1987) Comparison ofcortical and subcortical lesions in the production of poststroke mood disorders. Brain, 110:1045-1059.
Starkstein SE, RobinsonRG, Berthier ML, Parikh RM, Price TR (1988) Differential mood changes following basal ganglia versus thalamic lesions. Arch Neurol, 45:725-730.
Starkstein SE, Robinson RG, Berthier ML (1992) Post-stroke hallucinatory delusional syndromes. Neuropsychiatry Neuropsychol Behav Neurol, 5:114-118.
Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG (1993a) Apathy following cerebrovascular lesions. Stroke, 24:1625-1630.
Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG (1993b) Catastrophic reaction after cerebrovascular lesions: frequency, correlates, and validation of a scale. J Neuropsychiatry Clin Neurosci, 5:189-194.
Starkstein SE, Robinson RG (1997) Mechanism of disinhibition after brain lesions. J Nerv Ment Dis, 185:108-114.
Starkstein SE, Robinson RG (2000) Stroke. In Textbook of Geriatric Neuropsychiatry (Eds CE Coffey, JL Cummings):601-620,

Washington DC, American Psychiatric Publishing.
Tamam B, Taşdemir N, Tamam Y (2008) İnme sonrası demans: sıklığı ve risk faktörleri. Turk Psikiyatri Derg, 19:46-56.
Tang WK, Chan SSM, Chiu HFK, Ungvari GS, Wong KS, Kwok TCY et al. (2004) Frequency and determinants of poststroke dementia in Chinese. Stroke, 35:930-935.
Tang WK, Lu JY, Chen YK, Chu WCW, Mok V, Ungvari GS et al. (2011) Association of frontal subcortical circuits infarcts in poststroke depression: a magnetic resonance imaging study of 591 Chinese patients with ischemic stroke. J Geriatr Psychiatry Neurol, 24:44-49.
Tang WK, Lau CG, Mok V, Ungvari GS, Wong KS (2013) Impact of anxiety on health-related quality of life after stroke: across-sectional study. Arch Phys Med Rehabil, 94:2535-2541.
Tatemichi TK, Desmond DW, Mayeux R, Paik M, Stern Y, Sano M et al. (1992) Dementia after stroke: baseline frequency, risks, and clinical features in a hospitalized cohort. Neurology, 42:1185-1193.
Tateno A, Kimura M, Robinson RG (2002) Phenomenological charecteristics of poststroke depression. Am J Geriatr Psychiatry, 10:575-582.
Tateno A, Jorge RE, Robinson RG (2004) Pathological laughing and crying following traumatic brain injury. J Neuropsychiatry Clin Neurosci, 16:426-434.
Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T et al. (2006) Heart disease and stroke statistics-2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation, 113(6):e85-151.
Tohen M, Castillo J, Pope HG Jr, Herbstein J (1994) Concomitant use of valproate and carbamazepine in bipolar and schizoaffective disorders. J Clin Psychopharmacol, 14:67-70.
Turecki G, Mari JJ, Del Porto JA (1993) Bipolar disorder following a left basal ganglia stroke. Br J Psychiatry, 163:690-701.
Van Rijswijk E, Van Hout H, Van de Lisdonk E, Zitman F, Van Weel C (2009) Barriers in recognising, diagnosing and managing depressive and anxiety disorders as experienced by family physicians; a focus group study. BMC Family Practice, 10(52):1-7.
Vataja R, Leppavuori A, Pohjasvaara T, Mantyla R, Aronen HJ, Salonen O et al. (2004) Poststroke depression and lesion location revisited. J Neuropsychiatry Clin Neurosci, 16:156-162.
Wallin A, Ohrfelt A, Bjerke M (2012) Characteristic clinical presentation and CSF biomarker pattern in cerebral small vessel disease. J Neurol Sci, 322:192-196.
Wang S, Zhang Z, Guo Y, Teng G, Chen B (2008) Hippocampal neurogenesis and behavioural studies on adult ischemic rat response to chronic mild stress. Behav Brain Res, 189:9-16.
Watanabe Y (2005) Fear of falling among stroke survivors after discharge from inpatient rehabilitation. Int J Rehabil Res, 28:149-152.
Whyte EM, Lenze EJ, Butters M, Skidmore E, Koenig K, Dew MA et al. (2008) An open-label pilot study of acetylcholinesterase ınhibitors to promote functional recovery in elderly cognitively ımpaired stroke patients. Cerebrovasc Dis, 26:317-321.
Wilkinson PR, Wolfe CD, Warburton FG, Rudd AG, Howard RS, Ross-Russell RW et al. (1997) A long-term folluw-up of stroke patients. Stroke, 28:507-512.
Williams LS, Ghose SS, Swindle RW (2004) Depression and other mental health diagnoses increase mortality risk after ischemic stroke. Am J Psychiatry, 161:1090-1095.
Wolfe CD (2000) The impact of stroke. Br Med Bull, 56:275-286.
Yang L, Zhang Z, Sun D, Xu Z, Yuan Y, Zhang X et al. (2011) Low serum BDNF may indicate the development of PSD in patients with acute ischemic stroke. Int J Geriatr Psychiatry, 26:495-502.
Zhou DH, Wang JY, Li J, Deng J, Gao C, Chen M (2004) Study on frequency and predictors of dementia after ischemic stroke: the Chongqing stroke study. J Neurol, 251:421-427.
Zhou Z, Lu T, Xu G, Yue X, Zhu W, Ma M et al. (2011) Decreased serum brain-derived neurotrophic factor (BDNF) is associated with post-stroke depression but not with BDNF gene Val66Met polymorphism. Clin Chem Lab Med, 49:185-189.
Zifko UA, Rupp M, Schwarz S (2002) Sertraline in the treatment of post stroke depression- results of an open multicenter study. Wien Med Wochenschr, 17:211-214.

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