Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
JUL. 2022 VOL.1 NO.1

Advances in the Study of the Pathogenesis of Post-Stroke Depression

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doi: 10.56397/JIMR/2022.07.01

Abstract

Poststroke depression is a common psychiatric disease among stroke patients, can lead to higher disability and mortality rates in stroke patients, and there is a bidirectional relationship between stroke and depression (Medeiros, G.C., et al., 2020). Stroke increases the risk of PSD, and depression is an independent risk factor for stroke. Due to the high prevalence of depression, which seriously affects normal life, it is very necessary to effectively treat and prevent the occurrence of PSD. This paper will discuss the pathogenesis of post-stroke depression from both biological and social psychological perspectives. Only when the mechanism is clear, can more specific targeted therapy be carried out.

Keywords: post-stroke depression, biological mechanism, social psychological mechanism, review

1. Introduction

Post-stroke depression (PSD) is a common clinical neuropsychiatric disorder and a complication of stroke patients. The incidence of POST-stroke depression is as high as 30% within one year after stroke, especially within 3 months (Medeiros, G.C., et al., 2020). Clinical symptoms such as low mood, pessimism, anxiety, loss of interest, and energy loss can be seen in patients. Therefore, PSD is a common and serious mental complication of stroke. The occurrence of PSD not only affects the patient's daily physical activity ability but also causes serious harm to the patient's psychology. In recent years, the prevalence of post-stroke depression has been increasing, so it is very important to seek effective treatment for PSD. An in-depth study of pathogenesis can provide ideas for proposing new treatment methods. At present, studies on pathogenesis mainly focus on biological and social psychology, so this paper reviews these two aspects.

2. Biological Mechanisms

2.1 Neurotransmitter Theory

2.1.1 Monoamine Neurotransmitters

Monoamine neurotransmitter theory is the most classical theory proposed in the pathogenesis of PSD, and some studies have found that abnormal neurotransmitters can cause the occurrence of PSD. The major monoamine neurotransmitters in the brain include 5-HT, NE, and DA. Dysfunction of these neurotransmitters affects people's emotional regulation and causes anxiety. Symptoms of sadness, depression, or compulsion. Yao Jie (Jie Yao, Xiaolin Liu & Zhonghao GUI, 2018) proposed serotonin (5-HT), norepinephrine (NE), and acetylcholine (ACh) levels in the course of illness, are due to the parts of the brain ischemia blocked the neurotransmitter in the brain stem to the transport pathway of the cerebral cortex, reduces the utilization rate of brain neurotransmitters, the frontal lobe-the striatum-pallidum-the thalamus-cortical circuits to be destroyed, Reduced production of 5-HT and NE transmitters in the brain, leading to depression. However, some scholars have proposed that 5-HT is related to the regulation and control of brain energy, and the resources in the brain are

reused, thus improving the body's ability to fight depression. However, antidepressant drugs may disturb the state of energy balance, and even aggravate the symptoms of depression in the acute stage.

2.1.2 Glutamate Neurotransmitter

Some scholars have found that there is also a mechanism of glutamate neurotransmitters. Reduced glutamate activity can increase anxious behavior, and glutamate level in the hippocampus is particularly important. Xie Xiaobin (Xiaobin Xie & Wei Zhang, 2020) proposed that after stroke, excitatory neurotransmitters would be released from synaptic vesicles of neurons, and these transmitters combined with neurons' posterior membrane receptors, resulting in the post-potential remaining excited. When excitability reaches its limit, neurons fire and produces large amounts of glutamate neurotransmitters, which can't be fully utilized, leading to depression. James W (Murrough, J.W., C.G. Abdallah & S.J. Mathew, 2017) proposed that glutamate and its specific receptor subtypes can modulate the synaptic function and affect human emotion, and increase the glutamate/creatinine ratio in controlling the lateral frontal lobe area and increase plasma glutamate level after stroke.

2.1.3 Peptide Neurotransmitters

Neuropeptide (NPY) is a polypeptide with extensive and complex functions, which can regulate mood and endocrine, etc. In Ozsoy's (Ozsoy, S., E.O. Olguner and U. Abdulrezzak, 2016) study, it was found that the neuropeptide level of depressed patients was reduced, and the level could be restored to normal after the patients received antidepressant treatment. The link between antidepressants and NPY levels appeared to be stronger in some patients who were on long-term medication. NPY may be a marker of depression.

2.2 Inflammatory Cytokines

Studies have found that the inflammatory response of immune cells mediated by inflammatory factors is a key factor in the occurrence of depression. In the pathogenesis of acute ischemic stroke, brain injury gradually occurs, and the immune response occurs after the death of nerve cells in the brain. Sun W Z (Zhu Sui-qiang, Sun Wen-zhe & Zhu Zhou, 2018) proposed that the destruction of pro-inflammatory function would affect depression in stroke patients, and the general pro-inflammatory factors mainly include IL-1β, IL-6, TNF-α, IFN-γ, etc, which are mostly synthesized by mononuclear macrophages and have the function of stimulating inflammation. Indoleamine 2,3-dioxygenase (IDO) will be activated due to the presence of a large number of pro-inflammatory factors, resulting in a decrease in the level of 5-HT, resulting in depression. The study also found that patients with post-stroke depression had higher levels of pro-inflammatory cytokines before treatment. The main anti-inflammatory factors in the human body are IL-4, IL-10, etc. IL-10 is an anti-inflammatory factor that has been studied more and can inhibit the production and secretion of interferon -γ (IFN-γ), so as to control the role of inflammatory factors to a certain extent. C-reactive protein (CRP), which clears some dead tissue cells, is considered a risk indicator for cardiovascular disease. Wei Chunjie et al (Chunjie Wei et al., 2016) showed that CRP levels in both the PSD group and the non-PSD group were higher than in normal subjects, while the PSD group was significantly higher than the non-PSD group of stroke patients. Furthermore, it is concluded that the change in IL-6 level has a certain relationship with the occurrence of depression, which can mainly induce inflammatory response and damage nerve function by mediating the increase of C-reactive protein. Kim JM (Kim JM, & K.H.K.J., 2017) observed a significant association between IL-1β and PSD status in the study, and only in the acute phase of stroke. Zhang Zhiqiang (Zhang Zhiqiang & Zhang Li, 2018) found that increased levels of some cytokines IL-17 and IL-18 have a great impact on the occurrence of post-stroke depression, among which IL-18 can activate other pro-inflammatory factors, and the increase of the two will promote the increase of cortisol (COR), and when patients show depressive symptoms, the degree of COR will increase, resulting in stress. The body produces a lot of corticosteroids. On the other hand, IL-17 and IL-18 may cause damage to nerve cells, further damaging neurons. Several studies have shown a strong link between inflammatory cell theory and post-stroke depression, but more rigorous studies are needed.

2.3 Neurotrophic Factors

Brain-derived Neurotrophic Factor (BDNF) can regulate the formation of neurons and has a protective effect on damaged neurons. When BDNF dysfunction occurs, diseases occur. Clinically, it has been found that the degree of BDNF is low in patients with depression who have died. Therefore, the clinical development of antidepressants is mainly to increase the level of BDNF for the purpose of treatment. Zhang Hongmei et al (Hongmei Zhang, Hongya Zhang & Wei Liang, 2016) found that the level of this factor was low in the elderly with poststroke depression, and the degree of depression was negatively correlated with serum BNDF level and ADL score, and positively correlated with NIHSS score. Eric Zhang (Zhang, E. & P. Liao, 2020) believed that before the onset of stroke, some patients may have a low level of BDNF, which makes them prone to depressive symptoms. The serum BDNF level of stroke patients is slightly increased in the acute stage but decreased in the chronic stage.

2.4 Neuroendocrine Hypothesis

2.4.1 Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal axis was closely associated with post-stroke depression, and there were many studies, mainly because cortisol levels increased after HPA dysfunction. Amanda (Barugh, A.J., et al., 2014) conducted a systematic review of the correlation between cortisol levels and stroke severity and found that changes in cortisol levels were associated with stroke severity. The HPA axis is also linked to pro-inflammatory cytokines, which can cause cortisol levels to rise and further damage the nervous system. Some studies (Zhihan Gao & Weidong Jin, 2017) proposed that the normal function of the HPA axis is related to hormones. Some hormones can regulate the HPA axis and secrete GR and MR. GR and MR play a key role in the excitability and stress of neurons. So that patients have symptoms of depression.

2.4.2 Hypothalamic-Pituitary-Thyroid Axis

Thyroid-stimulating hormone (TSH) secreted by adenohypophysis could regulate the normal function of the thyroid, forming the hypothalamic-pituitary-thyroid system (HPT axis). Hypothyroidism will lead to insomnia, anxiety, palpitations, and other manifestations, which greatly affect the life of normal people. Studies have found that depressed patients have HPT axis disorder, which is mainly due to the insensitive response of TSH leading to reduced thyroid content, manifested in various emotional problems, and then anxiety and depression.

2.4.3 Hypothalamic-Pituitary-Gonad Axis

The main function of HPG was to maintain the normal development of human sexual organs and hormone secretion. Studies found that HPG activity in depressed patients was relatively low. Xu Lili et al (Xu Lili et al., 2016) proposed that estrogen may play an anti-anxiety and depression role through 5-HT, mainly because estrogen can combine with the central nervous system to promote the increase of 5-HT degree, and the decrease of estrogen will also promote the disorder of HPG axis.

2.4.4 Thyroid Stimulating Hormone

There are many hormones in the human neuroendocrine system, among which thyroid stimulating hormone (TSH) is an important hormone to evaluate thyroid function. Jin-song Chen (Chen J S, Lin G X & Yao J, et al, 2015) the study found that the TSH level has a certain relationship with the occurrence of PSD, TSH level lower stroke patients' neurologic injury is more serious than normal, with hypothyroidism cerebral infarction patients were more likely to occur depression, mainly due to a certain degree of brain injury in patients with stroke, appear even placeholder or edema, Produce inflammation, lead to thyroid hormone secretion disorder.

2.5 Lesion Site

May study found lesion has a relationship with the occurrence of PSD, Liu Liyang (Liu Liyang et al., 2017) found that depression after stroke in patients with left cerebral hemisphere infarction is more serious, that the left hemisphere damage serious stroke patients more susceptible to depression, mainly because of serotonin neurons in the hypothalamus, the part is serotonin neurons important pathways, It is more likely to cause injury, and after cerebral infarction in stroke patients, the blood flow channel is blocked, resulting in insufficient cerebral blood supply, ischemia and hypoxia in brain tissue, and brain cell necrosis will occur for a long time. Most people think it's probably because the left hemisphere is the dominant hemisphere and therefore more vulnerable. Their study also found that the size of cerebral infarction lesions may be associated with depression in stroke patients. Zhang Hongmei (Zhang Hongmei, 2019) also found through a retrospective analysis that patients with cerebral infarction in the frontal lobe were more likely to have depression than those in other parts of the brain. And damage to the frontal lobe can lead to schizophrenia. Xu Lili et al (Xu L l, Wang Y F & Wang N, et al., 2016) also conducted a cross-sectional study on the relationship between lesion site and cognitive dysfunction, and the results showed that the lesion site of stroke patients was in the frontal lobe and occipital lobe of the left hemisphere, which were more likely to cause cognitive impairment. Huang Wuyan (Huang Wuyan, 2017) found that in addition to the left hemisphere, frontal lobe, and temporal lobe of the brain, there are certain connections between the left basal ganglia, thalamus, and hippocampus. At present, some studies have proposed that there is a relationship between the lesion site and the occurrence of PSD, but most of the studies have a small sample size. Therefore, further studies are needed to clarify diagnostic criteria and minimize differences to determine whether there is a relationship between the two.

2.6 Gene Theory

Xue-bin Li (Li, X.B., et al., 2016) proposed that apolipoprotein E gene (APOE) polymorphism was associated with neurodegeneration. Through a hospital-controlled study, it was concluded that APOE patients with the rs429358-C allele were more likely to develop poststroke depression. Rs429358 polymorphism is associated with decreased cerebral blood flow in the left temporal lobe region of patients with post-stroke depression. Rs429358 polymorphism of APOE is the key factor of poststroke depression.

2.7 Homocysteine

Homocysteine can promote atherosclerosis, and the damage of vascular endothelial cells is caused by the free radical oxidation of homocysteine (HCY). When the level of HCY increases, nerve cells will be damaged and depression is more likely to occur. Li-shan Cheng (Cheng, L, et al., 2018) found that increased HCY level was associated with the risk of PSD occurring 1 year after stroke onset, and serum Hs-CRP and HCY levels were strong biomarkers of PSD occurring 1 year after stroke onset, and pro-inflammatory cytokines and HCY may have adverse effects on neurotransmitters. Inflammatory states and endothelial dysfunction can impair the expression of brain-derived neurotrophic factors (BDNF). Therefore, HCY may cause depression by altering the neurotransmitter, and HCY is an excitatory toxin that causes neurological impairment through the oxidative stress response.

2.8 Intestinal Microbiome Theory

The association between depression and intestinal microbes is a new hot topic recently proposed. The intestinal microbiota can play the function of immune defense, and the intestinal microbiota is the aggregation of a large number of microorganisms, which can activate the central nervous system. Intestinal microorganisms influence brain function through the microbiota-gut-brain axis (MGB). Jason M (Peirce, J.M. & K. Alvina, 2019) proposed that the function of the central nervous system and stress disorder are the targets of intestinal microbial imbalance. The mechanism of their interaction is that depression is followed by stress, which leads to changes in intestinal permeability and bacterial disruption, or the release of immunoglobulin, which leads to inflammation and depression. In addition to inflammatory responses, microbes in the gut can disrupt central nervous system function through changes in levels of the HPA axis and neurotransmitters. Zheng Fang (Zheng Fang et al., 2018) found that intestinal microflora disorder of mice would occur during depression modeling, which provides a target for the development of new drugs for the treatment of post-stroke depression.

3. Social Psychological Mechanisms

3.1 The Age

Stroke patients suffer from a series of symptoms such as headache, dementia, hemiplegia, and limb numbness, which lead to decreased self-care ability. Patients are prone to psychological disparity and imbalance, resulting in anxiety and depression. These factors have a certain impact on the generation of PSD. Some scholars found that older patients are more likely to develop the PSD, mainly because of their social life and how to live alone in the elderly, social participation is significantly lower than the young, and Wang Sibo (Wang Sibo et al., 2017) study mainly because age leads to brain aging and brain blood vessel and nerve system has been damaged, slow recovery after illness in the elderly, Low confidence and low self-esteem are more likely. Wu Yun (Wang Lin & Wu Yun, 2005) study found that women are more likely than men to have depression, age analysis showed a peak at the age of retirement and is sick, mainly is the phase when the person is in before retirement, so unable to highlight its own social value after retirement, may appear the situation of the self-denial, elderly face fear of death, depression will also happen. Therefore, the psychological stress of these two stages will increase.

3.2 Social Support

Li-yuan liu (Liu LIyuan, 2012) say a lack of social support is one of the factors that affect disease, social support is the individual feels the concern and support from others, is to be able to protect us from the impact of stressful events good interpersonal communication, due to the stroke patients after illness may face marital tension and even family damaged phenomenon, resulting in a decline in social support, The prevalence of PSD increases. Other studies have found that widowed, divorced and single people have higher rates of PSD than those in harmonious family relationships. Through a questionnaire survey of 160 stroke patients, Huang Lei (Lei Huang, Xiao-Ping Lou & Ai-xia Wang, 2016) concluded that when the social support level of stroke patients is high, the situation of depression will be less. Mainly, the improvement of social recognition will increase patients' self-affirmation. Others may receive support but reject social contact, raising the risk of depression.

3.3 Economic Income

Knesebeck believed that low economic income and low social status would increase the pressure of life, mainly reflected in the poor economic status of people generally have low requirements for quality of life, and the imbalance of medical care and other conditions, so stroke patients in this kind of situation are more prone to depression. De Ryck (De Ryck, A., et al., 2014) also proposed that economic level is an important factor affecting the occurrence of depression.

3.4 Lifestyle

ZuoQun (Zuo Qun et al., 2015) the study found that lifestyle has a relationship with the happening of depression, some unhealthy lifestyle is a risk factor for poststroke depression occurs, through contrast to unhealthy lifestyles, found that people who have a bad life factors were more likely to suffer from depression, including alcohol and

inadequate intake of fruits and vegetables were independent factors, And stroke patients with co-existing conditions such as high blood pressure, diabetes and heart disease are more likely to be depressed.

4. Summary

To sum up, the pathogenesis of depression after stroke mainly with neurotransmitters, an inflammatory cytokine, neurotrophic factors, gut microbes, social psychology, and so on, although this mechanisms research has made a valuable achievement, there are still some problems, such as the expression of these factors is involved in the part of the stroke, and how it affects the PSD symptoms? And how do you distinguish between pre-stroke depression and post-stroke depression? (Schottke, H. & C. Giabbiconi, 2015) at the same time, some research sample size is lesser, and included in the standard is different, further research may need more queue and consistent criteria for the diagnosis of PSD, so be on the basis of continuously exploring pathogenesis, find out more on poststroke depression early intervention measures, so as to improve the life quality of stroke patients, reduce the occurrence of depressive symptoms.

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