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Study of Risk Factors and Correlates of Migraine and Depression Comorbidity

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Abstract

Migraine and depression are common diseases in clinical practice. The comorbidity of migraine and depression makes clinical symptoms more complex and variable, reduces the therapeutic effect of the disease and affects the quality of life of patients. In recent years, the correlation between migraine and depression has been confirmed. Consulting relevant literature, it is found that there are certain similarities and correlations between migraine and depression from multiple perspectives. This article will mainly describe the comorbidity, influencing factors, correlation of pathogenesis and treatment.

Keywords: migraine, depression, comorbidity, pathogenesis, research, progress

1. Introduction

Migraine is a common chronic neurovascular disease, and depression is a common neuropsychiatric symptom. Migraineur are more likely to suffer from depression, so the comorbidity of migraine and depression is more common, making the clinical symptoms more complicated. Studies have confirmed that the most common mental migraine comorbidity is depression, the incidence of about 23%. The risk of depression in migraine patients is 2-4 times higher than in those without migraine, while the risk of migraine in depressive patients is about 2-4 times higher, suggesting a two-way correlation (Head and Face Pain Group of Pain Branch of Chinese Medical Association, 2016; Shengyuan Yu, 2020; Caponnetto V, Deodato M, Robotti M, et al., 2021).In addition to complicating diagnosis, depression with migraine may reduce treatment compliance, increase the risk of drug overuse, and make treatment more difficult, resulting in higher direct and indirect costs and poorer health-related outcomes, increasing disability (Yang Y, Ligthart L, Terwindt G M, et al., 2016). As two common independent diseases, migraine and depression interact in many ways. Exploring the risk factors, related mechanisms and treatment of comorbidity may help improve clinical diagnosis, treatment and research.

2. Correlation Between Migraine and Depressive Symptoms

The main clinical manifestations of migraine are recurrent, unilateral or bilateral pulsating severe headaches, mostly on the lateral side of the head, accompanied by nausea, vomiting, photophobia and phonophobia (Head and Face Pain Group of Pain Branch of Chinese Medical Association, 2016). Depression is an emotional disorder characterized by low mood, lack of interest and pleasure, lack of motivation, decreased self-esteem, poor sleep and appetite, reluctance to interact with others and low productivity (Jat M I, Afridi M I, Amar W, et al., 2018). Migraine is closely related to depression, and migraine is more likely to cause depression. Studies have shown (Fan Guimei, Rui Hanchen, Li Guangcong, et al., 2019) that 51.28 % of migraine patients have depression, which is significantly higher than the prevalence of healthy people, and will increase the probability

of disability. Moreover, studies have confirmed that (Yang Yiyao, Zhao Hongru, Lu Haifeng, et al., 2018) depressive disorder can lead to chronic migraine, and the incidence of chronic migraine depressive disorder is higher, the impact of headache is greater, and the degree of disability is more severe. Through scale evaluation, it is found that patients with chronic migraine with depression have more severe pain and decline is more obvious in vitality. The study found that (Huang Kairong & Huri Le Temuer, 2019) the proportion of headache attack frequency and headache duration in patients with comorbidity was significantly higher than those in non-comorbidity group. It can be seen that headache combined with depression will aggravate the condition, and depression is one of the main risk factors for headache to become chronic headache.

From the description of the symptoms of the above two diseases, although migraine and depression belong to different types of diseases, there is a certain correlation between the two. Recurrent migraine headaches may lead to chronic transformation, affecting daily life and work, which led to negative emotions, over time lead to depression; conversely, depression can also make migraine pain frequency, degree of heavier. Because clinicians have insufficient understanding of migraine and depression comorbidity, it is not easy to distinguish the two diseases. Patients with migraine cannot be found in time with depression, and migraine patients with depression are not identified (Shengyuan Yu, 2020), resulting in delayed treatment and affecting the treatment effect. It is suggested that migraine depression comorbidity should be found as early as possible in the future diagnosis and treatment process, and early intervention should be given to improve the quality of life of patients and reduce the burden caused by headache.

3. Migraine and Depression Comorbidity

Depression is one of the most common symptoms associated with migraine. Epidemiology (Huang Kairong & Huri Le Temuer, 2019) found that the proportion of migraine with depression is as high as 41%-47%, and the incidence of depression in non-migraine population is only 17%. Studies have shown that (Wang Sen, Yang Yingying & Pan Yonghui, 2016), if patients have depressive symptoms will increase the susceptibility of migraine, pain hypersensitivity symptoms and monthly headache frequency, and depression is one of the main risk factors for migraine.

Migraine in turn aggravates depression. Because of the recurrent characteristics of migraine itself, it will lead to emotional changes, poor sleep and other effects, affecting the daily life and work of patients. If there is no social support and family understanding, the lack of understanding and care for patients will aggravate the symptoms and depression of patients. The study found that (Luo Guogang, Ma Yuqing, Gou Jing, et al., 2012) migraine can make the incidence of depression in patients with higher, greater impact on headache, more severe disability, affecting the patient's social function, vitality, attention and so on. The study found that migraine is often accompanied by depression (Zhao Na & Ren Fenglong, 2015), and long-term recurrent headache, severe pain, high frequency of attack, poor sleep and other factors will affect migraine patients with depression, which has a greater impact on the quality of life of patients.

4. Risk Factors for Migraine with Depression

There are many risk factors for migraine and depression comorbidity, including age, gender, stress, social support, migraine intensity, frequency and other factors in addition to social support and psychological factors. Great impact on the quality of life of patients, so the summary of relevant risk factors is very important.

4.1 Gender and Age

In addition to risk factors such as anxiety and depression, one of the risk factors for migraine is female (Lipton R B, Fanning K M, Serrano D, et al., 2015). Like migraine, depression is diagnosed more often in women than in men (Bae J Y, Sung H K, Kwon N Y, et al., 2021). The prevalence of migraine was 13.5% in women and 6.2% in men. Patients with depression and migraine are more likely to be female, younger and more severe (Fugger G, Dold M, Bartova L, et al., 2020). A female prospective cohort study showed (Rist P M, Schurks M, Buring J E, et al., 2013) that migraine and non-migraine were associated with an increased risk of depression in middle-aged women.

4.2 Pressure

Stress is a common trigger for migraine, and chronic migraine is a key factor in sensing stress. Perceived stress can affect the quality of life of migraine sufferers. This suggests that depression and anxiety are major determinants of perceived stress in migraine sufferers. Stressful events are known to cause depression and anxiety (Moon H J, Seo J G, Park S P., 2017). A 6-week clinical study showed that migraine patients had a higher incidence of stress and depression, and a time-event analysis was performed to assess whether these baseline symptoms were associated with headache recurrence. 52% of patients reported moderate/high stress levels, and 18% had higher depressive symptom scores (Vgontzas A, Li W, Mostofsky E, et al., 2021). A prospective cohort study followed up for 8 years found that chronic stress was a particularly strong predictor after assessing multiple stressors, and many clear associations between migraine and depression can be

explained by stress (Swanson S A, Zeng Y, Weeks M, et al., 2013).

4.3 Social Environmental Factors

Social support may also be a factor in the co-morbidity of migraine and depression. A cross-sectional study (Demir U F, Bozkurt O., 2020) evaluated the level of depression and social support in migraine patients, and social support was significantly negatively correlated with depression scores in migraine patients, so social support may be crucial for preventing or reducing migraine attacks. The comorbidity of migraine and depression has a genetic basis, which may lead to the occurrence of the disease under the influence of the environment, which acts through a specific genetic structure (Qu Yuan, Hu Hua & Zhou Jiying, 2012).

4.4 Migraine Intensity and Frequency

The intensity of migraine pain is related to depression (Buse D C, Reed M L, Fanning K M, et al., 2020). Studies have found that compared with the intensity of mild and severe headache for the first time, moderate headache intensity is the highest risk factor for depression (Yong N, Hu H, Fan X, et al., 2012). Frequent migraine attacks (weekly or daily) are associated with the risk of depression (Rist P M, Schurks M, Buring J E, et al., 2013). Through the analysis of headache intensity and depression, it was found that the independent risk factors for headache and depression co-morbid patients were mainly headache frequency, duration and pain degree, and the study failed to further dynamically monitor the relationship between changes in patients' depression level and headache (Zuo Jian, Chen Houqin, Wang Wenbing, et al., 2017).

4.5 Family History

A family history of migraine is also a risk factor for depression (Yong N, Hu H, Fan X, et al., 2012; Dai, Zhang, Qiu et al., 2017). Studies have confirmed that there is a genetic correlation between migraine and depression (Ligthart L, Nyholt D R, Penninx B W, et al., 2010). The hereditary of migraine depends on the level of depression, and there may be a two-way causal relationship between migraine and depression. The study (Yang Y, Zhao H, Heath A C, et al., 2016) provides significant evidence of familial clustering of migraine and depression, reported increased risk of depression in relatives of migraineurs, and vice versa. However, among the relatives of people who reported depression, the observed risk of migraines was significantly higher than the reverse. These results further support previous research showing that patients with migraine and depression are more genetically similar to those with simple depression than those with migraine alone.

5. The Coincidence of Pathogenesis

Current studies suggest that migraine and depression share many complex pathogenic mechanisms, part of which includes brain anatomical structure and common genetic basis (Dai, Zhang, Qiu et al., 2017; Zhang Q, Shao A, Jiang Z, et al., 2019).

5.1 Genetic Correlation

The findings suggest a bidirectional relationship between migraine and depression, with each increasing the risk of the opposite disease, suggesting a possible common mechanism. Twin and family studies suggest that this bidirectional relationship can be explained, at least in part, by shared potential genetically-determined disease mechanisms (Yang Y, Ligthart L, Terwindt G M, et al., 2016). Many studies have demonstrated that migraine and psychiatric disorders share a genetic basis, and studies have identified shared genetic loci by using the largest sample and new statistical tools to determining the extent to which the polygenic structure of migraine overlaps with depression beyond genetic correlation. The study also identified specific sites shared between migraine and depression, hinted at the molecular mechanisms of sharing, and highlighted candidate migraine genes for experimental verification (Bahrami S, Hindley G, Winsvold B S, et al., 2022). Although there are no genes closely associated with the causes of migraine and depression, genes from the serotonergic, dopaminergic and GABAergic systems, as well as variants in the MTHFR and BDNF genes, are still strong candidates (Yang Y, Ligthart L, Terwindt G M, et al., 2016).

Relevant epidemiological studies have shown that migraine and depression share a common genetic basis, but overlapping studies at the molecular genetic level are insufficient. Some studies (Yang Y, Zhao H, Boomsma D I, et al., 2018) used single nucleotide polymorphism (SNP) and gene-based genome-wide association study analysis (GWAS) genotype data to find significant genetic overlap between these two diseases. The major pathways involved in the etiology of migraine and depression are neural-related pathways regulated by signaling pathways and ion channels, which provides strong molecular genetic support for the biological mechanism of the common genetic determination of migraine and depression. A study (Ligthart L, Hottenga J J, Lewis C M, et al., 2014) used a new applied multigene (genetic risk) score analysis to investigate the mechanism of genetic overlap between migraine and depression. Finding some novel and important results, this is the first study to show overlapping genetic effects on migraine and depression. The study confirmed the multigenetic characteristics of migraine and depression and said many SNPS were indeed correct, while the risk was weak but still to be

determined. Most importantly, a new genetic risk score application was developed to investigate causality, and the findings support the hypothesis that migraines are a symptom or result of depression in a subset of patients. However, a large sample of Australian twins that evaluated the genetic structure of migraine and depression and their potentially shared genetic components showed (Yang Y, Zhao H, Heath A C, et al., 2016) that the observed comorbidity between migraine and depression could be explained by common etiology rather than causation, which almost entirely contained shared and potential genetically determined disease mechanisms. The heritability of migraine and depression is estimated to be 56% and 42%, respectively. Genetic factors have a significant influence on the susceptibility to migraine and depression, and there is no significant gender difference or specific influence on the degree; the genetic association and bivariate heritability between migraine and depression were significantly detected, suggesting a shared genetic component between the two disorders. Moreover, both univariate and bivariate heritability of migraine and depression increase with the severity of these two diseases (Yang Y, Zhao H, Heath A C, et al., 2016).

5.2 Connections of Brain Structure

Currently, studies related to migraines have shown (Wang Sen, Yang Yingying & Pan Yonghui, 2016; Minen M T, Begasse D D O, Kroon V D A, et al., 2016) that abnormalities in the function, structure and connectivity of brain regions, which plays an important role in determining emotional responses to pain and other sensory stimuli, as well as determining emotions, may affect the common brain anatomy. Greater pain-induced functional activation and stronger functional connectivity in the pain area may help identify the emotional aspects of migraine and may partially explain the co-existence of psychiatric disorders with migraine. Emotionally-motivated brain regions that are commonly considered to have abnormal function or structure in migraine studies include: the anterior cingulate cortex, front island leaf, prefrontal cortex, hippocampus, and amygdala.

Relevant studies have confirmed that the relationship between pain and depression is bidirectional. For the first time, a study (Zheng C J, Van Drunen S & Egorova-Brumley N., 2022) analyzed the neural correlation between

pain and depression co-morbidities through ALE Meta-analysis. ALE analysis showed that pain accompanied by depression was related to the right amygdala, while depression accompanied by pain was mainly related to the left dorsolateral prefrontal cortex (DLPFC). Research evidence that pain and depression have a cumulative negative effect on a specific set of brain regions makes a difference in the initial diagnosis of depression and pain. It has been suggested (Burstein R & Jakubowski M., 2005) that projections of trigeminal vessels from the medullary dorsal horn to selective areas of the mesencephalon, hypothalamus, amygdala, and basal forebrain functionally produce migraine symptoms such as irritability, loss of appetite, fatigue, depression, or loneliness. In the current study (Yang Y, Wei K, Zhang H, et al., 2022), which identified unique and common alterations in brain function were identified in patients with migraine and co-morbid depression migraines with and without depression showed a widely shared network of regional functional changes associated with the default mode network (DMN), the pain processing network (PPN), the executive control network (ECN), and the visual network (VN). The study also demonstrated that migraine and depression co-exist in areas of the brain. Moreover, the results suggest that the right paracentral lobule, left calcarine sulcus, and dorsolateral superior frontal gyrus (SFGdor.L) may be the core region for the development of depression in migraine patients. The study found that (Asif N, Patel A, Vedantam D, et al., 2022) the changes of right paraventral lobule and right fusiform gyrus are the specific manifestations of migraine combined with depression, and the left thalamus, medial orbit of superior frontal gyrus and triangular part of inferior frontal gyrus are all changed in migraine patients. Emotional symptoms of migraine are associated with functional changes in the right paracentral lobule, left talus, and left dorsolateral superior frontal gyrus.

Neuroimaging studies have shown (Dresler T, Caratozzolo S, Guldolf K, et al., 2019) that specific pain-regulated brain regions, including the amygdala, anterior cingulate cortex, and periaqueductal gray matter, show functional and structural changes in migraine and affective disorders, indicating a common substrate for these diseases. It may mean dysfunction of the 'Neuro-edge' pain network behind migraine, and the presence of anxiety-depression symptoms affects the clinical presentation of migraine. Few studies have examined brain function in migraine co-morbid depressed patients, and a study that used resting-state functional magnetic resonance imaging (RS-fMRI) to explore depression-related abnormalities in brain activity in migraineurs. The finding (Ma M, Zhang J, Chen N, et al., 2018) that migraine and depression together affect the left medial prefrontal cortex, a region where abnormalities may help identify common symptoms of co-morbidity or even the cause of co-morbidity, and that perhaps this finding may lead to a target for co-morbidity between migraine and depression; the study also found that migraineurs with depression had different developmental trajectories in the right thalamus and fusiform, which were associated with pain and mood, suggesting that co-morbidity may arise through a specific mechanism rather than a simple superimposition of migraine and depression. In future studies, migraine studies may need to consider depression when interpreting functional magnetic resonance imaging data (Ma M, Zhang J, Chen N, et al., 2018). In a randomised controlled trial (Zhang Y, Liu Y, Han R, et

al., 2021), depressive symptoms were assessed by transcranial sonography and the Hamilton Depression Rating Scale (HAM-D) in a migraine group, a tension headache group and a healthy control group, and the results showed that midbrain raphe (MBR) hypoechogenicity was 28% higher in the migraine group than in the healthy and tension headache groups. This suggests that midbrain raphe hypoechoic abnormalities detected by transcranial sonography may be an imaging biomarker for patients with migraine and depression. However, further studies are needed to support and prove this conclusion.

6. Treatment of Migraine and Depression

6.1 Principle of Treatment

For migraine and depression comorbidity should be diagnosed as early as possible, early treatment, but also pay attention to mental state and other physical manifestations. Because migraine and depression belong to different disease categories, multidisciplinary cooperation should be carried out at the same time of treatment to comprehensively evaluate patients and select appropriate treatment options (Shengyuan Yu, 2020). Comorbidities between migraine and depression have been studied and proven to be associated with reduced quality of life, chronic disease, poor treatment outcomes and high medical costs. Depression-related screening is rarely performed clinically. All clinicians treating headache patients should include depression screening as part of their routine clinical evaluation. Drugs that aggravate one of these diseases can be avoided (Maizels M, Smitherman T A & Penzien D B., 2006; Fan Shanghua, Chen Kang, Lu Zuneng, et al., 2016). Decisions regarding treatment of comorbidity depression should be based on patient preferences, severity of disease, potential adverse events, and history of prior treatment and compliance (Peck K R, Smitherman T A & Baskin S M., 2015). For comorbidities, the use of a single drug to treat two different diseases has potential limitations (Silberstein S D, Dodick D, Freitag F, et al., 2007). When the psychiatric comorbidities are mild, a single drug can be considered to prevent migraine and psychiatric comorbidities. Such as the use of tricyclic antidepressants (TCA), serotonin-neuroadrenaline reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), beta blockers, anticonvulsants, divalproate sodium and other drugs (Minen M T, Begasse D D O, Kroon V D A, et al., 2016).

6.2 Substitution Therapy

In addition to the medications mentioned above, there are alternative therapies, the most common of which is the use of Botulinum toxin for patients with migraine co-existing with depression. Many studies have shown that Botox can be used to treat patients with depression (Wollmer M A, Magid M, Kruger T, et al., 2022) or migraine alone (Ray J C, Hutton E J & Matharu M., 2021; Valente M, Lettieri C, Russo V, et al., 2021), with some therapeutic effect, and also in patients with migraine combined with depression.

Botox has been shown to be more effective in treating migraine and depression co-morbidities. A Meta-analysis (Affatato O, Moulin T C, Pisanu C, et al., 2021) compared the efficacy of Botox in the treatment of migraine or depression versus patients with both disorders, and the results showed that Botox was more effective in the treatment of comorbidities than patients with migraine or depression alone, with significant improvements in depressive symptoms and quality of life, as well as significant improvements in the severity and impact of migraine pain and reduced headache frequency. One difference is that patients with comorbidity based on the BDI scale have a better prognosis for depression than patients with depression alone. In the case of chronic migraine, the difference is that patients with migraine alone have a more significant improvement in the MIDAS and VAS scales compared with patients with comorbidity. So, it may be more effective for people with migraines and depression (especially migraines) than for people with one of the two disorders alone.

Botox can not only achieve therapeutic effect, but also has certain safety. Improve headache, depression, improve sleep and other effects. An international, multi-center, open and prospective study (Blumenfeld A M, Tepper S J, Robbins L D, et al., 2019), involving 716 patients, evaluated the long-term safety and efficacy of Botox in migraine patients with concurrent migraine by injecting Botox at a fixed site and a fixed dose once every 12 weeks for 9 cycles (108 weeks in total). Among patients with significant depression at baseline, there was a significant reduction in the node Health Questionnaire (PHQ-9) score at all assessment times, with 78.0% of patients showing clinically significant improvement in depressive symptoms by week 108. In addition to reducing the frequency of headaches, patients can also improve sleep quality and fatigue levels. In a prospective cohort study (Al-Hashel J Y, Kh A H, Almutairi O, et al., 2020), injecting Botox to 131 migraine patients not only improved migraine symptoms, but also improved the mental state of the patients, improving depressive symptoms, lowering depression score (PHQ-9), and improving quality of life in about 79% of the patients. A prospective, open, multi-centre pilot study (Boudreau G P, Grosberg B M, McAllister P J, et al., 2015) administered Botox to 32 migraine patients with depression at day 0 (baseline) and week 12. The patients were well tolerated and followed up during and after treatment. It was effective in reducing the frequency of headache attacks, the impact of headache, and the disability associated with headache from baseline to week 24. It can significantly improve depressive symptoms in patients.

7. Conclusion

To sum up, migraine and depression are related and correlated from multiple perspectives. There are common risk factors for migraine and depression comorbidity, including gender and age, stress, social environment, migraine intensity and frequency, and family history. In terms of pathogenesis, migraine and depression comorbidity are related to genetic basis and brain anatomy. Therefore, doctors should not only pay attention to the relief of migraine symptoms, but also pay attention to other clinical manifestations of migraine complications. In terms of treatment, in addition to drug treatment, they should also pay attention to alternative therapies with high safety and fewer adverse reactions. The correlation and pathogenesis of migraine and depressive comorbidity need to be further studied in order to deepen the understanding of pathophysiology of migraine and depressive comorbidity, contribute to understanding the connection between migraine and depressive comorbidity, and explore new drug targets for clinical treatment.

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