Research Progress on Biomarkers of the Depression

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Abstract. Due to the increasing number of individuals suffering from depression, there is much attention paid to the detection of depression. This review paper addresses the critical field of depression detection, examining innovative methods including serological tests, cerebrospinal fluid analysis, and imaging techniques. Serological markers like C-reactive protein and cytokines are highlighted for their potential in identifying inflammation associated with depression. The role of cerebrospinal fluid in providing direct brain markers is discussed, alongside the utility of imaging in visualizing brain metabolism linked to depressive symptoms. Though there is a large amount of evidence, more and further research is still needed, which ensures that these methods are more quantitative and precise enough so that we can put them into practice. The overview and understanding of these approaches are crucial to improving diagnostic precision, which is quite essential for developing effective treatment strategies and enhancing patient outcomes in the management of depression.

Keywords: Depression, serology, cytokines.

1. Introduction

As a common and serious mental health disorder manifested by persistent sadness and loss of interest or pleasure in daily activities, depression affects all age groups. Nearly 4% of individuals in the world are suffering from depression, and among them, the teens account for a significant portion, according to World Health Organization (WHO) [1].Such a situation may have negative impacts on their academic performance and interpersonal relationships. Furthermore, individuals may have suicidal thoughts, which leads to death. This circumstance is often attributed to the high pressure and stress. When feeling ill, some seek medical attention, where hospitals often use more subjective methods to have a preliminary screening for depression, like Self-Rating Depression Scale (SDS) and Beck Depression Inventory (BDI). Though widely used, scale assessments have some limitations, such as social expectations, time limitations, and self-report, leading to potential bias in diagnosis. So, it is essential to incorporate more objective ways to diagnose this illness. To address these limitations, this review article will list and discuss research on a series of objective assessment indicators, including those in serology, cerebrospinal fluid, saliva and imaging techniques analysis. These ways provide more accurate and comprehensive approach to diagnosing depression and perhaps lead to better treatment for it.

2. Serology

Serology studies blood. It's used in disease detection by detecting antibodies, diagnosing diseases, monitoring progression, and in epidemiology. Many common diseases can be diagnosed by serology. This offers a possibility to detect these illnesses. Nowadays, scientists are trying to apply this method to diagnose depression. In the research, proteins like CRP and cytokines like IP-10 and TGF-β1 were detected.

2.1. Protein

These years witnesses the study on proteins, including C-reactive protein (CRP), IL-1β, IL-6, IFN-g, and TNF, for detecting the depression.

C-reactive protein (CRP) is a plasma protein synthesized by the liver which is in response to inflammation and tissue damage. It plays a vital part in as a sensitive biomarker for detecting and

monitoring inflammatory processes in the body. And it underscores the complex interactions between emotional and physical condition.

Investigators found that the increase of CRP is usually relevant to depression, thus indicates an underlying inflammatory mechanism behind depression. It is pointed that almost 30% of depressed patients exhibited high-grade inflammation (CRP >3 mg/L), while 60% of depressed patients exhibited lower CRP levels (>1 mg/L), suggesting a significant association between depression and inflammation [2]. Besides, 65 patients recovering from acute coronary syndrome were included in Miller's study also suggest that using both subjective methods (like self-report and observer ratings) and objective methods (like CRP,along with antibodies) to evaluate depression and explore relationship between depression and the markers of inflammation and infection. The result showed that the more severe the depressive symptoms, the higher the CRP level ($r = 0.27$, $p = 0.03$) [2]. This study finds a graded relationship between depressive symptoms and both systemic inflammation and pathogen burden among patients who were recovering from acute coronary syndrome. This relationship is significantly strong in patients of the highest tertile. Though there is no definite causal relationship,In the future study, longitudinal evaluation is essential to determine the potential mechanism.

However, opposite outcomes also existed in Adam' s study on the CRP level of old suffered from unipolar depression. The research indicates that the CRP level of the old is almost like which of the non-depressed [3]. However, it is hard to combine and match other variables that may affect CRP levels. (such as smoking, body weight, comorbidities, etc.). And it is unsure whether these variables have the same contribution to the concentration of CRP. What' s more, CRP is a nonspecific biomarker which may increase in most of the case. For example, the aging itself is relevant to CRP increase, as the proportion of elderly subjects with elevated CRP levels is significantly higher than that of young subjects. This element may hide the real relationship between depression and the level of CRP. Thus, firstly, in the following research, other factors that may affect the CRP levels should be refined. Secondly, longitudinal study should be considered, like long-term follow-up and regular CRP levels measure.

All in all, there are still many controversies regarding the use of CRP as an indicator for depression detection, but more outcomes support this opinion.

What' s more, researchers discovered that people with depression in Taiwan had much more of certain chemicals, like IL-1β, IL-6, IFN-g, and TNF, in their blood. Even after taking a medicine called fluoxetine for three months, these levels stayed high. And other studies have found the same thing: people with depression tend to have more of these chemicals, IL-1β, IL-6, and TNF, in their blood compared to people without depression [4].

This protein may assist future detection.

2.2. Cytokines

Implicated in cell signaling, cytokines are polypeptides or proteins which regulate immune responses, inflammation, and cell growth. They are tightly linked to health and disease, which can play a vital role in the detection of diseases. Of course, depression is no exception. Cytokines and depression have a serious mutual regulation, such as ,the inflammatory cytokines affect neural circuits and then lead to observable physical and action changes. These cytokines can be divided into two kinds of growth factor and others. That makes it a spotlight in these days' research. A host of assumption and clinical research have approved this kind of connection. It indicates that cytokines can not only cause depression, but act as a potential indicator of this disorder.

Brain-derived neurotrophic factor (BNDF) is a brain-derived neurotrophic and growth factor which has an essential impact on neuronal function. It converts precursor and mature forms and produces different effects through different receptors. It' s related to synaptic plasticity and neurotrophic factors. Synapses between neurons can change their strength and structure according to neuronal activity and environmental changes. This is particularly noticeable in depressed patients. In contrast to CRP, BNDF is negatively correlated with possibilities of suffering from depression. A

controlled clinical study, included 77 patients aged between 20 and 60 years, who were diagnosed with MDD according to the DSM - IV criteria, and 95 healthy controls. They were divided into the depression patient group (n = 77) and the healthy control group (n = 95) [5]. The research aim was to evaluate the differences in plasma BDNF levels between MDD patients and normal controls and their correlations with clinical characteristics. Data show that compared with the healthy control group, the BDNF mRNA, circulating protein, and full-length TrkB levels in the hippocampus and prefrontal cortex of the suicide individuals were significantly lower. Depressed individuals, especially those who have attempted suicide, have reduced levels of BDNF in their blood. Based on this principle, detection methods may be investigated and applied in the future.

Other cytokines also have potential to detect depression. It can be seen in three levels- gene level, mRNA level and protein level.

2.2.1. Gene level

Firstly, in the gene level, for example, Charlotte Martin showed that specific polymorphisms in the IL-1β gene relate to depression [4].The IL-10 gene, which encodes IL-10 with anti-inflammatory properties, is polymorphic in the chromosome 1. Their research also explored the TNF gene, revealing that its polymorphisms were differentially associated with depression varying from different populations. It was significantly associated with depression in the Korean population, while associated with depression in the old in the Caucasian population [4]. In addition, a large-scale candidate gene association study identified rs76917 as a single nucleotide polymorphism (SNP) observably associated with the depression phenotype.

2.2.2. mRNA level

In addition, the study has also shown that major depressive disorder (SDD) patients have elevated levels of IL-1B, IL-6 and TNF mRNA compared to controls, even after treatment with fluoxetine for 3 months. But the level of IL-4 mRNA was lower in the patients [4].

2.2.3. Protein level

At the protein level, IL - 6 is one of the widely studied cytokines. The outcomes of several former studies were summarized and analyzed, finding that serum or plasma levels of IL-6 have been proved to be higher repeatedly in depressed patients than in control subjects and four recent comprehensive analyses support this finding. At the same time, serum IL-6 levels were significantly connected with the severity of depressive symptoms, so it is one of the most reliable peripheral biomarkers of depression. For IL-1β, they noted that although it is not as markedly elevated in depressed patients as IL-6, there are studies that describe this elevation [4].

Although there are still several limitations in the use of cytokine markers alone for depression diagnosis, with deeper research on them and technological development, it is anticipated in the future, the accuracy of depression diagnosis can be improved by comprehensively analyzing multiple cytokine markers, combining with clinical symptoms and other diagnostic methods. For example, the development of diagnostic kits based on cytokine markers can assist doctors in the early screening and diagnosis of depression by detecting the combination of specific cytokines and their related indicators in the blood. The kits simplified the detection process. Maybe in the coming future, it is going to be able to have a rapid test just at home, saving time to go to the hospital.

3. Use of Cerebrospinal Fluid in Depression Detection

Cerebrospinal fluid is a transparent fluid surrounding the brain and spinal cord. It has important roles and is crucial in disease diagnosis. It delivers nutrients to the central nervous system and removes metabolites, thus making it an ideal biologic sample to detect depression. It' s a burgeoning research area, aiming of exploring the potential mechanisms. It focuses on identifying specific proteins and inflammatory markers related to depressive symptoms in cerebrospinal fluid. And it may contribute to advancing diagnostic techniques novel therapeutic approaches.

Depression can be detected by measuring the level of neurotransmitters. There are several neurotransmitters, including adrenaline and corticotropin-releasing hormone (CRH), can be used to assist this detection. It has been detected that the average level of adrenaline in depression patients (27 pg/ml) is significantly lower than that of control group (44pg/ml), while there is no strong difference in noradrenaline. Besides, after recovering from detection (assessed by HDS), the level of adrenaline increased by around 420%, which is from former 16pg/ml to 58pg/ml [5]. It forms a before-and-after contrast. What should be paid attention to is that though depression and adrenaline have some relevance, quantitative relationship have not been set up in the experiment. CRH plays a significant role in the pathophysiology of depression, particularly through its involvement in the hypothalamic-pituitary-adrenal (HPA) axis. The level of CRH decreases after one suffering from depression. Though there has not been research on how to apply them into detection, maybe in the future, further study is going to set up a model.

4. Imaging Techniques

Medical imaging techniques play a crucial role in clinical analysis and medical intervention. Emerging technologies are also being developed and adopted. Optical imaging is emerging as a new modality. Ultrasound is another common imaging technique. They also play a significant role in detection of depression. Technological innovations have led to the development of hybrid imaging modalities such as PET/CT, PET/MRI, and SPECT/CT, which integrate anatomical and functional data for more precise disease detection and treatment monitoring. They provide detailed 3D images and help doctors diagnose diseases accurately.

PET is an imaging examination technology that reveals metabolic activities in the body. It can characterize resting-state metabolic signatures and measure the density of neurotransmitter receptors or transporters for which a radioligand exists. Through these ways, PET can provide information about brain metabolic activity, thus helping researchers understand the abnormalities in the brains of patients with depression. Current research shows the volume reductions in the hippocampus, basal ganglia, subgenual anterior cingulate cortex (SCC), and orbitofrontal cortex are more prominent in patients with more severe or chronic forms of depression. For example, a smaller left hippocampal volume predicted a poorer treatment response among depressed inpatients treated with medication, and this effect was primarily driven by patients with recurrent major depressive disorder (MDD). At the same time, a reduction in hippocampal volume is associated with a poorer treatment outcome during several years of follow-up [6].

Besides, the importance of high metabolic activity in the subgenual anterior cingulate cortex (ACC) in predicting poorer treatment outcomes has been reported in several studies of medication and cognitive behavioral therapy (CBT) [6]. In the study of patients with depression, those who did not respond to both psychotherapy and escitalopram (P + SSRI nonresponders) demonstrated a clear pattern of hyperactivity in the ACC at baseline, and these patients also demonstrated hyperactivity in the superior temporal sulcus. This hyperactivity in the ACC was also present among patients with multiple treatment failures, including nonresponse to electroconvulsive therapy (ECT) [7]. For patients demonstrating higher pretreatment ACC activity, alternative interventions may be required.

In general, some features of brain imaging are related to the severity of depression and might be a reference for predicting treatment results. But more research is still needed to make these relationships clearer so that we can put them into practice.

5. Conclusion

As a worldwide mental health disorder, depression and its detection should be paid more attention to. However, traditional detection approaches have large discrepancy, which may cause misdiagnosis or missed diagnosis. But these years witness the research progress of detection of depression, which from traditional subjective approaches to emerging objective diagnostic tools. Serological testing has

shown promise in diagnosing depression, which is easy to get the sample. But it' s a kind of non-specific marker and can be influenced by other variables. So further study should be conducted to enhance specificity and rule out other factors. CSF analysis identified lower levels of adrenaline and alterations in CRH in the CSF of depressed patients. Though in early stage, CSF seems to be a potential sample as it straightly contacts with the brain so that it is closer to brain environment than peripheral samples like blood and saliva, and it can indicate the circumstance of the brain more precisely. But Collecting CSF requires lumbar puncture, which is an invasive medical procedure, may cause both physical and mental harm, so it could be used in further detection after other ways to have a more effective detection. Neuroimaging techniques, such as PET provide visual changes in patients' brain structure, and it is a kind of non-invasive imaging technique. However, due to its expensive cost of use and maintenance, it is only available in large hospital.

In a word, future research must continue integrating objective biomarkers with traditional assessments to improve diagnostic accuracy and develop personalized treatment strategies for depression, ultimately enhancing patient outcomes and quality of life. This not only holds great potential but also may ultimately lead to the development and implementation of significantly improved treatment modalities for this complex and often debilitating disorder.

References

[1] World Health Organization. Depressive disorder (depression). World Health Organization. https://www.who.int/news-room/fact-sheets/detail/depression.

[2] Osimo, E. F., Baxter, L. J., Lewis, G., Jones, P. B., & Khandaker, G. M. (2019). Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychological medicine, 49 (12), 1958 - 1970.

[3] Miller, G. E., Freedland, K. E., Duntley, S., & Carney, R. M. (2005). Relation of depressive symptoms to C-reactive protein and pathogen burden (cytomegalovirus, herpes simplex virus, Epstein-Barr virus) in patients with earlier acute coronary syndromes. The American journal of cardiology, 95 (3), 317 – 321.

[4] Wysokiński, A., Socha, K., Sołtysik, B. K., Kłoszewska, I., Sobów, T., & Kostka, T. (2016). Levels of C-reactive protein (CRP) in elderly patients with unipolar depression–case control analysis. Nordic Journal of Psychiatry, 70 (7), 503 - 507.

[5] Rong, J., & Liu, Y. (2024). Advances in medical imaging techniques. BMC Methods, 1 (1), 10.

[6] Colle, R., Dupong, I., Colliot, O., Deflesselle, E., Hardy, P., Falissard, B., ... & Corruble, E. (2018). Smaller hippocampal volumes predict lower antidepressant response/remission rates in depressed patients: A meta-analysis. The World Journal of Biological Psychiatry, 19 (5), 360 - 367.

[7] Prentice, A., Barreiros, A. R., Van Der Vinne, N., Stuiver, S., Van Dijk, H., van Waarde, J. A., ... & Arns, M. (2023). Rostral Anterior Cingulate Cortex Oscillatory Power Indexes Treatment-Resistance to Multiple Therapies in Major Depressive Disorder. Neuropsychobiology, 82 (6), 373 - 383.