Biomarkers in Psychiatric Disorders – A Perspective

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Abstract

Psychiatric disorders exert a considerable toll on society in various ways. Approximately 450 million people suffer from such conditions, which places mental disorders among the leading causes of ill-health and disability worldwide. The core definition of a psychiatric disorder is based on subjective symptoms/manifestations and/or behavioral criteria, which are always assessed clinically. Compared with some non-psychiatric disorders, our understanding of the pathophysiology of most psychiatric disorders is limited. The symptoms of different psychiatric disorders always overlap, and false-positive clinical diagnoses are possible. There are many instances where patients are under- or over- diagnosed, because there are no specific tests that can aid in diagnosis. As such, there is great interest in whether molecular biomarkers can assist in making clearer diagnostic decisions. To date several biomarkers are studied for various psychiatric disorders, however further research is needed to define a comprehensive set of biomarkers to improve confirmatory diagnosis, early interventions for treatment, and improve prognosis for particular disorders.

Introduction

Researchers have sought biomarkers of psychiatric illnesses. To use a biomarker clinically, it should be validated, feasible, easily reproducible, sensitive, and specific [1]. Apart from diagnosing specific conditions, biomarkers can also be used to predict the clinical course of a disease, identify specific subgroups within the diagnostic syndromes, assess the condition prior to and after interventions, and predict the drug response and likely adverse effects [1].

Almost all psychiatric disorders have implied underlying neuro-transmitter pathogenesis. However, biomarkers in psychiatry cannot be restricted to molecular biology considering the complexity of psychiatric disorders. Recent advances in neuro-imaging have revolutionized the understanding of the bio-clinical substrata of several psychiatric disorders [2,3]. Coupling molecular biology with neuroimaging to understand brain dysfunction in light of structure, neuro-hemodynamics, alterations in neuro-transmitters and their connections to various manifestations of psychiatric disorders might help determine clinically applicable biomarkers. In this mini review we will discuss the evidence for the sensitivity and specificity of different biomarkers for various psychiatric disorders, and then analyze whether these biomarkers could be used clinically to increase diagnostic certainty and improve prognosis.

Sensitivity, Specificity, and Clinical Implications of Biomarkers in Psychiatry

Depression is one of the most common and prevalent psychiatric illness worldwide. Studies have demonstrated the co-occurrence of depression particularly with atypical inflammatory markers (i.e., CRP, IL-6, TNF-α). However, analysis of the role of these markers is constrained because these markers are often present even before the first onset of depression. HsCRP has been reported as profoundly sensitive and specific in predicting the response to Infliximab in treatment- resistant depression (TRD) and discriminates the differential treatment response to escitalopram versus nortriptyline [4]. A blood test can determine the Major Depressive Disorder (MDD) score used to diagnose depression. The MDD score consists of nine biomarkers, namely α1 antitrypsin, brain-derived neurotrophic factor (BDNF), apolipoprotein C3, epidermal growth factor, cortisol, resistin, prolactin, myeloperoxidase, and soluble tumor- necrosis factor α receptor type II [5]. It has also

been found that brain-derived growth factors, cytokines, and insulin-derived growth factors not only serve as biomarkers for diagnosing depression, but they are also useful for predicting the response to treatment. Another neurotropic protein, the glial marker SB 100, is also considered a biomarker as it is elevated in patients with mood disorders, particularly in depression [6]. Schizophrenia is another condition that needs careful assessment because of its complexity. In patients with suspected schizophrenia, upregulation of the mRNA assists in diagnosis [7,8]. Another study revealed that a breath test for ammonia and ethylene can be used in patients with schizophrenia as it helps differentiate schizophrenia from other conditions with similar features and can thus be used as a confirmatory test [9]. The consideration of plasma inflammatory markers to diagnose schizophrenia and determine clinical prognosis has been proposed since long time [10]. In one study, samples from patients with schizophrenia and controls were read via multiplexed immunoassay. This 51-plex biomarkers test for schizophrenia had both sensitivity and specificity of 83% [11].

Bipolar disorder is another important psychiatric condition that needs careful evaluation. Recently, it was demonstrated that six proteins expressed in the brain distinguish patients with mood disorder, especially bipolar I, from healthy controls [12]. The researchers concluded that these proteins are potentially biomarkers for the diagnosis of bipolar disorder. Recent studies have also focused on understanding the neuroimaging markers for bipolar disorder, based on the activity in different regions of brain [3]. A new EEG- based diagnostic test (NEBA: Neuro-psychiatric EEG-based Assessment Aid) is considered a biomarker for diagnosing ADHD more accurately [13]. PTSD is considered extremely difficult to diagnose accurately based on clinical evaluation. Accordingly, the need for biomarkers to diagnose PTSD is great. In PTSD, the startle response may be helpful for diagnosis, and increased startle response as assessed by cortisol level is considered confirmatory [14]. Additionally, brain natriuretic peptide levels are low in patients who suffer chronically from PTSD [15]. Other studies have reported that increased levels of corticotrophin-releasing hormone (CRH) are found in the CSF of patients with PTSD [2,16], supporting the attenuation of the HPA axis in patients with PTSD without comorbid depression. Recently, evidence has been found that certain MRI findings are diagnostic for PTSD, particularly a small right- hippocampal volume in patients with PTSD compared to normal subjects [17]. Dementias are the most concerning illness in the elderly. They are the foremost cause of disability in the elderly with the cognitive and behavioral sequel they cause in long-term. Biomarkers in dementias help us differentiate the various underlying pathologies and aid in staging the disease. Clinically for dementias, the major biomarker that is used widely is neuro-imaging, like structural brain imaging and functional imaging [18]. For example, in Alzheimer's disease (AD) complete atrophy of brain on structural MRI is a diagnosing criteria and is sensitive. Likewise, positive β-amyloid PET scan is specific for AD. In addition, there are also CSF biomarkers like CSF-β amyloid, tau and phospho-tau, when elevated are specific diagnostic criteria for AD [19]. But unlike neuro-imaging markers, CSF biomarkers are still emerging in the clinical application for all the dementias [20]. Yet so far, no blood or urine biomarkers have been found with evidence for any kind of dementias.

Discussion

Determining biomarkers that can be used for diagnosing psychiatric disorders and predicting prognosis following interventions is simultaneously crucial and intricate. As mentioned, most psychiatric disorders share symptoms and molecular pathways. Although some biomarkers have been shown to be highly associated with a particular psychiatric disorder with high sensitivity, the specificity of the biomarkers for the disorder can be controversial. In the past decade many studies have focused on highlighting the biomarkers for psychiatric disorders, especially PTSD, MDD, bipolar disorders, and schizophrenia. However, no studies have conclusively related a specific biomarker to one particular disorder. The most important factor confounding the utility of the many potential biomarkers is that they are altered in many psychiatric and neurologic disorders. Some markers are also readily influenced by environmental and lifestyle factors such as diet, stress, activity levels, and substance abuse, and also by co-morbidities. Additionally, the confounding effect of psychotropic medications on biomarker findings remains an ongoing issue.

Given the lack of specificity due to involvement of multiple molecular pathways in the pathogenesis of psychiatric disorders and the very intrinsic essence of these disorders to be multifactorial in etiology and heterogeneous in expression, it is very unrealistic that one biomarker will greatly impact the diagnosis and treatment. Future studies should focus consolidating a range of biomarkers that might be associated with a particular psychiatric disorder. Taking such an approach will likely be beneficial to the field of psychiatry, but large studies are needed to analyze biomarker data in psychiatric disorders to define patient subgroups and test whether these markers predict at-risk patients before the advent of clinical symptoms, as well as predict treatment response in clinically diagnosed patients. If biomarkers suggest an early response to drug treatment, the efficacy of medication can be assessed sooner and continued use of unsuccessful treatments can be minimized. A further issue is determining whether this approach is practical and economical in clinical practice. To make this determination, plausible differences in diagnosis and treatment response must be first characterized for a manageable set of biomarkers before a more comprehensive set is considered. In addition, there should a protocol for standardization of biomarker use in clinical settings. Integrating a range of biomarkers sensitive and specific for a particular disorder that are feasible to use in clinical settings will likely provide improved outcomes compared to current clinical diagnosis methods.

References

1. Scarr E, Millan MJ, Bahn S, Bertolino A, Turck CW, Kapur S, et al. Biomarkers for psychiatry: the journey from fantasy to fact, a report of the 2013 CINP Think Tank. Int J Neuropsychopharmacol. 2015; 18.

2. Bremner JD, Licinio J, Darnell A, Krystal JH, Owens MJ, Southwick SM, et al. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. Am J Psychiatry. 1997; 154: 624-629.

3. Phillips ML, Vieta E. Identifying functional neuroimaging biomarkers of bipolar disorder: toward DSM-V. Schizophr Bull. 2007; 33: 893-904.

4. Young JJ, Silber T, Bruno D, Galatzer-Levy IR, Pomara N, Marmar CR. Is there Progress? An Overview of Selecting Biomarker Candidates for Major Depressive Disorder. Front Psychiatry. 2016; 7: 72.

5. Bilello JA, Thurmond LM, Smith KM, Pi B, Rubin R, Wright SM, et al. MDD Score: confirmation of a blood test to aid in the diagnosis of major depressive disorder. J Clin Psychiatry. 2015; 76: 199-206.

6. Yang K, Xie GR, Hu YQ, Mao FQ, Su LY. The effects of gender and numbers of depressive episodes on serum S100B levels in patients with major depression. J Neural Transm. 2008; 115: 1687-1694.

7. Shi W, Du J, Qi Y, Liang G, Wang T, Li S, et al. Aberrant expression of serum miRNAs in schizophrenia. J Psychiatr Res. 2012; 46: 198-204.

8. Sun XY, Lu J, Zhang L, Song HT, Zhao L, Fan HM, et al. Aberrant microRNA expression in peripheral plasma and mononuclear cells as specific blood-based biomarkers in schizophrenia patients. J Clin Neurosci. 2015; 22: 570-574.

9. Popa C, Petrus M, Bratu AM. Ammonia and ethylene biomarkers in the respiration of the people with schizophrenia using photoacoustic spectroscopy. J Biomed Opt. 2015; 20: 57006.

10. Hope S, Hoseth E, Dieset I, Mørch RH, Aas M, Aukrust P, et al. Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls. Schizophr Res. 2015; 165: 188-194.

11. Bahn S, Schwarz E, Harris L W, Martins-de-Souza D, Rahmoune H, Guest PC. Biomarker blood tests for diagnosis and management of mental disorders: focus on schizophrenia. Archives of Clinical Psychiatry. 2013; 40: 02-09.

12. Frye MA, Nassan M, Jenkins G, Kung S, Veldic M, Palmer B, et al. Feasibility of investigating differential proteomic expression in depression: implications for biomarker development in mood disorders. Transl Psychiatry. 2015; 5: 689.

13. Snyder SM, Rugino TA, Hornig M., Stein MA. Integration of an EEG biomarker with a clinician's ADHD evaluation. Brain Behav. 2015; 5.

14. Butler RW, Braff DL, Rausch JL, Jenkins MA, Sprock J, Geyer MA. Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. Am J Psychiatry. 1990; 147: 1308-1312.

15. Berger W, Mehra A, Lenoci M, Metzler TJ, Otte C, Tarasovsky G, et al. Serum brain-derived neurotrophic factor predicts responses to escitalopram in chronic posttraumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2010; 34: 1279-1284.

16. Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, et al. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. Am J Psychiatry. 1999; 156: 585-588.

17. Douglas J. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry. 1995; 152: 973-981.

18. Risacher SL, Saykin AJ. Neuroimaging biomarkers of neurodegenerative diseases and dementia. Semin Neurol. 2013; 33: 386-416.

19. Ahmed R, Paterson R, Warren J, Zetterberg H, O'Brien J, Fox N. Biomarkers in dementia: clinical utility and new directions. J Neurol Neurosurg Psychiatry. 2014; 85: 1426-1434.

20. Humpel C. Identifying and validating biomarkers for Alzheimer's disease. Trends Biotechnol. 2011; 29: 26-32.