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Review

Anti-neuronal antibodies in schizophrenia spectrum disorders

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ABSTRACT

Schizophrenia is the most complex and overwhelming mental disorder. Agreement on what symptoms are considered for schizophrenia has major importance for clinicians and researchers that work on this disorder since it vanquishes many obstacles. However, many complications remain and preclude having a better understanding of schizophrenia. First, the cause of schizophrenia is unclear. Second, the translation of the molecular alterations to behavioral phenotypes is unknown, and lastly, the origin of the neuroanatomical changes remains unsolved. Anti-neuronal antibodies are found in autoimmune encephalitis and paraneoplastic disorders affecting the nervous system but also anti-neuronal antibodies have links with other several neurologic disorders, even psychiatric disorders. The importance of anti-neuronal antibodies in patients with psychiatric disorders is unclear, and studies are still progressing on this matter. The purpose of this review was to investigate the link between schizophrenia and anti-neuronal antibodies.

Keywords: Anti-neuronal antibodies, encephalitis, psychiatric disorder treatments, schizophrenia.

SCHIZOPHRENIA: CHARACTERISTICS AND SYMPTOMS

Schizophrenia is a complicated, varied behavioral and cognitive condition that appears to be caused by genetic or environmental causes, or both, disrupting brain development.[1] Positive symptoms (delusions, hallucinations, thought disorders) coexist with negative symptoms (anhedonia, avolition, social retreat, thought poverty) and cognitive impairment in schizophrenia, which is a heterogeneous disorder.[2] Positive symptoms are those that are not typically observed but are present in people suffering from schizophrenia during a psychotic episode. Hearing voices is the most frequent hallucination, but it can also involve any of the other senses of taste, sight, smell, or touch. Passivity phenomena, or distortions of self-experience, include feeling as if one's ideas or feelings are not truly one's own, and believing that thoughts are being injected into one's head.[3] Positive symptoms frequently diminish throughout the disorder. Negative symptoms are a basic component of schizophrenia that accounts for a major portion of long-term disability and poor functional outcomes in patients with the condition.[4] Negative symptoms have been defined as a decrease in normal functions associated with motivation and interest. Negative symptoms are common; in two major cross-sectional retrospective investigations including over 1,000 people with schizophrenia, more than half of the study participants exhibited at least one negative symptom. They are linked to poor functional outcomes and place a significant burden on persons living with schizophrenia, their families, and healthcare systems.[5] Negative symptoms are significant for developing treatments. Attempts to identify successful treatments are likely to result in great efforts rewarded by small rewards unless the heterogeneity within the negative symptom dimension is reduced.[6] Negative symptoms are the most difficult to cure since they are less responsive to medicine. Cognitive impairment

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appears early in the disorder and might last long after the psychosis has passed.[7,8] They are a distinguishing trait but are not considered fundamental symptoms, as are positive and negative symptoms. Cognitive deficiencies are believed to be a key characteristic of schizophrenia, and they have been proven to be significantly linked with functional impairments. The capacity to accurately detect, attend to and retain information, such as verbal fluency, memory, processing speed, reasoning, problem-solving, attention, understanding, seeing, and interpreting the social environment, and mental activities such as recognizing emotion in faces and inferring what individuals are thinking and feeling, can be classified as cognitive impairments.[9] Individuals with this condition have a loss in cognitive function of 1-2 standard deviations, equivalent to a mean drop in performance IQ of 70-85 (versus the normative value of 100).[10] Antipsychotics do not generally assist with cognitive impairments, therefore a variety of therapies are employed to try to address them; cognitive remediation therapy is particularly helpful.[11] Symptoms might appear and go. Nobody possesses all of them at all times. They generally begin between the ages of 10 and 25 for men and between the ages of 25 and 35 for females; however, there is a second peak beyond the age of 40.[12] Before visible symptoms appear, there is often a gradual shift in the person. The prodrome phase is a term used to describe this period.

GENDER DIFFERENCES IN SCHIZOPHRENIA

Every year, one in every 10,000 adults (12 to 60 years old) develops schizophrenia. Many researchers made about gender differences in schizophrenia and for now, it seems like gender doesn't affect it. Although, the fact that women start at a later age than males is a consistent observation.[13,14] These advantages appear to help women during the start of their disorder, but the benefits tend to fade over time. As a result, gender disparities in outcome vary depending on the patient's age.[15] There is growing evidence that estrogens are psychoprotective in women and that hypothalamic-pituitary-gonadal dysfunction occurs in both sexes. More studies are needed to better understand the pathophysiology and etiologies of schizophrenia psychoses in women and men. This will lead to better-tailored treatments and improved outcomes.[13]

THE CAUSES OF DISORDER

Schizophrenic patients are not born into a bad environment or a bad social situation.[16,17] Although the cause of schizophrenia has not been fully resolved, environmental factors and genetics are known to have a great influence. According to magnetic resonance imaging (MRI) research, neuron connections are disturbed, and the prefrontal lobe is nearly destroyed in patients. It's a strongly inherited trait. Variations in the major histocompatibility complex (MHC) genes have been discovered to be a risk factor for schizophrenia, according to genome scans.[18] We can identify three facts based on current genetic studies on schizophrenia. Firstly, schizophrenia is extremely polygenic, as genetic epidemiology data indicated many years ago, with hundreds, if not thousands, of different genetic loci implicated at the population level. The second key takeaway from recent genomic research is that genetic risk appears to be very pleiotropic and does not correspond to existing disorder classifications. The third argument is that, although much of the hereditary risk for schizophrenia remains unaccounted for at the DNA level, and the complexity of the already emerging picture, there are hopeful signals of convergence on a set of plausible biological processes.[1] Although genetics is frequently highlighted, the start is linked to environmental factors such as early life trauma, growing up in an urban setting, minority group membership, and cannabis usage, implying that exposure may have an impact on the developing "social" brain during critical periods.[19] Prenatal infections and nutrition, maternal substance usage, early life stresses, and obstetric problems are all more frequent in persons with schizophrenia than in the general population, according to several types of research. Early environmental variables may have a greater negative impact on the brains of people who have a genetic predisposition to schizophrenia than those who don't.[20] Environmental risk factors, as well as the discovery of a polygenic risk score for schizophrenia and studies on gene-environment and environment-environment interaction, have

greatly enhanced our understanding of the disorder.[21,22]

TREATMENT

Long-term hospitalization is ineffective and a contributory factor in schizophrenia-related impairment. Many people with mental disorders are sent to mental institutions, but the rehabilitation and follow-up treatment provided is insufficient.[23] A limited percentage of persons with severe schizophrenia are admitted to long-term hospitals.[24] Doctors may order a brief involuntary hospitalization if they believe there is a danger of damage to oneself or others.[25] Over the long run, around half of schizophrenia patients recovered or considerably improved, suggesting that functional remission is achievable. Demographic, clinical, and therapeutic features, as well as socio-economic determinants, all have a role in predicting the course of schizophrenia.[26] First-generation antipsychotics or second-generation antipsychotics are commonly used in the treatment of these patients. In some cases, these two types of drugs are combined. In addition to antipsychotic medications, lithium, anticonvulsants, beta-blockers, antidepressants, benzodiazepines, glycine, and electroconvulsive therapy are used.[27-29] Although there are various antipsychotic medicines available to treat the symptoms of schizophrenia, their response rate is lower than anticipated, they are slow-acting, and they frequently have substantial unpleasant side effects.[2] Antipsychotics are an important part of schizophrenia treatment, however, the antipsychotics that are now accessible have major drawbacks.[26]

Accurate diagnosis and selection of successful therapies for schizophrenia remain difficult due to a lack of reliable diagnostics.[30] It would be fair to say that schizophrenia is obscure and a huge burden on the patients and those around them. It is one of the biggest challenges in medicine even to this day. Therefore, numerous studies are being conducted. Multiple lines of evidence have recently discovered, albeit inconsistently, several immune system abnormalities in people with schizophrenia spectrum disorders, including raised levels of pro-inflammatory cytokines, T cell abnormalities, and evidence of increased microglial activation.[31]

ANTI-NEURONAL ANTIBODIES

Anti-neuronal antibodies are seen in the serum of individuals with nervous system paraneoplastic disorders. These disorders manifest with a wide variety of clinical symptoms and are frequently seen in the differential diagnosis of complicated neurological conditions. Several neurological disorders have been linked to antibodies against antigens present in the central nervous system.[32] It might be difficult to tell the difference between autoimmune encephalitis caused by anti-neuronal autoantibodies and primary mental problems.[33] Anti-neuronal antibodies' clinical relevance in people with mental disorders but no encephalitis, is unclear. However anti-neuronal antibodies are linked to autoimmune encephalitis, which is frequently accompanied by mental disorders.[34] Autoimmune processes producing a wide range of mental symptoms are becoming more widely understood, resulting in a paradigm change in neuropsychiatry. Since the discovery of underlying antibodies against brain ion channels or receptors, some individuals may be misdiagnosed with a main mental disorder. Nevertheless, there is no clear agreement on whether clinical indications in psychiatric patients should trigger additional testing, such as anti-neuronal autoantibodies assessment.[35]

SIGNIFICANCE OF ANTI-NEURONAL ANTIBODIES IN MENTAL DISORDERS

Anti-glutamic acid decarboxylase (anti-GAD) antibodies associated with progressive cerebellar disorders and autoimmune polyendocrinopathies could be an expression of the autoimmune nature of certain neurological degenerative processes affecting the central nervous system, but their significance outside of paraneoplastic syndromes is unknown.[32] Further surface-directed antibodies have yet to be proven to play such an obvious causal role in mental symptoms. Psychotic symptoms are, however, frequent in a variety of different autoimmune encephalitides. Patients with antibodies to the voltage-gated potassium channel complex (VGKCc), for example, frequently experience hallucinations, depression, and memory problems. Neuropsychiatric symptoms were identified in 44% of VGKCc antibody-positive individuals, who were treated for the main

psychiatric diagnosis on occasion.[35,36] Patients with antibodies against intracellular targets can also present with mental symptoms, which are less well documented.[35] A group of individuals with a negative clinical diagnosis of encephalitis had positive findings of anti-neuronal antibodies. Autoantibodies are seen in autoimmune encephalitis, aside from anti-N-methyl-D-aspartate receptor (NMDAR) antibodies, which appear to be negative in individuals with isolated early psychotic symptoms. Approximately 80% of individuals with anti-NMDAR antibody encephalitis show behavioral and mental symptoms at first. Increased understanding regarding the significance of NMDAR in generating psychosis-like behavior and being engaged in etiologically important brain processes in psychosis has piqued interest in anti-NMDAR antibodies. At the same time, some individuals with antiNMDAR encephalitis have had isolated mental symptoms, i.e. psychiatric symptoms without neurological symptoms.[33] Patients hospitalized for acute mental inpatient treatment with and without antibodies to NMDAR, contactin-associated protein-like 2 (CASPR2), or glutamic acid decarboxylase-65 (GAD65) showed comparable clinical characteristics. This does not rule out the possibility of clinical relevance in some patient subgroups, and more research into the clinical importance of anti-neuronal antibodies in patients with mental symptomatology is required.[34]

HYPOTHESES

Anti-neuronal antibodies targeting neuronal cell surface antigens and intracellular antigens can be used to classify antibody-mediated encephalitides. Autoantibodies directed against cell surface proteins are more common in individuals with mental disorders, maybe because of a hypothesized direct pathogenic impact.[35] Immunosuppressants can be used to treat autoimmune encephalitis, and the result is determined by the length of time between diagnosis and therapy. Early identification of this cause of psychosis could have significant therapeutic consequences. But, in the few cases when neuronal antibodies are identified, the titers are often low, and identical titers can be found in individuals with various neuropsychiatric disorders or even healthy people. On the other hand, in individuals with autoimmune encephalitis, pathogenic neuronal autoantibodies might be undetectable in the serum but positive in the cerebrospinal fluid (CSF), especially in those who have better outcomes.[37]

ANTI-NEURONAL ANTIBODIES IN SCHIZOPHRENIA

There is currently inconclusive and contradictory data on the role of anti-neuronal antibodies in the pathophysiology of psychosis in schizophrenia spectrum disorders, owing to methodological discrepancies between research. Besides, even though there is slight evidence with the tested serum, it is not right to say that antibodies directed against α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor (AMPAR), gamma-aminobutyric acid B receptor (GABABR), leucine-rich, glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), dipeptidyl-peptidase-like protein 6 (DPPX), or immunoglobulin A/immunoglobulin M (IgA/IgM) NMDAR antibodies, help us better understand the symptoms of a subgroup of patients with schizophrenia spectrum disorders because most studies were either negative or found positive results for both patients and healthy controls.[31] A small number of studies have looked at clinical aspects in anti-neuronal antibody-positive and -negative psychiatric patients, independent of diagnostic category.[34] When comparing individuals with schizophrenia who were positive or negative for NMDAR antibodies, Hammer et al.[38] found no changes in the Positive and Negative Syndrome Scale (PANSS) or Global Assessment of Function (GAF). NMDAR antibody-positive individuals had more severe psychotic symptoms (PANSS scores) than NMDAR antibody-negative patients, according to the authors of research that included patients with both first episode and chronic schizophrenia.[34] In contrast to NMDAR antibodies from healthy controls, Jézéquel et al.,[39] and Schou et al.[34] have demonstrated that NMDAR antibodies from schizophrenia patients change the surface dynamics of the NMDAR using a new single molecule-based imaging method. Fixed cell-based assays (such as the one employed in this study) had poorer sensitivity for detecting immunoglobulin (IgG) antibodies in psychotic patients than live cell-based assays, according to Jézéquel et al.,[40]

and Schou et al.[34] As a result, the outcomes of the current study might likely have been slightly different if other antibody detection methods had been used. However, the lack of phenotypic differences between individuals with and without anti-neuronal antibodies does not rule out the possibility that these antibodies are of little therapeutic use. Even if anti-neuronal antibodies were only involved in a small percentage of mental patients, this would have significant therapeutic consequences since these individuals could benefit from immunomodulatory therapy.[34] It is not clear whether there is an unrecognized autoimmune load in ostensibly chronic or treatment-resistant schizophrenic patients, leading to the lack of response to therapy. Monosymptomatic variants of autoimmune encephalitis (AE) likely exist, with solely psychotic presentations lasting far longer than previously thought. Unfortunately, there is no information on the incidence of misdiagnosed AE in schizophrenic populations in current studies. To answer this question, investigations examining serum and CSF for the aforementioned antibodies in chronic and treatment-resistant schizophrenia patients are needed.[31]

In conclusion, the findings studies indicate that schizophrenia remains a mystery. While scientists are trying to solve this big problem that lies in the brain and collapses the lives of humans, people that suffer from schizophrenia are trying to live with this disorder. There are so many unknown things but progress happens with the research and efforts of scientists. All this effort is for finding a permanent solution for schizophrenia. As is well established, deeper linkages between disorders and unknowns should be made in the light of results and information, not just in schizophrenia but also in many other psychiatric disorders. Currently, there are contrasts, little information and research, and also multiplicity in the studies with anti-neuronal antibodies. A better understanding of this field is essential. Since the connections even show people may have been diagnosed wrong or treatment for complicated disorders like schizophrenia is possible. It is possible to correct inaccuracies in treatments and diagnosis by obtaining discoveries with better results. There may be a relationship between anti-neuronal antibodies and psychiatric conditions, however, investigations have shown no conclusive results. Nonetheless, the existence of a connection means a lot for better understanding and reaching a solution.

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