

Is Schizophrenia an Autoimmune Condition?

Introduction

Schizophrenia is a chronic psychiatric disorder, with a worldwide incidence of approximately 1%. It is characterized by numerous psychiatric phenomena including third person auditory hallucinations, delusions of perception, control and thought interference, as well as negative symptoms. The disease course can be variable, ranging from a continuous, progressive condition to one with a relapsing and remitting course. Schizophrenia is more common in males than females with an approximate incidence of 15 and 10 per 100,000 per year, respectively.¹ When compared to the general population, mortality statistics for schizophrenia are especially concerning. It has been estimated that comparatively, people diagnosed with schizophrenia have a three-fold risk of dying- per year. Suicide rates are thought to be the strongest contributing factor which are in the region of 10 times that of the general population.^{1, 2} Unsurprisingly, there has been reported to be significant reductions in these patient's life expectancy of between 10 and 20 years.² Furthermore, evidence suggests that whilst over time the general mortality rates and life expectancy of the general population are improving, people with schizophrenia are not benefitting from this trend, leading to concerning disparity between the mortality rates of the two groups.^{1, 3}

Despite these trends that cannot be overlooked, the pathophysiology is still seemingly poorly understood. There have been many theorised mechanisms, with the Dopamine hypothesis being the most widely accepted. Excess neurotransmission of Dopamine was initially proposed as the cause of schizophrenia. This theory later attempted to explain the cause of positive and negative symptoms by suggesting that the effects and levels of dopamine could vary depending on the region of the brain involved.⁴ More recently, presynaptic dopamine receptor function has been reported to be significant, with findings suggesting that there is a rise in Dopamine synthesis capacity and presynaptic dopamine release in patients with schizophrenia.⁵ Consequently, the majority of the therapeutic strategies for managing schizophrenia, specifically first and second generation antipsychotics, have been aimed towards targeting the D2 and D3 receptors, in line with this hypothesis. Other theories include the glutamate hypothesis, where NMDA receptor dysfunction has been a hypothesised cause, as shown by receptor blockers such as Ketamine inducing the symptoms of schizophrenia in subjects.⁶ More recently, GABA receptor dysfunction has also been implicated in the pathogenesis.⁷

However, an avenue less explored and less widely known about is immune system dysfunction, which has been associated with schizophrenia since the mid-1900s. There is a growing body of evidence suggesting that inflammatory and autoimmune processes play a role in the pathophysiology of schizophrenia. Research has been

conducted in this area to analyse numerous links between schizophrenia and autoimmune diseases, prenatal and childhood infections and inflammatory markers such as cytokines. Furthermore, post-mortem brain studies have taken place looking for evidence of neuro-inflammation in schizophrenics and trials of some anti-inflammatory agents have already been conducted to explore this theory and its therapeutic uses. Therefore, the purpose of the report will be to explore the evidence suggesting there is an autoimmune element to the disorder, in the possibility that this could be an important and significant avenue of exploration and treatment for patients affected by this devastating condition.

Association with autoimmune disorders.

A number of autoimmune conditions have been explored for possible links to schizophrenia in order to examine any underlying association between the disorders. Rheumatoid Arthritis, Inflammatory Bowel Disease and Multiple Sclerosis which all share the common characteristics of being chronic, inflammatory disorders proposed as having autoimmune causes, have been investigated for an association to schizophrenia. One meta-analysis of over 19,000 patients with immune-mediated inflammatory disorders (IMID) and 97,000 matched controls, compared the incidence of mental health disorders including schizophrenia. They demonstrated a significantly increased incidence of schizophrenia in patients with IMIDs.⁸ However, these results must be interpreted with caution, as despite the large sample sizes, the use of administrative data means there may have been discrepancies between the ways different clinicians coded their patients. However, this association has been reinforced by further small studies which have suggested an increased risk of schizophrenia with other autoimmune disorders including Coeliac disease, Graves' disease, Multiple Sclerosis and Psoriasis.^{9, 10, 11}

Despite this apparent trend, an inverse relationship between schizophrenia and Rheumatoid arthritis (RA) has been noted. Patients with Rheumatoid Arthritis are seemingly 'protected' from developing schizophrenia, with reduced risk of schizophrenia in RA patients when compared to matched controls.^{11, 12} This is not consistent with other autoimmune conditions and their link to schizophrenia, and it poses the question as to why is there an inverse relationship with Rheumatoid Arthritis but not the other autoimmune conditions? One cohort study states there are similar results with both patients with Osteoarthritis and Ankylosing Spondylitis, which raises questions of the significance of the results and suggests the influence of other factors as osteoarthritis specifically, is a non-inflammatory joint disorder with no links to autoimmunity. Despite this, it cannot be ruled out that an underlying genetic connection between the two disorders is potentially responsible.¹²

Conversely, a number of multi-system autoimmune disorders exhibit psychiatric manifestations. The most relevant perhaps is SLE (Systemic Lupus Erythematosus) which shows multiple psychiatric symptoms, specifically those classically associated with schizophrenia, including psychosis.¹³ Numerous antibodies have been suggested as a cause for psychiatric symptoms in SLE including anti-ribosomal P autoantibodies, which have been found in patients with both SLE and patients with

psychosis (independent of SLE). However, multiple studies of these antibodies have failed to establish consistent results.^{14, 15} Additional autoimmune disorders such as Sjogren's syndrome also display psychiatric symptoms including cognitive dysfunction and personality change.¹⁶ Furthermore, a group of disorders called limbic encephalopathies also provide significant evidence of an association between autoimmune disorders and psychiatric symptoms. These encephalopathies were previously thought to be only secondary to infection or malignancy, however they have been shown to occur independently. At a molecular level they influence neurotransmitter receptor sites via the action of specific autoantibodies and hence have been classified into 3 main subgroups based on the synaptic receptor site targeted; anti-NMDA, anti-AMPA and anti-GABA receptor encephalitis.¹³ The presence of autoantibodies in the serum and CSF of affected patients and the positive response to treatment with immunological agents, such as intravenous immunoglobulin, supports these findings.¹³ Importantly, these conditions manifest with a number of psychiatric symptoms including behavioural and personality change. Most relevant is the anti- NMDA subtype which has specifically presented with features of psychosis.^{17, 18}

Taken together, the overall findings suggest that there are links between both schizophrenia and autoimmune disorders, and between autoimmune disorders and the psychiatric symptoms found in schizophrenia. Therefore, the evidence suggests the possibility of an underlying autoimmune component in the pathophysiology of schizophrenia.

Association with prenatal and childhood infections

There is a well-established link between prenatal infections and an increased risk of offspring with schizophrenia. A recent meta-analysis of 21 case-control and cohort studies exemplified this, showing links between schizophrenia and a number of maternal infections, including *Toxoplasma gondii* (TG), influenza and Herpes simplex virus (HSV). Three of the 4 studies investigating the effect of raised maternal TG IgG levels, found a statistically significant increased risk of schizophrenia in offspring. One of the study's found the increased risk to be as high as two-fold. Likewise, elevated levels of HSV IgG showed statistically significant increased risk of schizophrenia in 3 of the 5 studies. However, although Influenza was reported to increase future risk when contracted in the first half of gestation, these results were not significant due to small sample sizes.¹⁹ Despite these findings, up to half of the studies assessed failed to adjust for family history of psychosis and many had small samples sizes and short follow up periods, meaning the results should be interpreted with care. By the same token, viral CNS infections during early age have similarly been associated with increased schizophrenia risk in later life.²⁰ A systematic review of 7 articles found there was a two-fold increase in the incidence of schizophrenia in cases of viral CNS infections during the first years of life. Largely, these findings are based on robust and reliable cohort studies, but in one of the studies the control group suffered from acute infections making it difficult to draw reliable conclusions from that data set without the effects of confounders. The significance of these

findings as a whole in terms of schizophrenia and autoimmunity, is that the nature of the body's immune response to the pathogen appears to be more important than the specific pathogen itself. Numerous different infections were associated and viral CNS infections during childhood were also associated as a whole. In this sense, it suggests that there may be an abnormal immune response to pathogens involved in the pathophysiology. Whilst the nature of this remains unclear, mechanisms including the involvement of pro-inflammatory proteins such as cytokines and the initiation of autoimmunity as a result of the infective processes could be linked.

Cytokines and Schizophrenia

Cytokines are pro or anti-inflammatory proteins which are involved in the signalling in both innate and adaptive immunity in the body.²¹ They act to recruit a host of immune system cells including those involved in the adaptive response, B and T cells, and also cells of the myeloid lineage central to the innate response.²¹ Ultimately therefore, cytokines trigger an immune response and subsequent inflammation in the host. Cytokine levels have been studied in schizophrenia, in an attempt to determine if there are ongoing inflammatory processes in these patients which may provide evidence of autoimmune activity. A meta-analysis of 40 studies concluded that during acute relapses and first presentations of the disorder, a number of inflammatory cytokines were significantly raised. Some were shown to normalize (IL-1 β , IL-6, TGF- β) after treatment with antipsychotic agents which have been shown to have anti-inflammatory properties, whereas others remained high despite treatment (TNF- α , IL-2, IFN- γ).^{22, 23} Whilst many did importantly adjust for anti-psychotic medication use, many of the studies failed to address other important confounders including body mass index (BMI) and race. These findings suggest increased cytokine levels are found throughout multiple phases of the disorder. The significance of these findings is that they act to illustrate the presence of an immune response occurring in a number of patients with schizophrenia. Although this does not specifically suggest an underlying autoimmune process, it does appear to suggest the presence of possible immune system activation and subsequent inflammation, which may in turn be caused by autoimmune activity.

Organic evidence

Organic evidence in psychiatry is often rare, however post-mortem brain studies have provided a useful tool in assessing the presence of neuro-inflammatory processes in schizophrenia. Whilst the presence of neuro-inflammation does not provide a direct link to an autoimmune cause, it does indicate an inflammatory process, which may in turn be caused by autoimmunity. Studies have assessed a number of immune system cells which importantly include Microglia, the immune cells of the central nervous system (CNS).²⁴ These cells become activated by pro-

inflammatory signals or CNS injury, subsequently triggering an inflammatory processes within the CNS. Therefore they are an appropriate measure of ongoing inflammation.^{24, 25} Other markers of inflammation, such as various Chemokines, Cytokines and Glial fibrillary acidic protein (GFAP), have been additionally investigated.^{25, 26}

A meta-analysis including 41 studies of over 700 patients and 700 controls, investigated immune involvement in the post-mortem brains of schizophrenic patients. It concluded that there was an increase in the microglia density when compared with matched controls.²⁵ Although there was no significant difference between the number or activity of these cells in this analysis, considering the role of microglia, this may provide evidence of an ongoing inflammatory process in the central nervous system of people with schizophrenia. Despite this, there is considerable variation in the results of post-mortem brain studies as demonstrated by a previous systematic review of the evidence. Microglia were found to be increased in 11 of the 22 studies; undifferentiated Glial cells were elevated in just 2 of the 34 studies and GFAP expression was increased in only 6 of the 43 studies.²⁶ Cytokine and Chemokine levels were similarly inconsistent, with the same proteins displaying differing levels across the studies.²⁶ Furthermore, the effects of anti-psychotic medication use was not taken adjusted for, meaning the anti-inflammatory properties of anti-psychotics may have influenced the results. These should hence be interpreted with caution.

The number of studies which show a lack of association between neuro-inflammatory cells and schizophrenic patients mean that a definitive statement on whether neuro-inflammation is present in schizophrenia cannot be made. However, the meta-analysis and a number of studies included in the review do show evidence of inflammatory processes in some patients, so there is a subgroup of patients with schizophrenia which demonstrate evidence of ongoing neuro-inflammation. Whether this is caused by autoimmune activity is unclear.

Therapeutic evidence and implications

In line with the inflammatory hypothesis for schizophrenia supported by the evidence above, many studies have explored the use of anti-inflammatory agents to attempt to improve the treatment of schizophrenia. It appears rational that a disorder with a hypothesized inflammatory component could be effectively treated with anti-inflammatory agents. A number of randomised control trials (RCTs) have investigated this through the use of the COX-2 inhibitor, Celecoxib, in addition to antipsychotics. A meta-analysis which examined 6 RCTs of Celecoxib (in addition to Risperidone, Olanzapine and Amisulpride) showed that patients in 4 of the trials showed benefit in having an anti-inflammatory agent.²⁷ Significantly, in one of the studied included, Celecoxib alongside Amisulpride showed benefits to patient's negative symptoms compared to the control group. A further meta-analysis, which included 8 RCTs and also 3 unpublished studies, indicated only a very small

improvement of positive symptoms with NSAID use with a very low effect size.²⁸ This analysis did importantly include unpublished studies, which removed the possibility of publication bias and likely improved the reliability of the results.

A supporting factor relating to cytokine levels, is that it has been found that antipsychotics have anti-inflammatory effects alongside their action on the Dopamine receptor sites.²³ A meta-analysis found that anti-psychotic medication acted to reduce the levels of certain pro-inflammatory cytokines (IL-12, IL-6, TGF- β) in schizophrenic patients where levels were found to be initially raised.²² This could mean that the anti-inflammatory action of these agents are helping to improve the symptoms of the disorder, therefore implying an inflammatory component to the disorder. On the other hand, it could well be a coincidence and this action has no implications in treating the disorder.

Conclusion

In conclusion, there is a large base of evidence surrounding inflammation as a possible cause of schizophrenia. The areas discussed above provide reasonable links between the immune system, and its activation or dysfunction in the form of inflammation, and schizophrenia. Whilst these areas do suggest a potential inflammatory component in schizophrenia, evidence of the cause being specifically autoimmune in nature, is more limited. The association with autoimmune disorders is present however. The further evidence provided, such as abnormally raised cytokines and the link to prenatal and childhood infections, may be viewed as abnormal immune system activation and responses which, as a feature of autoimmune disease, can support the autoimmune theory.

Despite this, the evidence for inflammation and autoimmunity was found to be often inconsistent between studies. Likewise, the evidence is almost exclusively associative at this stage and does not demonstrate causality between autoimmunity and schizophrenia. Therefore, it is not possible to say definitively that there is an inflammatory or autoimmune component. However, the evidence explored does indicate a possible inflammatory and even autoimmune component to the pathophysiology of the disorder and therefore warrants further investigation. The modest yet promising results with the use of anti-inflammatory agents as a therapeutic strategy also demonstrates potential for further larger studies, perhaps with the use of different anti-inflammatory agents.

Bibliography

1. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev* 2008;30:67-76.
2. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World Psychiatry* 2014;13(2):153-60.
3. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 2007;64(10):1123-31.
4. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophr Bull* 2009;35(3):549-62.
5. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry* 2012;69(8):776-86.
6. Kantrowitz JT, Javitt DC. N-methyl-d-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? *Brain Res Bull* 2010;83(3-4):108-21.
7. de Jonge JC, Vinkers CH, Hulshoff Pol HE, Marsman A. GABAergic Mechanisms in Schizophrenia: Linking Postmortem and In Vivo Studies. *Front Psychiatry* 2017;8:118.
8. Marrie RA, Walld R, Bolton JM, Sareen J, Walker JR, Patten SB, et al. Increased incidence of psychiatric disorders in immune-mediated inflammatory disease. *J Psychosom Res* 2017;101:17-23.
9. Marrie RA, Fisk JD, Tremlett H, Wolfson C, Warren S, Tennakoon A, et al. Differences in the burden of psychiatric comorbidity in MS vs the general population. *Neurology* 2015;85(22):1972-9.
10. Benros ME, Pedersen MG, Rasmussen H, Eaton WW, Nordentoft M, Mortensen PB. A nationwide study on the risk of autoimmune diseases in individuals with a personal or a family history of schizophrenia and related psychosis. *Am J Psychiatry* 2014;171(2):218-26.
11. Chen SJ, Chao YL, Chen CY, Chang CM, Wu EC, Wu CS, et al. Prevalence of autoimmune diseases in in-patients with schizophrenia: nationwide population-based study. *Br J Psychiatry* 2012;200(5):374-80.
12. Sellgren C, Frisell T, Lichtenstein P, Landen M, Askling J. The association between schizophrenia and rheumatoid arthritis: a nationwide population-based Swedish study on intraindividual and familial risks. *Schizophr Bull* 2014;40(6):1552-9.
13. Kayser MS, Dalmau J. The emerging link between autoimmune disorders and neuropsychiatric disease. *J Neuropsychiatry Clin Neurosci* 2011;23(1):90-7.
14. Eber T, Chapman J, Shoenfeld Y. Anti-ribosomal P-protein and its role in psychiatric manifestations of systemic lupus erythematosus: myth or reality? *Lupus* 2005;14(8):571-5.
15. Diamond B, Huerta PT, Mina-Osorio P, Kowal C, Volpe BT. Losing your nerves? Maybe it's the antibodies. *Nature reviews. Immunology* 2009;9(6):449-56.
16. Tobón GJ, Pers JO, Devauchelle-Pensec V, Youinou P. Neurological Disorders in Primary Sjögren's Syndrome. *Autoimmune Dis* 2012;2012.
17. Kayser MS, Kohler CG, Dalmau J. Psychiatric manifestations of paraneoplastic disorders. *Am J Psychiatry* 2010;167(9):1039-50.
18. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;7(12):1091-8.
19. Khandaker GM. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. 2013;43(2):239-57.
20. Khandaker GM, Zimbron J, Dalman C, Lewis G, Jones PB. Childhood infection and adult schizophrenia: A meta-analysis of population-based studies. *Schizophr Res* 2012;139(1-3):161-8.
21. Zhang JM, An J. Cytokines, Inflammation and Pain. *Int Anesthesiol Clin* 2007;45(2):27-37.

22. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-Analysis of Cytokine Alterations in Schizophrenia: Clinical Status and Antipsychotic Effects. *Biol Psychiatry* 2011;70(7):663-71.
23. Drzyzga L, Obuchowicz E, Marcinowska A, Herman ZS. Cytokines in schizophrenia and the effects of antipsychotic drugs. *Brain Behav Immun* 2006;20(6):532-45.
24. Muller N, Weidinger E, Leitner B, Schwarz MJ. The role of inflammation in schizophrenia. *Front Neurosci* 2015;9:372.
25. van Kesteren CF, Gremmels H, de Witte LD, Hol EM, Van Gool AR, Falkai PG, et al. Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. *Transl Psychiatry* 2017;7(3):e1075.
26. Trepanier MO, Hopperton KE, Mizrahi R, Mechawar N, Bazinet RP. Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. *Mol Psychiatry* 2016;21(8):1009-26.
27. Marini S, De Berardis D, Vellante F, Santacroce R, Orsolini L, Valchera A, et al. Celecoxib Adjunctive Treatment to Antipsychotics in Schizophrenia: A Review of Randomized Clinical Add-On Trials. *Mediators Inflamm* 2016;2016:3476240.
28. Nitta M, Kishimoto T, Muller N, Weiser M, Davidson M, Kane JM, et al. Adjunctive use of nonsteroidal anti-inflammatory drugs for schizophrenia: a meta-analytic investigation of randomized controlled trials. *Schizophr Bull* 2013;39(6):1230-41.