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Editorial

Schizophrenia, Inflammation and *Toxoplasma gondii* Infection

Jeffrey B. Eells*

Department of Basic Sciences, Mississippi State University College of Veterinary Medicine, USA

***Corresponding author**

Jeffrey B. Eells, Department of Basic Sciences, Mississippi State University College of Veterinary Medicine, USA, Tel: 662-325-1085; Email: Eells@cvm.msstate.edu

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Genetic analysis suggests that schizophrenia is a polygenetic disease, mostly consisting of common mutations with low risk and rare mutations with higher risks [1]. Although data suggests a strong genetic component to the risk of developing schizophrenia, environmental and/or developmental risk factors also contribute. Currently, there are no interventions that target and mitigate the effects of any genetic risks for schizophrenia. Therefore, a better understanding the environmental risk factors for schizophrenia is also important. A growing body of evidence is accumulating linking schizophrenia risk with inflammation and alterations in the immune response. One specific example is the increase in schizophrenia risk associated with infection by the protozoan parasite *Toxoplasma gondii*. The mechanisms associated with increasing the risk of schizophrenia due to infectious disease and immune response has the potential to be manipulated to mitigate the risk and to potentially reduce the number of schizophrenia cases. As genetic sequencing data has been shown to better predict schizophrenia, inclusion of environmental risk factors, such as infectious agents, is likely to enhance the prediction of individuals most at risk for developing schizophrenia.

One mechanism contributing to schizophrenia that has received growing attention in recent years is the activation of the immune system and inflammation. Data to support this include consistent associated with schizophrenia risk and a variant in the major histocompatible region, including HLA regions, has been reported. Other gene variants in toll-like receptors and complement proteins have also been shown to be associated with schizophrenia [2]. More recently, Pandey et al., found one immunoglobulin gene allele significantly associated with schizophrenia [3]. Additional data to support the link between immune activation and inflammation include evidence of elevated inflammatory cytokine patterns in patients with schizophrenia consisting of an attenuated type 1 (IL-2 and interferon gamma) and elevated type 2 (IL-6 and IL-10) immune response [4]. More recently, autoimmunity has been implicated as a potential contributing factor for schizophrenia. Although studies are limited, approximately 10% of acute, unmedicated patients with schizophrenia show autoimmunity to the NMDA receptor [5]. Another mechanism linking glutamate neurotransmission and the immune system is that immune activation alters kynurenine production which can elevate levels of kynurenic acid, an NMDA receptor antagonist [6]. Changes in kynurenine metabolism resulting in an increase in kynurenic acid were reported in patients with schizophrenia [7]. Anti-NMDA receptor autoimmunity and enhanced synthesis of kynurenic acid are particularly relevant as decreased activation of the NMDA receptor is an important mechanism contributing to psychosis and the pathophysiology of schizophrenia. Furthermore, both epidemiological data and animal studies have also implicated previous infections and immune activation with an increased risk of schizophrenia [8].

Infection with the protozoan parasite *T. gondii* has been found to be a relatively strong risk factor for schizophrenia with an average odds ratio of 2.7 [9]. This association is based on an increased incidence of schizophrenia in individuals with antibodies to *T. gondii* [10]. Additionally, a dose–response relationship exists such that the risk of schizophrenia increases with increasing levels of *T. gondii* antibodies [11,12]. In addition to an association with the incidence of schizophrenia, infection with *T. gondii* has also been found associated with both an increase in the severity of schizophrenia symptoms as well as the amount of pathological changes in the brain, specifically a reduction in gray matter [13-15].

In addition to the epidemiology data, animal studies have shown that *T. gondii* infection can alter behaviors in rodents and produce neurochemical, molecular and biochemical changes in the brain that are similar to those found in patients with schizophrenia. *T. gondii* infection in rodents has been reported to affect dopamine neurochemistry and behaviors associated with dopamine neurotransmission [16,17]. *Toxoplasma gondii* expresses two tyrosine hydroxylases which can convert tyrosine to DOPA, the rate limiting step in dopamine synthesis [18]. This increase in dopamine synthesis has been proposed as the mechanism through which *T. gondii* infection contributes to an increased risk for schizophrenia. However, *T. gondii* cysts that form in brain tissue also produce inflammation [19]. Notarangelo et al., reported that *T. gondii* infection elevates cerebral kynurenic acid [20]. Recently, Xiao et al., found that *T. gondii* infection elevated matrix antigen MAG1 antibodies which correlated with cyst burden and alterations in amphetamine stimulated activity [21]. Antibody titers to *T. gondii* were also associated with open

field activity [22]. Furthermore, behavioral changes can persist even after clearance of *T. gondii* cysts, which argues against the enhanced production of dopamine via the cysts for some behavioral changes [23]. More recently, Kannan et al. found that *T. gondii* infections in juvenile mice had a differential effect on MK-801 altered prepulse inhibition and had a significantly greater increase in NMDA receptor auto antibodies [24]. *Toxoplasma gondii* infection also elevated complement protein C1q expression and activity [24]. Collectively, these data suggests that the mechanism through which *T. gondii* infection increases the risk of schizophrenia is likely due, at least in part, on the activation of the immune system and the subsequent inflammatory changes. Therefore, *T. gondii* infection could contribute to an increase risk of schizophrenia via shared pathways with other types of infectious agents and autoimmunity.

Currently, a serious gap in treating schizophrenia patients is the inability to reliably predict individuals that will develop the disease and identify the most effective therapies for each patient. As the causes of schizophrenia are multifaceted, involving both genetic and environmental risks, predicting the course of the disease will require a combination of both of these variables. The advancement of gene sequencing has provided a better understanding of how multiple genetic variants interact to contribute to schizophrenia and will likely aid in determining individuals at risk for developing schizophrenia and potentially be useful for guiding treatment. The epidemiology and animal studies suggest that antibody titers to *T. gondii* could be useful in enhancing value of genetic sequencing information and/or family history to predict at risk individuals, the severity of the disease and potential treatments. The timing of *T. gondii* infection could also be very informative, as infections in childhood are likely to have a greater effect.

In addition to *T. gondii*, the immune response to other infectious agents could also be useful for predicting risk of developing schizophrenia and/or guiding therapy. Xu et al., demonstrated a method to assess multiple antigens from infectious agent that an individual has been exposed [25]. Therefore, gene sequencing information in combination with knowledge of the pathogens an individual has been exposed and when that exposure occurred is likely to greatly enhance the ability to predict who will develop schizophrenia and severity of the disease [26]. As several anti-inflammatory treatments have shown efficacy in attenuating schizophrenia symptoms, this information could also be used to select patients that could benefit the most from this type of treatment [27]. The ability to predict disease provides an opportunity to develop therapies to stop or mitigate the disease process to prevent occurrence of schizophrenia cases or minimize the severity of the disease [28]. The combination of genetic liability with knowledge about exposure to infectious agents also has the potential to determine the mechanisms for these interactions as there is a likely overlap between the genetic risk factors and the genes and pathways modified by environmental risk factors that contribute to schizophrenia.

REFERENCES

1. Schork AJ, Wang Y, Thompson WK, Dale AM, Andreassen OA. New statistical approaches exploit the polygenic architecture of schizophrenia--implications for the underlying neurobiology. Curr Opin Neurobiol. 2016; 36: 89-98.
2. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia risk from complex variation of complement component 4. Nature. 2016; 530:177-183.
3. Pandey JP, Namboodiri AM, Elston RC. Immunoglobulin G genotypes and the risk of schizophrenia. Human genetics. 2016.
4. Muller N, Schwarz M. Schizophrenia as an inflammation-mediated dysbalance of glutamatergic neurotransmission. Neurotoxicity research. 2006; 10: 131-148.
5. Steiner J, Walter M, Glanz W, Sarnyai Z, Bernstein HG, Vielhaber S, et al. Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia: specific relevance of IgG NR1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. JAMA psychiatry. 2013; 70: 271-278.
6. Stone TW, Stoy N, Darlington LG. An expanding range of targets for kynurenine metabolites of tryptophan. Trends Pharmacol Sci. 2013; 34: 136-143.
7. Linderholm KR, Skogh E, Olsson SK, Dahl ML, Holtze M, Engberg G, et al. Increased levels of kynurenine and kynurenic acid in the CSF of patients with schizophrenia. Schizophr bull. 2012; 38: 426-432.
8. Muller N, Weidinger E, Leitner B, Schwarz MJ. The role of inflammation in schizophrenia. Front Neurosci. 2015; 9: 372.
9. Torrey EF, Bartko JJ, Yolken RH. Toxoplasma gondii and other risk factors for schizophrenia: an update. Schizophr bull. 2012; 38: 642-647.
10. Torrey EF, Bartko JJ, Lun ZR, Yolken RH. Antibodies to Toxoplasma gondii in patients with schizophrenia: a meta-analysis. Schizophr bull. 2007; 33: 729-736.
11. Pedersen MG, Stevens H, Pedersen CB, Norgaard-Pedersen B, Mortensen PB. Toxoplasma infection and later development of schizophrenia in mothers. Am J Psychiatry. 2011; 168: 814-821.
12. Blomstrom A, Karlsson H, Wicks S, Yang S, Yolken RH, Dalman C. Maternal antibodies to infectious agents and risk for non-affective psychoses in the offspring--a matched case-control study. Schizophr Res. 2012; 140: 25-30.
13. Bachmann S, Schroder J, Bottmer C, Torrey EF, Yolken RH. Psychopathology in first-episode schizophrenia and antibodies to Toxoplasma gondii. Psychopathology. 2005; 38: 87-90.
14. Horacek J, Flegr J, Tintera J, Verebova K, Spaniel F, Novak T, et al. Latent toxoplasmosis reduces gray matter density in schizophrenia but not in controls: voxel-based-morphometry (VBM) study. World J Biol Psychiatry. 2012; 13: 501-509.
15. Holub D, Flegr J, Dragomirecka E, Rodriguez M, Preiss M, Novak T, et al. Differences in onset of disease and severity of psychopathology between toxoplasmosis-related and toxoplasmosis-unrelated schizophrenia. Acta psychiatr Scand. 2013; 127: 227-238.
16. Hay J, Aitken PP, Arnott MA. The influence of congenital Toxoplasma infection on the spontaneous running activity of mice. Z Parasitenkd. 1985; 71: 459-462.
17. Stibbs HH. Changes in brain concentrations of catecholamines and indoleamines in Toxoplasma gondii infected mice. Ann Trop Med Parasitol. 1985; 79: 153-157.
18. Prandovszky E, Gaskell E, Martin H, Dubey JP, Webster JP, McConkey GA. The neurotropic parasite Toxoplasma gondii increases dopamine metabolism. PloS one. 2011; 6: 23866.

19. Hermes G, Ajioka JW, Kelly KA, Mui E, Roberts F, Kasza K, et. Neurological and behavioral abnormalities, ventricular dilatation, altered cellular functions, inflammation, and neuronal injury in brains of mice due to common, persistent, parasitic infection. J Neuroinflammation. 2008; 5: 48.

20. Notarangelo FM, Wilson EH, Horning KJ, Thomas MA, Harris TH, Fang Q, Hunter CA, Schwarcz R Evaluation of kynurenine pathway metabolism in Toxoplasma gondii-infected mice: implications for schizophrenia. Schizophr Res. 2014; 152: 261-267.

21. Xiao J, Li Y, Prandovszky E, Kannan G, Viscidi RP, Pletnikov MV, Yolken RH. Behavioral Abnormalities in a Mouse Model of Chronic Toxoplasmosis Are Associated with MAG1 Antibody Levels and Cyst Burden. PLoS neglected tropical diseases. 2016; 10: 0004674.

22. Eells JB, Varela-Stokes A, Guo-Ross SX, Kummari E, Smith HM, Cox E, et al. Chronic Toxoplasma gondii in Nurr1-null heterozygous mice exacerbates elevated open field activity. PloS one. 2015; 10: 0119280.

23. Ingram WM, Goodrich LM, Robey EA, Eisen MB. Mice infected with low-virulence strains of Toxoplasma gondii lose their innate aversion to cat urine, even after extensive parasite clearance. PloS one. 2013 ; 8:75246.

24. Kannan G, Crawford JA, Yang C, Gressitt KL, Ihenatu C, Krasnova IN, et al. Anti-NMDA receptor autoantibodies and associated neurobehavioral pathology in mice are dependent on age of first exposure to Toxoplasma gondii. Neurobiol Dis. 2016; 91: 307-314.

25. Xu GJ, Kula T, Xu Q, Li MZ, Vernon SD, Ndung'u T, et al. Viral immunology. Comprehensive serological profiling of human populations using a synthetic human virome. Science. 2015; 348: 0698.

26. Benros ME, Mortensen PB, Eaton WW. Autoimmune diseases and infections as risk factors for schizophrenia. Ann N Y Acad Sci. 2012; 1262: 56-66.

27. Muller N. The role of anti-inflammatory treatment in psychiatric disorders. Psychiatr Danub. 2013; 25: 292-298.

28. Millan MJ, Andrieux A, Bartzokis G, Cadenhead K, Dazzan P, Fusar-Poli P, et al. Altering the course of schizophrenia: progress and perspectives. Nat Rev Drug Discov. 2016; 15: 485-515.

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