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Biomarkers of gluten sensitivity in patients with non-affective psychosis: A meta-analysis

Laura R. Lachance [a,b,*,1], Kwame McKenzie [a]

[a] Social Aetiology of Mental Illness Training Program, Centre for Addiction and Mental Health, 455 Spadina Avenue, Suite 300, Toronto, Ontario M5S 2G8, Canada
[b] University of Toronto, 455 Spadina Avenue, Suite 300, Toronto, Ontario M5S 2G8, Canada

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ABSTRACT

Background: Dohan first proposed that there may be an association between gluten sensitivity and schizophrenia in the 1950s. Since then, this association has been measured using several different serum biomarkers of gluten sensitivity. At this point, it is unclear which serum biomarkers of gluten sensitivity are elevated in patients with schizophrenia. However, evidence suggests that the immune response in this group is different from the immune response to gluten found in patients with Celiac disease.
Methods: A systematic literature review was performed to identify all original articles that measured biomarkers of gluten sensitivity in patients with schizophrenia and non-affective psychoses compared to a control group. Three databases were used: Ovid MEDLINE, Psych INFO, and Embase, dating back to 1946. Forward tracking and backward tracking were undertaken on retrieved papers. A meta-analysis was performed of specific biomarkers and reported according to MOOSE guidelines.
Results: 17 relevant original articles were identified, and 12 met criteria for the meta-analysis. Five biomarkers of gluten sensitivity were found to be significantly elevated in patients with non-affective psychoses compared to controls. The pooled odds ratio and 95% confidence intervals were Anti-Gliadin IgG OR = 2.31 [1.16, 4.58], Anti-Gliadin IgA OR = 2.57 [1.13, 5.82], Anti-TTG2 IgA OR = 5.86 [2.88, 11.95], Anti-Gliadin (unspecified isotype) OR = 7.68 [2.07, 28.42], and Anti-Wheat OR = 2.74 [1.06, 7.08]. Four biomarkers for gluten sensitivity, Anti-EMA IgA, Anti-TTG2 IgG, Anti-DGP IgG, and Anti-Gluten were not found to be associated with schizophrenia.
Conclusions: Not all serum biomarkers of gluten sensitivity are elevated in patients with schizophrenia. However, the specific immune response to gluten in this population differs from that found in patients with Celiac disease.

1. Introduction

An association between gluten sensitivity and schizophrenia has been reported (Dohan, 1966; Reichelt and Landmark, 1995; Kalaydjian et al., 2006). Gluten is a protein that usually stays in the digestive tract. If the lining of the gut is compromised, it enters the bloodstream and can trigger an immune reaction. In neuropsychiatric disorders, gluten breakdown products are also important as they can act as ligands at opioid receptors in the central nervous system (Ziodrou et al., 1979; Severance et al., 2012).

The immune response to gluten has been investigated in a number of non-affective psychoses and there are reports that this immune response is different from that seen in Celiac disease (Samaroo et al., 2010). However, there is inconsistency with regard to which serum antibodies are studied. There are several different serum biomarkers of gluten sensitivity that can be measured, and some antibodies exist in both the IgG and IgA isotype. IgG antibodies represent 75% of human immunoglobulins found in serum. Alternatively, IgA antibodies are primarily involved in the mucosal immune system, which protects epithelial surfaces in the body from pathogens. However, IgA antibodies can also exist in the serum where they serve to initiate the inflammatory response to pathogens (Janeway et al., 2001).

Further difficulty in identifying a specific reaction to gluten in patients with schizophrenia comes from the fact that there are general immune alterations in schizophrenia that are also common to patients with Celiac disease and other autoimmune disorders (Smith, 1991; Kalaydjian et al., 2006; Saetre et al., 2007). In addition, adults with psychiatric disorders, exhibit increased immune reactivity to foodstuffs (Mascord et al., 1978; Dickerson et al., 2011; Severance et al., 2012). It may be that gluten sensitivity can be a surrogate marker for increased gastrointestinal permeability or inflammation (Severance et al., 2012).

It is worth clarifying here that gluten sensitivity is a separate condition from Celiac disease. Nevertheless, patients who are gluten-sensitive experience symptoms when they consume gluten. It is postulated that only the innate immune response is involved in gluten sensitivity whereas both the innate and adaptive immune responses are involved in Celiac disease (Volta and De Giorgio, 2012). Volta et al. (2012) sought

* Corresponding author at: Social Aetiology of Mental Illness Training Program, Centre for Addiction and Mental Health, 455 Spadina Avenue, Suite 300, Toronto, Ontario M5S 2G8, Canada. Tel.: +1 647 970 5755, +1 416 545 8501x39377.
E-mail address: laura.lachance@mail.utoronto.ca (L.R. Lachance).
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to characterize the immune response to gluten in gluten sensitivity. They found that 56.4% of individuals with gluten sensitivity had elevations in AGA IgG, 7.7% had elevations in AGA IgA, and elevations in anti-TTG2, anti-EMA, and anti-DGP were rare (Volta et al., 2012).

This study aims to address the following questions: Do individuals with non-affective psychoses have higher levels of serum biomarkers of gluten sensitivity compared to the general population? If so, which biomarkers of gluten sensitivity are elevated in non-affective psychoses and at what rate? Lastly, is the specific immune response to gluten, as indicated by the pattern of elevated biomarkers of gluten sensitivity, in non-affective psychoses different from that seen in Celiac disease?

A review of this kind has never been performed. Our results will help inform research design of future studies and to increase our understanding of gluten sensitivity in patients with non-affective psychosis. Specifically, we hope to help inform researchers which biomarkers of gluten sensitivity are worth measuring in patients with non-affective psychoses in various research designs exploring this area including epidemiological studies or clinical trials.

2. Materials and methods

2.1. Selection of articles for inclusion

To identify studies relevant for the current literature review and meta-analysis, a computerized OVID search of Medline, PsychINFO, and Embase was performed. All abstracts from 1946 to October Week 1 2011 were retrieved using the following MeSH terms: Glutens, Gliadin, Triticum, food hypersensitivity, and wheat hypersensitivity, along with their associated keywords. These results were combined with the MeSH terms "schizophrenia" and "psychotic disorders" and their corresponding keywords. The above search was completed a second time in order to retrieve articles published from October Week 1 2011 to November Week 1 2013. Searches were performed by a resident physician, and a librarian at the Centre for Addiction and Mental Health (CAMH) was consulted to help design the above search strategy.

We included only English language articles that had been published in peer-reviewed journals or books, with independent data. All abstracts were read, and full papers were read by two raters for all articles, which met the criteria for the review. The inclusion criteria for the review were: original research article, measurement of serum or blood markers indicating increased immune reactivity to gluten/wheat/gliadin, and studies of groups with a diagnosis of schizophrenia or psychotic disorder (non-affective psychosis). In order to be included in the meta-analysis, additional inclusion criteria had to be met: Inclusion of a defined control group without evidence of Celiac disease, psychiatric illness, or increased risk of schizophrenia (i.e. first degree relative). The presence of a control group was necessary in order to allow for a comparison in the rates of immune reactivity to gluten between the two groups. In addition, given the heterogeneity of the study and control samples, we attempted to restrict our quantitative analysis to

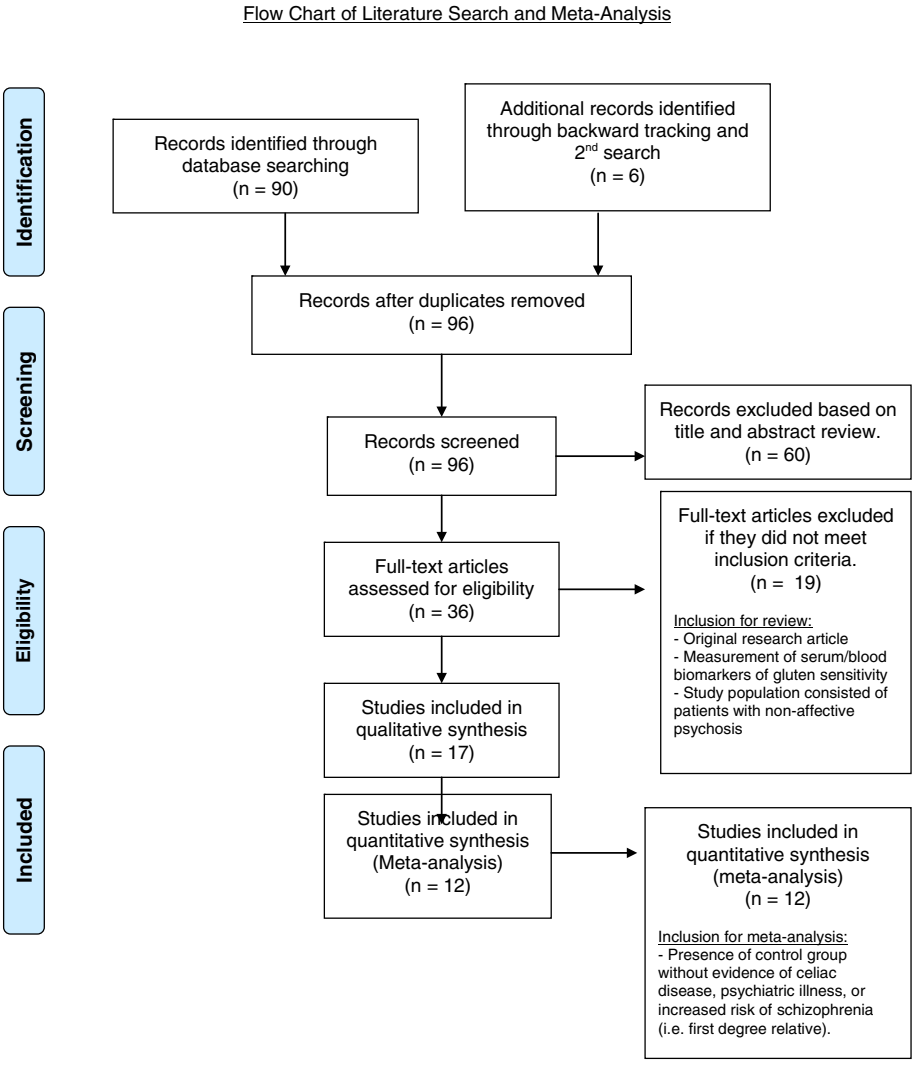

Fig. 1. Flow chart of literature search and meta-analysis.