Short communication

“Bread madness” revisited: screening for specific celiac antibodies among schizophrenia patients

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Abstract

Purpose. – A possible association between gluten consumption and schizophrenia has been reported. The objective was to compare patients with chronic schizophrenia and matched controls for sociodemographic variables, prevalence of celiac-specific anti-endomysial antibodies and disease-related variables.

Subjects and methods. – The study group was comprised of 50 consecutive patients diagnosed with schizophrenia, 18 years of age and older attending the out-patient clinic of the Mental Health Center in Beer-Sheva, Israel. The control group was comprised of mentally normal volunteers who came to primary care clinics for blood tests unrelated to gastrointestinal tract complaints and who were not diagnosed with celiac disease. Known celiac patients and those who refused to participate, did non-speak Hebrew or were incoherent were excluded from the study. All participants in both groups underwent a blood test for anti-endomysial IgA antibody and completed a questionnaire.

Results. – Each group was comprised of 50 participants. There were no significant differences between the groups in gender, BMI or country of birth. The mean age of the study group was significantly higher than the controls. All tests for anti-endomysial antibody in both groups were negative.

Discussion and conclusions. – In contrast to previous reports, we found no evidence for celiac disease in patients with chronic schizophrenia as manifested by the presence of serum IgA anti-endomysial antibodies. It is unlikely that there is an association between gluten sensitivity and schizophrenia.

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1. Introduction

Sensitivity to gluten, clinically known as the celiac sprue or celiac disease, is commonly manifested by malnutrition and pathological changes in the small intestinal mucosa that are usually reversible when gluten is excluded from the diet [14]. Samuel Gee first described the disease in 1888 [8]. However, it was not until 1955 that Dicke described the association between celiac and gluten [14].

Until recently celiac disease was considered uncommon in the United States, with an estimated prevalence of 1:3000 population. However, greater awareness of its varying presentation and the availability of new serologic tests have led to the realization that celiac disease is relatively common, affecting 1:120 to 1:300 persons in Europe and North America [6].
The classic manifestations of celiac disease, particularly in children, include restlessness, underweight, delayed development, failure to thrive, chronic diarrhea, muscular degeneration and anemia [14]. The disease is easily diagnosed when signs appear in childhood, usually at 9–18 months of age, but is more difficult to diagnose at an older age. In addition to the typical presentation, some non-typical and/or latent forms of the illness have been described. Less common presentations of celiac disease include neurological disorders such as epilepsy and brain calcification [9,10]. An atypical symptom profile may lead to a delayed diagnosis in the individual or to under-diagnosis in the population [13].

An association has been described between celiac disease and other disorders, leading to the appellation of celiac disease as a “many headed hydra” [11]. A possible association between gluten and schizophrenia has been suggested in sporadic case reports [2–5,12,16]. It has been suggested that the consumption of full wheat bread could cause “madness”. Most of the latter concepts were based on observations made during World War II [3,20]. In one case a woman diagnosed with celiac disease presented with schizophrenia symptoms. A HMPAO SPECT (99 mTc) scan showed hypo-perfusion of the left frontal region of the brain, which resolved when the patient adhered to a gluten-free diet [1].

The idea for the present study stemmed from a clinical observation of two patients in a primary care setting who were diagnosed with both celiac disease and schizophrenia. The study hypothesis was that a subgroup of our schizophrenic patients has celiac disease. The aim was to compare the prevalence of serologic markers of celiac disease (antiendomysial antibodies) between schizophrenia patients and non-schizophrenia patients visiting general practice clinics.

2. Subjects and methods

2.1. Study population

The study group consisted of consecutive Hebrew-speaking patients, 18 years of age or above, with a diagnosis of chronic schizophrenia for at least one year who visited the out-patient clinic of the Mental Health Center in Beer-Sheva and consented to participate in the study. Patients who refused to participate in the study, who were incoherent, or who were previously diagnosed with celiac disease were excluded from the study.

The control group was comprised of mentally normal volunteers who came to primary care clinics for blood tests unrelated to gastrointestinal tract complaints and who were not diagnosed with celiac disease.

The Helsinki committee of the Soroka Medical Center approved the study and after complete description of the study to the subjects, all patients and controls signed their written informed consent to participate.

2.2. Questionnaires

All participants in both groups completed a questionnaire containing items on sociodemographic variables, disease characteristics, and symptoms possibly related to celiac disease.

2.3. Blood tests

Serum samples were drawn from all participants in both groups and compared for the presence of IgA anti-endomysial antibodies. The serology test was performed at the gastroenterology–biochemistry laboratory of the Soroka University Medical Center. Each serum sample was divided into two test tubes (7 ml each) to conduct reliability testing. In total, 200 sera were delivered to the laboratory within one hour after being drawn. The same technician conducted all blood tests. The technician was blinded to group affiliation at the time the tests were conducted.

Serum anti-endomysial IgA antibodies were assessed by indirect immunofluorescence, using a commercial kit (Imco Diagnostics, USA). Sections of smooth muscle from distal monkey esophagus were incubated with the subject’s sera, diluted 1:2.5 with phosphate-buffered saline. Samples were rinsed, incubated with fluorescein-labeled anti-human immuno-globulin conjugate and examined with a fluorescence microscope equipped with appropriate filters. Sera were considered positive if a brilliant green network of the endomyosal lining of smooth muscle bundles was observed and negative if it was not.

2.4. Statistical analyses

The data was entered into the Epi-Info software and data analysis was conducted with the SPSS software. Univariate analyses used $\chi^2$ and $t$-tests as appropriate. Statistical significance was set at $P < 0.05$.

3. Results

The study population consisted of 50 consecutive schizophrenia patients who attended the out-patient clinic of the Mental Health Center, and 50 mentally normal volunteers. Only one schizophrenia patient refused to participate in the study. No differences were found between the two study groups in terms of gender, body mass index (BMI), or country of birth (Table 1). However, the mean age of the study group was significantly higher than the control group. Table 1 also shows a comparison of the two groups for family medical history, symptoms and chronic co-morbidity. Eleven patients in the schizophrenia group (22%) reported abdominal pain compared to four patients (8%) in the control group ($P < 0.05$).

No serum sample in either group was positive for serum anti-endomysial IgA antibodies.
4. Discussion

The hypothesis of our study was that significantly more schizophrenia patients would have a positive serological test for celiac disease than control subjects. This was based on clinical observation and sporadic case reports [2–5,12,16], most from the World War II period when the phenomena was labeled “bread madness” [3,20].

Abnormal intestine permeability has been suggested as a possible etiology for chronic psychiatric disorders [25]. Furthermore, some evidence suggests that viruses and exogenous peptides, including gluten in cereal grains, may be a primary trigger for schizophrenia. Schizophrenia might result from impaired gene expression causing transport organ dysfunction, characterized by a basal laminar immunopathy at the tissue level, possibly driven by localized changes in prostaglandins. These pathophysiological changes could lead to dysfunctional neurotransmission in the periventricular limbic system [7,19].

There is some data to suggest that systemic illness or immune reaction may cause significant neuropsychiatric dysfunction. Tertiary syphilis is one historical example of a systemic illness that has profound neuropsychiatric effects. Although rare today, it was once common to see poor impulse control and paranoid behavior secondary to syphilis [18]. Certain autoimmune disorders such as multiple sclerosis, subacute sclerosing panencephalitis (SSPE) appearing months or years after a measles episode, and systemic lupus erythematosus (SLE), can also lead to central nervous system complications. As many as 12–27% of SLE patients with involvement of the central nervous system may develop episodes of psychosis that are indistinguishable from the acute signs and symptoms of schizophrenia [23]. Thus, when the brain is challenged by infectious agents or it’s own immune system, it may respond by producing neuropsychiatric symptoms similar to those seen in classic psychiatric disorders [18].

Chronic schizophrenia patients, including patients who never received medication for their illness, have a significantly higher frequency of antinuclear antibodies than control subjects [22]. Anti-nuclear antibodies are also found in systemic autoimmune disorders, but their role in the pathogenesis of autoimmunity against the targeted tissue is not always clear and many are considered to be non-specific [17]. Thus, it is unknown whether the autoantibodies findings in neuropsychiatric disorders such as schizophrenia have a pathophysiological significance or are merely epiphenomena.

The reported sensitivity for anti-endomysial IgA antibodies in adult patients with untreated celiac disease is 68–100% and in untreated children 85–100%. Its specificity may be as high as 99.7–100% [21,24]. Thus, it is regarded as the most reliable serological marker for this disease [15]. However, the definitive diagnosis is based on typical findings in intestinal biopsies.

In the present study the anti-endomysial screening test was used in 50 schizophrenia patients and 50 controls. All serological tests in both groups were negative. We believe that this result is noteworthy since the possible association between celiac disease and schizophrenia has not been studied in a controlled study before, or at least the results of such a study have not been published. Indeed, there is a well-recognized publication bias towards publishing primarily positive study results in the medical literature.

5. Conclusion

We conclude that there is no direct association between gluten sensitivity and schizophrenia disease as past observations may have suggested.

References