Iranian Red Crescent Medical Journal

SHORT COMMUNICATION

Autism and Celiac Disease: Failure to Validate the Hypothesis of a Possible Link

R Abolfazli[1]*, SA Mirbagheri[2], AA Zabihi[3], M Abouzari[4]

[1]Department of Neurology, [2]Gastroenterology Department, [3]Occupational Therapy, [4]General Practitioner, Amir-Alam Hospital, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Background: Autism is a heterogeneous condition and the possible pathogenic role of several different factors was postulated. Previous studies reported the existence of a linkage between autism and celiac disease (CD). The aim of this study was to determine the association between autism and CD by anti-gliadin (AGA), anti-endomysial (AEA) and tissue transglutaminase (tTG) antibodies.

Methods: Thirty four consecutive autistic children (18 boys and 16 girls) aging 9.2±4.1 years (range 4-16 years) and thirty four age- and sex- matched healthy anonymous blood donors (18 boys and 16 girls) aging 10.8±4.0 years (range 4-16 years) were included. None of the patients and controls had symptoms (or positive family history) suggestive of specific gastrointestinal diseases. AGA and AEA antibodies (IgG and IgA), and IgA-tTG were detected by ELISA. The individuals with positive serology were offered duodenal biopsies.

Results: IgG-AGA was found in 4 patients (11.8%) and 2 controls (5.9%), while IgA-AGA was found in none of the patients and controls. All patients presented normal values of IgG and IgA-AEA similar to the control group. There was no significant relationship between the levels of AGA and AEA antibodies and the severity of autism in the patient group. The levels of IgA-tTG in four patients (but no controls) were in the borderline range and two of them were found to have mild villous changes with chronic inflammatory cells. However, characteristic histological features of CD were absent.

Conclusions: No evidence was found that children with autism were more likely to have celiac disease than children without autism.

Keywords: Celiac disease; Autism; Anti-gliadin antibody; Anti-endomysial antibody; Tissue transglutaminase antibody

Introduction

Celiac disease (CD) is known to produce a variety of neurological and psychological complications in children. Association between celiac disease (CD) and neurological manifestations such as drug resistant epilepsy and cerebral calcifications is well known.[1] Some authors have also reported the existence of a linkage with autism.[2-4] Wakefield *et al.*[5] suggested an association between chronic inflammatory intestinal disease and autism in 1998. They described 12 children with autism and gastrointestinal symptoms, including diarrhea, pain, and food intolerance. Colonoscopy and biopsy showed ileal-lymphoid-nodular hyperplasia and non-specific colitis. The authors hypothesized that chronic intestinal disease and malabsorption may be causal factors in the development of autism. This has raised concerns about gastrointestinal disease as a risk factor for autism.

The aim of this study was to determine the association between autism and CD by anti-gliadin (AGA) and anti-endomysial (AEA). We also compared the seroprevalence of tissue transglutaminase antibody (tTG), a recently discovered serological marker of CD,[5-9] in a group of autistic children and an age- and sex- matched control group.

***Correspondence:** Roya Abolfazli, MD, Department of Neurology, Amir-Alam Hospital, Tehran University of Medical Sciences, Tehran, Iran. Tel: +98-21-66703819, Fax: +98-21-66704805, e-mail: abolfazl@sina.tums.ac.ir

Received: January 26, 2009 Accepted: April 12, 2009

Materials and Methods

In this case-control prospective study, we recruited 34 autistic children attending Neurology Clinic, Amir Alam Hospital, Tehran, Iran during 2005-2006. Thirty four consecutive autistic children (18 boys and 16 girls) aging 9.2±4.1 years (range 4-16 years) and thirty four age- and sex- matched healthy anonymous blood donors (18 boys and 16 girls) aging 10.8±4.0 years (range 4-16 years) were enrolled. None of the patients and controls had symptoms (or positive family history) suggestive of specific gastrointestinal diseases. AGA and AEA antibodies and IgA-tTG were detected by ELISA (Orgentec Diagnostika GmbH, Mainz, Germany) and the individuals with positive serology were offered duodenal biopsies. Written informed consent was obtained from the parents of all the participants and the Ethics Committee of Tehran University of Medical Sciences approved the study protocol.

The data were analyzed, using SPSS statistical package (version 15, Chicago, Illinois, USA). All the tests were two-sided, and $p<0.05$ was considered as statistically significant. Student's *t*-test and the Chi-Square test were performed to assess the relationship between the studied variables.

Results

IgG-AGA was found in 4 patients (11.8%) and 2 controls (5.9%, $p=0.690$), while IgA-AGA was found in none of the patients and controls. All the patients presented normal values of IgG and IgA-AEA similar to the controls. There was no significant relationship between the levels of AGA and AEA antibodies and the severity of autism in the patient group. The levels of IgA-tTG in four AGA seropositive patients (but no controls) were in the borderline range ($p=0.110$) and two of them were found to have mild villous changes with chronic inflammatory cells. However, characteristic histological features of CD were absent. There was also no significant association between the levels of IgA-tTG and the severity of autism in the patient group.

Discussion

In general, gastrointestinal disease can cause neurological dysfunction due to different mechanisms such as immunological abnormality related to the underlying disease, nutritional deficiency of substances, particularly vitamin B12, vitamin D, and vitamin E, reduced intake or malabsorption for a variety of causes, toxic metabolic agents, and genetic factors.[6] Celiac disease can be associated with a wide variety of central and peripheral nervous system disorders such as epilepsy, myoclonus, cerebellar ataxia, multifocal leukoencephalopathy, dementia and peripheral axonal and demyelinating neuropathies.[7-10] Previous studies have also shown the existence of a linkage between CD and autism.[2-4]

Furthermore, neurological involvement has been reported in CD with disappearance of symptoms for a gluten-free diet (GFT) in a proportion of early treated patients.[11,12] Patients with CD often show circulating antibodies to gliadin (AGA) or endomysium (AEA); the latter is more specific for mucosal damage with fewer neurological complications.[6] On the other hand, the absence of high levels of AEA antibodies in our patients supports the latter hypothesis.

Among autism patients, 11.8% and 5.9% of the controls had levels of IgG-AGA, while duodenal biopsies in both groups were not specific for CD and more than 10% of the normal cases were AGA positive, so it would appear that positive serology of this normal nature has a very low positive predictive value in CD.[13] Regarding AGA positivity (especially IgG) as so non-specific,[14,15] it requires further tests such as IgA-tTG. IgA-tTG has been recently identified as a specific autoantigen of CD and nowadays it represents the most reliable test for CD.[16] ELISA is a highly sensitive (86-100%) and specific (94-96%) method for detecting IgA-tTG in children.[6,9] On the other hand, IgA-tTG has been shown to have very high sensitivities (92-98%) and specificities (94-98%) for the diagnosis of CD.[10-12]

In a previous study,[1] AGA and AEA antibodies were assayed in 11 patients with infantile autism and 11 age- and sex-matched controls. No celiac case was detected among the group of autistic patients and, although two of them had slightly increased levels of IgG-AGA and AEA, subsequent antibodies determination and jejunal biopsies gave normal results. In another case control analysis matching age at index date, calendar time and general practice, Black *et al.*[17] found no increase in a history of chronic gastrointestinal inflammation, celiac disease, food intolerance, or recurrent gastrointestinal symptoms among children with autism compared with those without autism. Our results are consistent between CD and autism.[1,17]

The minimum prevalence of gluten sensitivity

among apparently healthy urban Iranian blood donors is 1/166.[18] Therefore, AGA and AEA levels in any autistic patient should be interpreted with caution. However, IgA-tTG was not helpful in this regard. We cannot exclude the possibility that CD may be associated with autism in certain individuals. Still, our results indicate that if this occurs, it is likely to be uncommon.

Therefore, we are far from strongly concluding the usefulness of serologic tests in determining the relationship between the two diseases. However, the statistical significance is still low and any negative conclusion should, therefore, be treated with caution. Studies with larger sample sizes are needed to confirm the results obtained in this study.

Acknowledgement

The authors would like to thank the Office of Vice Chancellor for Research of Tehran University of Medical Sciences for their support.

Conflict of interest: None declared.

References

1 Pavone L, Fiumara A, Bottaro G, Mazzone D, Coleman M. Autism and celiac disease: failure to validate the hypothesis that a link might exist. *Biol Psychiatry* 1997;**42**:72-5. [9193744] [doi:10.1016/S0006-3223(97)00267-9]

2 Ashkenazi A, Levin S, Krasilowsky D. Gluten and autism. *Lancet* 1980;**1**:157. [6101497] [doi:10.1016/S0140-6736(80)90643-1]

3 McCarthy DM, Coleman M. Response of intestinal mucosa to gluten challenge in autistic subjects. *Lancet* 1979;**2**:877-8. [90968] [doi:10.1016/S0140-6736(79)92688-6]

4 Walker-Smith J, Andrews J. Alpha-1-antitrypsin, autism, and coeliac disease. *Lancet* 1972;**2**:883-4. [4116595] [doi:10.1016/S0140-6736(72) 92258-1]

5 Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998;**351**:637-41. [9500320] [doi:10.1016/S0140-6736(97)11096-0]

6 Ghezzi A, Zaffaroni M. Neurological manifestations of gastrointestinal disorders, with particular reference to the differential diagnosis of multiple sclerosis. *Neurol Sci* 2001;**22**:S117-22. [11794474] [doi:10.1007/s100720100048]

7 Luostarinen L, Pirttilä T, Collin P. Celiac disease presenting with neurological disorders. *Eur Neurol* 1999;**42**:132-5. [10529537] [doi:10.1159/000008086]

8 Wills AJ. The neurology and neuropathology of coeliac disease. *Neuropat Appl Neurobiol* 2000;**26**:493-6. [11123714] [doi:10.1046/j.0305-1846.2000.00292.x]

9 Mäki M, Collin P. Coeliac disease. *Lancet* 1997;**349**:1755-9. [9193393] [doi:10.1016/S0140-6736(96)70237-4]

10 Ciclitira PJ, King AL, Fraser JS. AGA technical review on Celiac Sprue. American Gastroenterological Association. *Gastroenterology* 2001;**120**:1526-40. [11313324] [doi:10.1053/gast.2001.24056]

11 Hadjivassiliou M, Gibson A, Davies-Jones GA, Lobo AJ, Stephenson TJ, Milford-Ward A. Does cryptic gluten sensitivity play a part in neurological illness? *Lancet* 1996;**347**:369-71. [8598704] [doi:10.1016/S0140-6736(96)90540-1]

12 Volta U, De Giorgio R, Petrolini N, Stangbellini V, Barbara G, Granito A, De Ponti F, Corinaldesi R, Bianchi FB. Clinical findings and anti-neuronal antibodies in coeliac disease with neurological disorders. *Scand J Gastroenterol* 2002;**37**:1276-81. [12465725] [doi:10.1080/00365520276102054 2]

13 Hadjivassiliou M, Grünewald R, Sharrack B, Sanders D, Lobo A, Williamson C, Woodroofe N, Wood N, Davies-Jones A. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain* 2003;**126**:685-91. [12566288] [doi:10.1093/brain/awg050]

14 Salur L, Uibo O, Talvik I, Justus I, Metsküla K, Talvik T, Uibo R. The high frequency of coeliac disease among children with neurological disorders. *Eur J Neurol* 2000;**7**:707-11. [11136360] [doi:10.1046/j.1468-1331.2000.00130.x]

15 Cross AH, Golumbek PT. Neurologic manifestations of celiac disease: proven, or just a gut feeling? *Neurology* 2003;**60**:1566-8. [12771239]

16 Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, Schuppan D. Identification of tissue transglutaminase as the autoantigen of celiac disease. *Nat Med* 1997;**3**:797-801. [9212111] [doi:10.1038/nm0797-797]

17 Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. *BMJ* 2002;**325**:419-21. [12193358] [doi:10.1136/bmj.325.7361.419]

18 Shahbazkhani B, Malekzadeh R, Sotoudeh M, Moghadam KF, Farhadi M, Ansari R, Elahyfar A, Rostami K. High prevalence of coeliac disease in apparently healthy Iranian blood donors. *Eur J Gastroenterol Hepatol* 2003;**15**:475-8. [12702902] [doi:10.1097/00042737-200305000-00003]