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"An Assertion of the Association of Celiac Disease in Children with Autism"

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Abstract | **Original Research Article**

This cross sectional analytic study was conducted in the Centre for Neurodevelopment and Autism in children Bangabandhu Sheikh Mujib Medical University (BSMMU) from October 2011 to march 2012. The main objective of the study was to ascertain the association of celiac disease among children with autism. For the study purpose 50 autistic children were investigated to see the association with celiac disease. Fifty age sex matched children were also investigated as control. Children with autism in the "Centre for Neurodevelopment and Autism in Children, BSMMU were included in this study on the basis of following selection criteria: age 3- years to 10 years and fulfilling the definition of autism and whose clinical diagnosis was autism. Distribution of the autism child by age at diagnosis. Among the autism patiets 54.4% were diagnosed by age of five years, 39.2% were diagnosed between 5 – 10 years and 6.4% were diagnosed after reaching 10 years. Distribution of the subjects by birth order. In the healthy group 60% were the first child and in autism group 71.1% were 1st child. In healthy group 3(6.7%) sample developed meningitis in their early life and among the cases 11(24.4%) developed meningitis in their early life. Positive family story of autism was found in 6% and 2% in case and control group respectively. Diarrhea and constipation were not found statistically significant ($p>0.05$) between two groups, whereas nausea/vomiting and pallor were found statistically significant ($p<0.05$) between two groups in chi square test. Celiac disease affects individuals of all ages and is characterized by permanent gluten intolerance. It has been associated with neurological and psychiatric diseases. Diagnosis of celiac disease is increasing day by day because of more research and more focus on investigation.

Key Words: Neurodevelopment, Autism, Celiac Disease (CD), Diarrhea, Constipation, Neurological.

INTRODUCTION

Celiac disease is an immune-mediated malabsorption syndrome triggered by gluten-containing grains (wheat, rye, barley, and oats). Patients with this condition present with gastrointestinal symptoms including diarrhea, bloating, fatigue, weight loss, and nutrient deficiencies, but there is increasing evidence that celiac disease can present with a variety of clinical symptoms that are not apparently gastrointestinal in nature. Serological diagnosis is made with antiendomysial antibodies and anti-tissue transglutaminase antibodies which have a high specificity and sensitivity for celiac disease [1]. A definitive diagnosis can be made by tissue biopsy of the intestinal tract. The symptoms are generally ameliorated with avoidance of triggers that contain gluten. In a seminar paper published in 1943 titled "Autistic Disturbances of Affective Contact," Leo Kanner first described a series of children with the neuropsychiatric condition currently known as autism [2]. According to the latest revision of the Diagnostic and Statistical Manual of Mental Disorders [3], autism is a disorder of impaired social interaction and communication, limited activities and interests, as well as stereotyped behaviors-difficulties that are usually evident by 30months of age. Concomitant with isolative behavior, children with autistic disorders frequently manifest significant aggression, tendencies toward self-injury and self-harm irritability, as well as hyperactive and erratic behavior. Diagnosis is made using a number of different measures and screening tools, many based on observation by a team of professionals. The prognosis is generally unfavorable with chronic impairment for the effected individuals and a sustained impact on loved ones and caregivers. Population-based studies in America and United Kingdom have demonstrated that the prevalence of autism is increasing significantly and that these disorders had become a serious public health issue [4]. From an insurance of as low as 1: 2500 in the mid-1980s, the reported rate of autism rose to about 1:300 in 1996 and has continued the climb to an

unprecedented rate of 1:150 in 2002 (Centers for disease control and prevention [5]. The increasing incidence and prevalence of this condition has generally been thought to result from expanding definitions of autism, as well as earlier diagnosis and increased inclination for parents of disabled children to seek care [6]. Recent studies, however, have demonstrated that only a small portion of increased autism rates can be accounted for by these factors [7]. The authors of these recent reports speculate that changes in the environment might be a significant determinant of autistic spectrum disorder. Ongoing research is investigating many possible determinants including genetic influences, pre and post-natal development, environmental factors, nutritional compromise, and immune deficiencies [8]. The association between celiac disease and central nervous system dysfunction has been known for several decades [9] especially in relation to neuropathy, ataxia, migraine, and epilepsy [10]. In fact, May new cases of celiac disease are detected following an initial presentation of neurological complaints [11]. A recent clinical case report discusses in the journal of internal medicine, for example, confirms that signs and symptoms of schizophrenia may be a presentation of celiac disease a clinical problem that may resolve after institution of a gluten free diet [12]. A pediatric case study suggesting a direct link between celiac disease and symptoms characteristic of autistic disorder is presented here for consideration. Autism is a heterogeneous condition and the possible pathogenic role of several different factors was postulated. Previous studies reported the existence of linkage between autism and celiac disease (CD). Abolfazli *et al*. [13] have done a study to determine the association between autism and CD by anti-gliadin (AGA), anti-endomysial (AEA) and tissue transglutaminase (tTG) antibodies, thirty-four consecutive autistic children (18 boys and 16 girls) again 9.2±4.1. 1 years (range 4-16 years) and thirty age- and sex- matched health anonymous blood donors (18 boys and 16 girls) again 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 (lgG and lgA), and lgA-tTg were detected by ELISA. The individuals with positive serology were offered duodenal biopsies. lgG-AGA was found in 4 patients (11.8%) and 2 controls (5.9%), while lgA-AGA was found in none of the patients and controls. All patients presented normal values of lgG and lgA-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 lgA-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 if CD were absent. No evidence was found that children with autism were more likely to have celiac disease than children without autism. Genuis *et al*. [14] reported in their study that Gluten-restricted diets have become increasingly popular among parents seeking treatment for children diagnosed with autism. Some of the recorded response to celiac diet in children with autism may be related to amelioration of nutritional deficiency resulting from undiagnosed gluten sensitivity and consequent malabsorption. A 5-years old boy diagnosed with severe autism at a specialty clinic for autistic spectrum disorders was reviewed by genuis *et al*. [14]. Initial investigations suggested underlying celiac disease and varied nutrient deficiencies, a gluten-free diet was instituted along with dietary and supplemental measures to secure nutritional sufficiency. The patient's gastrointestinal symptoms rapidly resolved, and signs and symptoms suggestive of autism progressively abated. Tis case in an example of a common malabsorption syndrome associated with central nervous system dysfunction and suggest that in some contexts, nutritional deficiency may be a determinant of developmental delay. It is recommended that all children with neurodevelopmental problems be assessed for nutritional deficiency and malabsorption syndromes.

OBJECTIVES

a) General objective

1. To ascertain the association of celiac disease among children with autism in Bangladesh

b) Specific Objectives

1. To determine the association between autism and CD by tTG (tissue transglutaminase-antibody)
2. To observe the sign symptoms of CD on the children with autism.

METHODOLOGY AND MATERIALS

Children having autism from 3years to 10 years of age attending the Paediatric Neurology OPD were enrolled in this study. Estimated sample size is 384, but due to limitation resources and time constraint, only for the study purpose first 50 patients attending the outpatient department were included in this study and 50 children with age and sex matched normal children were considered as control. Data entered into SPSS software and measure p-value.

1. Inclusion Criteria

1. Children with autism diagnosed by DSM-IV-TR and ICD-10.
2. Age between 3 years to 10 years.

2. Exclusion Criteria

1. Sick children associated with severe medical problem and not willingly to participate in this study were excluded.

RESULTS

A total 100 patients were included in this study. Figure I: shows the distribution of the autism child by age at diagnosis. Among the autism patients 54.4% were diagnosed by age of five years, 39.2% were diagnosed between 5 – 10 years and 6.4% were diagnosed after reaching 10 years. (Table I) shows the distribution of the subjects by birth order. In the healthy group 60% were the first child and in autism group 71.1% were 1st child. No statistically significant difference was found in birth order in two groups (P>.05). (Table II) shows the family history of the studied patients. The difference was not statistically significant (p>0.05) between two groups in chi square test. (Table III) shows in healthy group 5(6.7%) sample developed meningitis in their early life and among the cases 13(24.4%) developed meningitis in their early life. There was a significant association between meningitis and autism (P=0.036). (Table VII) shows the presenting complaints of the studied patients. Nausea/ Vomiting and pallor were statistically significant (p<0.05) but diarrhea and constipation were not statistically significant (p>0.05) between two groups in chi square test.

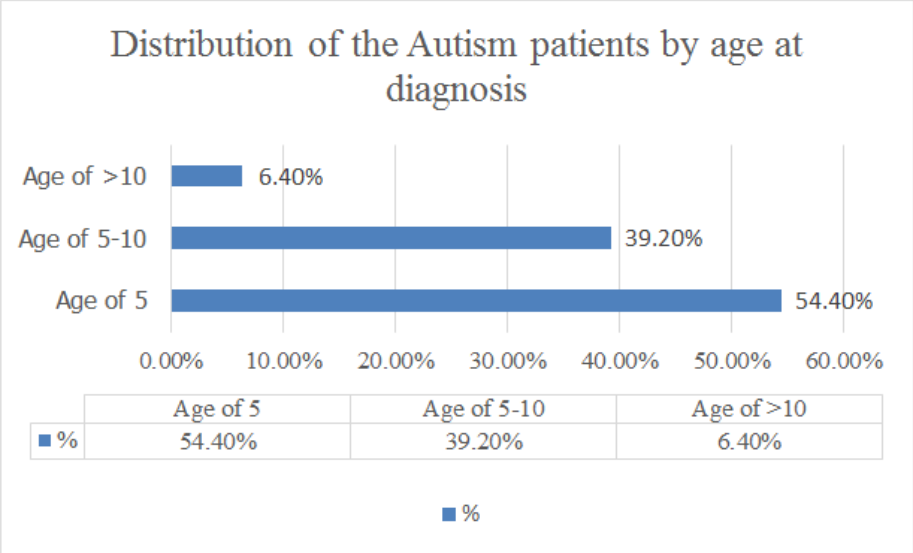

Fig-I: Distribution of the Autism patients by age at diagnosis (n=100)

Table-I: Distribution of the autism patients according to birth order (n=100)

Birth order	Healthy (n=50)	Percentage (%)	Autism (n=50)	Percentage (%)	Total
1st	27	60.0	32	71.1	59(65.6)
2nd	18	33.3	10	22.2	25(27.8)
3rd	5	6.7	8	6.7	6(6.7)
Total	50	100.0	50	100.0	90(100.0)

No statistically significant difference was found in birth order in two groups (P>.05).

Table-II: Distribution of the studied patients according to family history of Autism (n=100).

tTG level	Case (n=50)	Percentage (%)	Control (n=50)	Percentage (%)	P value
Positive	3	6.0	0	0.0	0.121^{ns}
Negative	47	94.0	50	100.0	

Ns= not significant, P value reached from unpaired t-test

Table-III: Distribution of the autism studied patients according to meningitis in their early life (n=100)

Meningitis	Healthy (n=50)	Percentage (%)	Autism (n=50)	Percentage (%)	Total
Present	5	6.7	12	22.2	13(24.4)
Absent	45	93.3	38	77.8	77(85.6)
Total	50	100.0	50	100.0	90(100.0)

There was a significant association between meningitis and autism (P=0.036).

Table- IV: Distribution of the studied patients according to presenting complaints (n=100).

Complaints	Case (n=50)	%	Control (n=50)	%	P value
Diarrhea					
Yes	13	26.0	11	22.0	0.639^{ns}
No	37	74.0	39	78.0	
Constipation					
Yes	20	40.0	23	46.0	0.544^{ns}
No	30	60.0	27	54.0	
Nausea/Vomiting					
Yes	0	0.0	15	30.0	0.001^{s}
No	50	100.0	35	70.0	
Pallor					
Yes	12	24.0	25	50.0	0.007^{s}
No	38	76.0	25	50.0	

S= significant, Ns= not significant, P value reached from unpaired t-test

DISCUSSION

Celiac disease (CD) has been associated with neurologic and psychiatric disorders including cerebellar ataxia, peripheral neuropathy, epilepsy, dementia, and depression. Earlier reports mainly have documented the involvement of the nervous system as a complication of pre-diagnosed CD. Clinicians are increasingly utilized noninvasive serologic test for the diagnosis and screening if celiac disease (CD). Regarding the tTg status it was observed in this current study that 94.0% patients were negative and 6.0% positive in case group. In control group all of the studied patients were negative in case group. In control group all the studied patients were negative for tTG. No statistically significant (P>0.05) difference was found between the two groups. The distribution of the autism child by age at diagnosis. Among the autism patients 54.4% were diagnosed by age of five years, 39.2% were diagnosed between 5 – 10 years and 6.4% were diagnosed after reaching 10 years. The distribution of the subjects by birth order. In the healthy group 60% were the first child and in autism group 71.1% were 1st child. No statistically significant difference was found in birth order in two groups (P>.05). In one study, Luostarinen *et al.* [11] showed 7.0% celiac disease (CD) patients presented with autism. In patients having autism tTG status was found to be 16.0% in the study [15], 16.7% in the study of wills *et al.* 12.5% in the study of pellecchia *et al*. [16] and 1.9% in study of Burk *et al*. [17], Vivas *et al.* [18] and hill *et al.* [19] reported in their respected studies that duodenal biopsy my not always necessary for the diagnosis of CD in children with autism. In this present series it was observed that positive family history of autism was found 6.0% and 2.0% in case and control group respectively, which is not statistically significant (P>0.05). In this study nausea/vomiting pallor were significantly (P<0.05) higher in control group but diarrhea and constipation were almost similar in both groups. Alanay *et al.* [20] found diarrhea in 23.0%, constipation in 29.0% and vomiting in 7.0% cases, which support the current study findings. Shamaly *et al.* [6] showed 13.8% had pallor, 11.9% had diarrhea, 1.6% had vomiting and 25.8% and constipation. Nisihara *et al.* found 2.8% had diarrhea and 17.4% had pallor, which support the current study findings. Plauche *et al.* and irva *et al.* found almost similar clinical features in their studies which support the current study findings.

LIMITATIONS OF THE STUDY

Small sample size was also a limitation of the present study. Although small intestinal biopsy is the gold standard for the diagnosis if celiac disease but due to technical limitation it was not possible in this present situation.

CONCLUSION AND RECOMMENDATIONS

Six percent of the studied Bangladeshi children were suspected to have CD who presented with autism. It is important to test children to text children with autism for celiac disease by measuring serum tTG level. So by the present study it can be recommended that tTG can be a useful screening test for autistic patients with GI symptoms. Larger studies involving large sample size is need to find out the exact prevalence of celiac disease in autism.

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