

Assessing the prevalence of coeliac disease in patients with intellectual disabilities

Abstract

Previous studies have suggested a high prevalence of coeliac disease in patients with intellectual disabilities (Nisihara, 2005; Shamaly, 2007). To further explore any possible relationship, 196 patients with intellectual disabilities were identified in rehabilitation centres in the province of East Azerbaijan in Iran. They were matched with 196 healthy controls and screened for coeliac disease. Anti-tissue transglutaminase IgA antibodies (tTGA) and total serum IgA levels were measured, and the Marsh-Rostami criteria used to evaluate histological findings. Two patients (1%) were positive for tTG and duodenal biopsies showed Marsh I in one patient and Marsh 0 in the other. IgA deficiency was detected in three patients in the study group and tTGA was positive in one individual. Biopsies from this patient showed Marsh IIIc. From the control group only one individual had positive tTGA and five cases were IgA deficient. Two of these patients had positive tTG but both had normal histology. Coeliac disease was not found to be more prevalent in patients with intellectual disorders which suggests that screening for coeliac disease in these patients would not be cost effective.

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Coeliac disease is a multisystem autoimmune disorder predominantly associated with 'atypical' and vague symptoms such as fatigue and extraintestinal symptoms (Pellecchia et al, 1999; Rostami et al, 2001). Neurological presentations such as epilepsy, cerebellar ataxia, dementia, neuropathies and depression, have all been reported in adults with coeliac disease and literature suggests that coeliac disease may present with atypical and neurological disorders (Gobbi et al, 1992; Kelkar et al, 1996; Pellecchia et al, 1999; Bürk et al, 2001).

In 1975, Bentley first reported an association between coeliac disease and Down's syndrome. Several reports in the following years confirmed an increased frequency of coeliac disease in patients with Down's syndrome compared to healthy controls in different populations. These studies suggested a prevalence of coeliac disease in patients with Down's syndrome ranging from 3.2–10.3% (Failla et al, 1996; Hansson et al, 1999; Csizmadia et al, 2000; Book et al, 2001; Rumbo et al, 2002; Kolek et al, 2003; Tesei et al, 2003; Nisihara et al, 2005; Shamaly et al, 2007). The mechanisms underlying this association remain uncertain but Down's syndrome is also associated with other autoimmune diseases, including type 1

diabetes and thyroid disease (Zori et al, 1990; Kaukinen et al, 1999), suggesting that Down's syndrome is associated with impaired immune system function.

There are many reports and evidence supporting an association between neuro-psychiatric conditions and gastrointestinal disorders. For example, White (2003) suggested that children with autism are at an increased risk of food allergy and intolerance than healthy controls. However, patients with intellectual disabilities are often unable to verbalize symptoms and therefore identifying occult illnesses in this group of patients is a challenging practice. This study was therefore undertaken to explore any possible relationship between coeliac disease and intellectual disability, in order to identify the potential to improve quality of life in these patients through a gluten-free diet.

Methods

Participants

The study population consisted of all patients diagnosed with intellectual disabilities from rehabilitation centres, matched to a control group of healthy subjects without intellectual disabilities, neurological disorders, autoimmune

or other coeliac disease-related conditions with respect to demographic feature including sex, age and birthplace.

In this study, 196 patients with intellectual disabilities were identified and recruited. The presence of any intellectual disabilities was the sole selection criteria. The median age of the patients recruited was 32.7 years (range 5–86 years). Sixty-nine per cent of patients were female (median age 27 years, range 5–67 years) and 31% patients were male (median age 37 years, range 16–86 years). More than half (54.5%) of the participants lived in rehabilitation centres with the remainder living with their families. Intellectual disabilities were diagnosed at birth in 80% of the individuals in the study group. However, the authors do not have accurate information regarding the specific aetiologies of the intellectual disabilities, which is a limitation of this study.

In addition, 196 healthy participants with a mean age of 33 years (range 15–81 years) were selected as controls, matched for age and birthplace. The patients and control subjects were interviewed by a physician regarding any history of symptoms or signs compatible with coeliac disease, and a questionnaire completed. The study population was interviewed by the same physician. In most of the cases, carers were involved in filling the questionnaires.

Both groups were recruited from the native population of Tabriz, in the province of East Azerbaijan in Iran. Informed consent was obtained from patients and/or next of kin and the control group were chosen from healthy blood donors referred to the blood transmission center. The study was approved by the ethics committee at the Liver and Gastrointestinal Diseases Research Center, Emam Reza Educational Hospital, Tabriz, Iran.

Serological testing

Patients with coeliac disease may be recognized through non-invasive, sensitive and specific serological tests. After obtaining informed consent, 5 ml of fasting blood were collected. Samples were centrifuged, serum was separated and divided into two aliquots and immediately stored at -20° Celsius. Serological screening for coeliac disease based on anti-tissue transglutaminase IgA antibodies (tTGA) was performed in the group with intellectual disabilities (consisting of

61 males and 135 females) and in the control group (also consisting of 61 males and 135 females), with a median age 32.33 years (range 4–77 years, $P>0.1$).

Anti-endomysium (EMA) and tTG antibodies have a sensitivity of 99–100% in patients with severe small bowel problems like total villous atrophy, and are less sensitive with milder mucosal damages like partial villous atrophy. The specificity of these tests are very high, at around 98–100% (Rostami and Villanacci, 2009).

tTGA were determined by enzyme-linked immunosorbent assay (ELISA) with human recombinant tTGA as antigen, using a commercial kit (Eu-tTG IgA, Eurospital S.p.A, Trieste, Italy). Results were considered positive when higher than 7 arbitrary units (AU/mL). Total serum IgA levels were determined by immunoturbidimetric assay and IgA deficiency were considered positive when less than 70 ng/dL (Rostami Nejad et al, 2009). The tTGA positive and IgA deficient subjects were submitted to upper gastrointestinal endoscopy. The biopsy samples, taking from distal duodenum, were evaluated by a pathologist who was unaware of the tTGA test results or group assignment.

The diagnosis of coeliac disease was based on the characteristic histological finding of increased intra-epithelial lymphocytes (Marsh I), crypt hyperplasia (Marsh II) and villous atrophy (Marsh III), classified according to the standard classification proposed by Marsh (1990; 1992) and modified by Rostami et al (1999). The modified Rostami criteria classify mild villous atrophy and pathological increase of intraepithelial lymphocytes (Marsh IIIa), moderate villous atrophy and pathological increase of intraepithelial lymphocytes (Marsh IIIb) and total villous atrophy and pathological increase of intraepithelial lymphocytes (Marsh IIIc).

The Statistical Package for Social Science (SPSS) version 11.5 was used for the statistical analysis. The chi-square and *t*-test were used for comparison. *P* values were considered statistically significant when they were lower than 0.05.

Results

Among the participants with intellectual disabilities, two patients (1%), one male and one female (aged 19 and 47 years respectively) were positive for tTGA. In the control group, one of the 196

individuals (0.5%) was positive for tTGA. There was no significant difference in proportion of tTGA positive cases between the patients with intellectual disabilities and control subjects.

Three individuals in the study group (1.5%) and five individuals in the control group (2.55%) were IgA deficient. IgG tTG antibody was positive in one of the three patients with intellectual disabilities and two of the five healthy controls. There was no significant difference in proportion of IgA deficient cases between study and healthy control subjects. The characteristics of the tTGA-positive participants compared with the tTGA-negative patients in the intellectual

disabilities study group are considered in *Table 1*. There was no significant difference in age, gender, IQ, medication use, setting of ongoing care, schizophrenia, Down's syndrome, autism, problems at birth or familial history of intellectual disabilities between tTGA-positive participants and tTGA-negative participants in the intellectual disabilities study group.

All of the tTGA positives (two patients in the intellectual disabilities study group and one in the control group) and IgA deficient patients with IgG tTG positive (one patient in the study group and two in the control group) underwent duodenal biopsy. One of the two tTGA positive participants in the intellectual disabilities study group had Marsh I and other case was Marsh 0 in histology. However, duodenal histology showed Marsh IIIc in one of the IgA deficient patients with intellectual disabilities (*Table 2*). None of the tTGA positives or IgA deficient subjects in the control group had abnormal histology. Therefore, coeliac disease was confirmed by biopsy and serology in 1% of individuals with intellectual disabilities.

Table 1. Characteristics of tTGA positives compared with tTGA negatives in the study group

Characteristics	tTGA positives n (%)	tTGA negatives n (%)	P value
Sex (female/male)	1(50)/1(50)	134(69)/60(31)	0.788
IQ ranges			
0-20	0	17 (9)	0.547
20-34	2 (100)	83 (43)	
35-49	0	59 (30)	
50-70	0	35 (18)	
Taking drug (anti-depressants and anti-anxiety medications)	1 (50)	116 (60)	0.499
Receiving care at rehabilitation centres	0	107 (55)	0.260
Living with family	2 (100)	87 (45)	
Problems at birth	1 (50)	27 (14)	0.001
History of familial intellectual disability	0	34 (17)	0.525
tTGA=tissue transglutaminase antibodies			

Table 2. Results of serological tests (tTGA and IgA) and histological aspects in cases with intellectual disabilities who underwent duodenal mucosal biopsy

Patients	Sex	Age	tTG	IgA deficiency	Histological aspects
1	Male	53	Positive	Negative	Marsh I
2	Female	23	Positive	Negative	Normal
3	Female	16	Negative	Positive	Marsh IIIc
IgA=immunoglobulin A; tTGA=tissue transglutaminase antibodies					

Discussion

The prevalence of coeliac disease in most European countries is around 1:100 (Jansson and Johansson, 1995; George et al, 1996). The clinical presentation of coeliac disease is highly variable, ranging from asymptomatic to severe malnutrition. In the atypical forms of coeliac disease which are being increasingly recognized, gastrointestinal symptoms may be absent or less pronounced, while patients present with extra-intestinal features such as depression, cognitive impairment, ataxia, and infertility (Emami et al, 2008). The positive predictive value of serology (tTGA) is low in the general population as it is less associated with abnormal histology and malabsorption syndrome compared to those in high-risk group. The high-risk group includes those with a first-degree relative with coeliac disease, those with type 1 diabetes mellitus, autoimmune diseases, autoimmune thyroiditis, IgA deficiency, Down's syndrome, unexplained osteoporosis, and cryptogenic hypertransaminasemia.

The prevalence of coeliac disease in the cohort with intellectual disabilities did not exceed the frequency of this disorder in the general population (1%). In contrast to the findings in

this study, intellectual disability associated with various neuropsychiatric disorders, including Down's syndrome, neuropathy, ataxia, chorea and epilepsy, has been highlighted in patients with coeliac disease. The mechanism of neuronal damage in patients with Down's syndrome and other gluten-sensitivity associated disorders is most likely to be immunological or related to trace vitamin deficiency (Collin et al, 1991; Cronin et al, 1998; Chin et al, 2003; Pereira et al, 2004).

Previous studies on intellectual disability (Gobbi et al, 1992; Zachor et al, 2000; Book et al, 2001) have reported an increased prevalence of coeliac disease among patients with epilepsy and Down's syndrome. Similarly a study in Brazil on 71 patients showed a prevalence of 5.6% (4/71) confirmed cases of coeliac disease among the investigated Down's syndrome patients (Nisihara et al, 2005). However, there are limited studies exploring gluten sensitivity in those patients with intellectual disabilities without Down's syndrome and epilepsy. The question is whether patients with intellectual disabilities without Down's syndrome are also at high risk for gluten sensitivity. In a recent study the biopsy proven prevalence of coeliac disease in Iranian epileptic patients was 2.7% (Emami et al, 2008) and this prevalence was 2 times higher than coeliac disease in general population. It is not clear whether accumulative effects of nutritional, immunologic, or inflammatory factors might play some role on learning abilities or attention span in patients with Down's syndrome.

Nevertheless, none of the tTGA positive cases in this study reported a history of autism, Down's syndrome, schizophrenia, chronic diarrhoea, anaemia, liver disease, dermatitis, autoimmune disease or thyroid disease. On the other hand a weakness of this study is the fact that there is limited information about the aetiology of intellectual disabilities in this study group. So far, according to this study and limited data on non-epileptic and intellectual disability without Down's syndrome, gluten sensitivity does not seem to be a threat for intellectual disabilities with other aetiologies.

Conclusions

In contrast to the usual male preponderance of gluten sensitivity in patients affected with

intellectual disabilities, male and female patients in this study were almost evenly affected. The frequency of coeliac disease was 1% with biopsy confirmation in patients with intellectual disabilities and therefore there were no significant differences in frequency of the tTGA positive participants between the study and control groups. This study provides evidence for non-existence of any association between coeliac disease and intellectual disability. Based on these findings there is no basis to recommend the routine screening of people with intellectual disabilities unless the patients have symptoms or known risk factors for coeliac disease such as epilepsy or Down's syndrome. ■

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