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ORIGINAL ARTICLE

ANTITHYROID PEROXIDASE ANTIBODY AND EXTRACTABLE NUCLEAR ANTIGEN ANTIBODY IN CELIAC DISEASE-A PRELIMINARY COMMUNICATION

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Key words:

CD –Celiac disease,
Ttg –Transglutaminase,
TPO –Thyroid Peroxidase,
ANA –Antinuclear antibodies,
ELISA –Enzyme linked immunosorbent assay,
ENA –Extractable nuclear antigen,
TIDM –Type 1 diabetes mellitus,
SmAb –Anti smith antibody,
SLE –Systemic Lupus erythematosus,
IgA – Immunoglobulin A.

ABSTRACT

Celiac disease is very common in our place. Aim was to find out prevalence of various autoantibodies in CD.

Material and method: Total 22 cases of celiac disease along with 50 healthy cases were studied within a period of 6 months. Anti tissue transglutaminase (Ttg), anti thyroid peroxidase (TPO), Anti nuclear antibodies (ANA) were done by ELISA method, while antibody to extractable nuclear antigen (ENA), (Sm,RNP,SSA,SSB,Scl70,Jo-1,centromere) and antigliadin antibody were done by dot blot method.

Result: Males (59.09%) were more affected than females (40.92%).In males disease was mostly seen between 1.5 to 15 years (76.92%) while in females disease was found in 15 to 30 years (77.77%). Chronic diarrhoea was the most common manifestation (68.18%), followed by failure to thrive (31.81%), pain in abdomen, nausea vomiting (22.72%),fullness of abdomen, belching (18.18%)and loss of appetite (13.63%). One case was associated with Type 1 Diabetes mellitus (TIDM) while in 3 cases patient had Type 2 Diabetes mellitus. About 11 cases (50%) had some kind of autoantibodies. Commonest was anti TPO antibodies detected in 27.27% cases followed by ANA and centromere Ab (9.09%), anti smith (Sm) Ab and anti scleroderma 70 and anti Jo-1 antibody (4.54%) each. Clinically only 3 patients had symptoms of hypothyroid. None of the patient positive for anti centromere antibody had feature of scleroderma. One patient positive for both anti Jo-1 and Scl 70 had muscle weakness. Two patients were positive for ANA out of which one was positive for anti Sm Ab also but clinically no evidence of SLE was present. Antigliadin Ab detected by dot blot method in 68.18% cases. Thus our study concludes that celiac disease in 50%cases is associated with some kind of antibodies of hypothyroidism, scleroderma, SLE or polymyositis, but clinically hypothyroidism is more common.

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INTRODUCTION

Celiac disease is immune mediated enteropathy triggered by the ingestion of gluten containing grains eg wheat, rye and barley (Turner, 2014). It is common in western population and its prevalence is around 1% (Kolho *et al*., 1998; West *et al*., 2003; Tommasini *et al*., 2004). Histopathology of second part of duodenum shows inflammation, crypt hyperplasia, villous atrophy, intraepithelial CD8 T Lymphocyte, increased plasma cells and eosinophils in upper part of lamina propria (Turner, 2014) . It is seen in genetically susceptible persons specially those who have HLA DQ2and DQ8 (Nishihara *et al*., 2011).

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Association of CD with organ specific autoimmune diseases like Hashimoto's thyroiditis, type 1 diabetes mellitus (TIDM), dermatitis herpetiformis, Addison's disease, autoimmune hepatitis and primary biliary cirrhosis have been described (Kotz, 2005). Association with connective tissue diseases e.g. Sjogren's syndrome, polymyositis and scleroderma have also been found (Kotz *et al*., 2005; Iltanen *et al*., 1999; Rosato *et al*., 2009) Celiac disease is common in our area. Aim of present study was to find out prevalence of autoimmune disease and autoantibodies in patients of CD.

MATERIALS AND METHODS

Total 22 Cases of celiac disease and 50 healthy controls were taken from outpatient Department of Endocrinology and, Pediatric.

Table 1. Age wise distribution of patients of CD

Age in years	Males		Females		Total	
	no	(%)	no	(%)	no	(%)
Less than 1.5	2	15.38%	0	0%	2	9.09%
1.5-5	3	23.07%	0	0%	3	13.63%
5.1-15	2	15.38%	1	11.11%	3	13.63%
15.1-30	3	7.69%	6	66.66%	9	31.81%
30.1-70	3	38.46%	2	22.22%	5	31.81%
Total 22	13	59.09%	9	40.90%	22	

Table 2. Clinical manifestation of celiac disease

Clinical features	No of cases	Percentage (%)
Diarrhoea	15	68.18%
Pain in abdomen	5	22.72%
Failure to thrive	7	31.81%
Nausea and vomiting	5	22.72%
weakness	4	18.18%
Loss of appetite	3	13.63%
Unable to gain weight	2	9.09%
pallor	1	4.5%
Belching, fullness of abdomen, dyspepsia	4	18.18 %
Hepatomegaly	1	4.5%
Stone in urinary bladder	1	4.5%
pain in calf muscle	1	4.5%
Swelling of left side of body and loss of sensation	1	4.5%
Cough and breathlessness	1	4.5%
Type 2 DM	3	13.5%
TYPE 1 DM	1	4.5%
Family history positive	1	4.5%
Hypothyroid	3	13.5%
Intolerance to milk chicken and egg	1	4.5%

Table 3. Autoantibodies in celiac disease

Auto antibodies	Present		Absent	
	no	%	no	%
Antithyroid peroxidase antibodies	6	27.27%	16	72.72%
Antinuclear antibodies	2	9.09%	20	90.90%
Anti Sm antibody	1	4.54%	21	95.45%
Anti scleroderma Ab and Anti Jo-1 antibody	1	4.54%	21	95.45%
Anti centromere Ab	2	9.09%	20	90.90%
Anti Ttg Ab	22	100%	0	0.0%
Antiglidin Ab	15	68.18%	7	31.81%

Clinical details of each case were recorded by clinicians. Diagnosis of celiac disease was made by anti TTG antibody and or duodenal biopsy along with clinical features. About 5ml of blood was taken in plain vial for serological study and 2ml was taken in EDTA tube for HLA typing. Antinuclear antibody (ANA), antithyroid peroxidase antibody (anti TPO) were done by ELISA kit of Eurodiagnostica. This kit was supplied by M/S OSB agency, Geeta colony, New Delhi. Antibody to gliadin and extractable nuclear antigen (ENA), (anti SSA, anti SSB, anti centromere, anti Sm, anti scleroderma 70, anti Jo- 1 antibodies were done by dot blot kit of D Tek company supplied by M/S Anand brother,Anand house 5,local shoping center, Karampura. Anti Ttg antibody was done by ELISA kit of AESKU cosupplied by M/S Immunoshop India Pvt Ltd, 309, Raheja arcade, sector 11 CBD Birlapur, Navi Mumbai. ANA ratio above 1.2, anti Ttg above 18 IU/ml, anti TPO antibody above 110 U/ml was taken as positive. In dot blot test if colour of test dot was more than colour of negative control dot then it was taken as positive.

RESULTS

Out of 22 cases, 59.09% were males and 40.9% were females. About 36.35% patients were children below 15 years in which 22.72 % were below 5 years and 9% were below 1.5 years of age also. In males disease was more common in children (53.83%) whereas in females majority cases were seen between 15-30 years (66.66%). (Table 1) Most common clinical manifestation were diarrhoea (68.18%) followed by inability to gain weight and height (31.81%), pain in abdomen ,nausea and vomiting (22.72%),weakness, fullness of abdomen, dyspepsia and loss of apetite (18.18%). In one case CD was associated with type 1 diabetes mellitus, in 3 cases (13.5%) it was associated with type 2 diabetes mellitus and in another 3 cases it was associated with autoimmune hypothyroidism. One case had positive family history of CD in cousin. One patient had swelling of left side of body and loss of sensation. One had severe pain in calf muscle. One patient had breathlessness. (Table 2) We tested 2 antibodies for diagnosis of CD. We took only those cases where anti Ttg antibodies were positive. Antigliadin antibody had low sensitivity of 68.18%.Antinuclear antibody, anti thyroid peroxidase antibody (TPO) and antibodies to extractable nuclear antigen (ENA) were done in all patients. About 50% cases (11cases) had some kind of antibodies alone or in combination. (Table 3) Anti TPO Ab was most frequent autoantibody detected in 6 cases (27.27%) and 50% of anti TPO positive cases were males of 1.5,16 and 62 years. Three female patients positive for anti TPO antibodies were of 25, 26 and 64 years old. Clinically hypothyroidism was seen in 3 cases (13.63%). Two cases were positive for anticentromere antibody. Here also males (62years) and females (14years) were equally affected. One 64 year

female patient was positive for both anti scleroderma 70 antibody and anti Jo-1 antibody. Both ANA positive patients were female.

DISCUSSION OF CELIAC DISEASE

CD is frequently diagnosed in children than in adults (Sachdev 2011). In our series 53.83% patients were children and rest were adults. CD manifest mostly with malabsorption syndrome, diarrhoea, weight loss and nutritional deficiencies (Barton and Hand Murray, 2008). Besides this, patient may also manifest as headache, fatigue, arthralgia, inflammatory bowel disease like symptoms. Sometimes presentation may be extra intestinal like anemia, osteoporosis, unexplained neurological syndromes, infertility and, dermatitis herpetiformis, autoimmune diseases and cancer (Turner, 2014; Barton and Hand Murray, 2008; Ching *et al*., 2007). In present series dominant symptom were of gut in the form of diarrhoea (68.1%), pain in abdomen (22.7%), weight loss (22.72%), weakness, dyspepsia (18.68%).Second important manifestation was failure of growth (31.8%).Failure to thrive have also been reported by several workers (Sachdev, 2011; Sachdev *et al*., 2002; Yachha and Poddar, 2007). One of our patient presented with sciatica like pain in left lower limb and severe pain in calf muscle accompanied by loss of sensation. Neurological symptoms are also reported by other workers (Morris *et al*., 1970). More common neurological complications are ataxia and neuropathy. Seizure, dementia, myopathy, headache (Hadjivassi Liou *et al*., 1998).

Turner *et al* in 2007 reported a case of right sided spastic hemiparesis with wasting and intermittent painful spasm of quadriceps. They proposed that neuronal symptoms are due to perivascular inflammations causing breakdown of blood brain barriers allowing antibody to cross react with neuronal tissue. Cerebellum also contains Ttg IgA in blood vessels. One of our patients had intolerance to milk, chicken and eggs. Food intolerance might be due to IgA deficiency (Sachdev, 2011) although we did not test it in our study in place of case. Two of our patient had type 2 diabetes mellitus and one child had type 1 diabetes mellitus. Association of CD with type 1 DM is well known. About 1 to 19%patients of T1DM have CD (Komer *et al*., 2002; Ching *et al*., 2007; Ergur *et al*., 2010; Al-Sinani Siham *et al*., 2013). Association with CD with type 2 DM may be due to age related phenomenon. Among the autoimmune diseases, association with thyroid disease was strong. Three of the patient had clinically evident hypothyroid while in others it was not apparent. Anti TPO antibody in our study was detected in 27.27% cases. Association of thyroid disease with CD in Hashimoto's thyroiditis and Graves disease in children ranges from 2 to 7.8 % (Ching *et al*., 2007). In adults hyperthyroidism was found in 0.1 to 5.2% and hypothyroidism was found in 0 to 5.8% cases (Collen *et al*., 2002). One study (Butt *et al*., 2011) noticed that 10% patient of CD have subclinical hypothyroidism but anti TPO antibody is detected in 16% cases. Some studies (Velluzzi *et al*., 1998; Naiyer *et al*., 2008) have reported a very high frequency of anti TPO antibody in CD up to 50%. Scleroderma is autoimmune disease .It is also associated with diarrhoea due to loss of peristalsis by fibrous involvement of smooth muscle and intraluminal bacterial growth which causes damage to mucosa (Varga, 2008). Association of scleroderma with CD is controversial. One study (Luff *et al*., 2003) reported prevalence of celiac disease in scleroderma to be 7.5% while other study done in 50 cases of scleroderma found positivity of anti Ttg antibody in 10% cases. Contrary to this, study done by Nishihara *et al*., 2011 in 105 cases of scleroderma did not find higher frequency of IgA endomysial antibody.

In present study by dot blot test we found that anticentromere antibody positive in 9.09% patients of CD. Although clinically none of the patient had evidence of scleroderma. Another one patient was positive for both antiscleroderma 70 antibody and anti Jo-1 antibody although this patient had evidence of muscle tenderness. Like us Sachdev 2011 also reported that polymyositis may be found in CD patients. Two of our patient had positive antinuclear antibody and one also was positive for anti Sm antibodies. Clinically patient had off and on arthritis but no full blown picture of SLE was associated with CD. SLE may develop 2 to 10years after the diagnosis of CD (Freeman, 2008). In 23.3% patients of SLE, anti endomysial antibody without histological evidence of CD can be present (Rensch *et al*., 2001; Hadjivassiliou *et al*., 2004). In present study antigliadin antibody detected in only 68% cases. This kit used gliadin peptide as antigen. Anti Ttg antibody is more sensitive test than anti gliadin antibody. Now deaminated gliadin peptide antibody (DGA) is found to be more sensitive (90%) and specific (98%) test for diagnosis of CD.DGA diagnosed 6 out of 9 cases, anti Ttg diagnosed 2 out of 9 cases and anti endomysial antibody detected none of the cases of small bowel damage presenting on gluten free diet (McPherson *et al*., 2012). In our study we have not used dominated gliadin peptide antigen hence low sensitivity can be there. Thus our study concludes that celiac disease is very common in our area and this disease is associated with antibody to many autoimmune diseases like hypothyroidism, scleroderma and SLE.

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