CROSS SECTIONAL STUDY OF PANCREATIC, THYROID AND CELIAC ANTIBODY POSITIVITY IN PEDIATRIC PATIENTS WITH DIABETES MELLITUS IN WESTERN INDIA

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ABSTRACT

Type 1 diabetes (T1D) is the most common endocrine disease encountered in the pediatric age group. T1D results from a complex interplay of genetic, immunological and environmental factors. Although the disease is characterized by β cell destruction and presence of pancreatic autoantibodies, the autoimmune attack may involve other organs particularly thyroid, gut, adrenals and gastric parietal cells. The presence of autoimmunity of other organs in patients with T1D influences the disease prognosis and screening for associated autoimmunity is therefore recommended. There is however wide variation in the frequencies of various auto antibodies in different populations of the world and the frequency of screening and the follow up of patients with positive auto antibodies remain controversial. Only a few studies have evaluated more than 3 auto antibodies at a time. Therefore more research is needed to evaluate pancreatic, thyroid, celiac autoantibody positivity in Indian children with DM.

INTRODUCTION

Diabetes mellitus (DM) is a complex multifactorial and heterogeneous syndrome characterized by hyperglycemia resulting from inadequate insulin secretion and/or insulin action. Several pathogenic processes ranging from autoimmune (AI) destruction of the β-cells of pancreas to abnormalities that result in resistance to insulin are involved in the development of diabetes. The incidence of childhood onset T1D is rapidly increasing in many parts of the world, especially in children below the age of five years. It is more likely to develop in children with certain HLA genes (Human leukocyte antigen) (B8, B15, DR3, DR4, and particularly DQB1*0302, DQB1*0201, DQA1*0301 and DQA1*0501) which control related immune responses. Enormous diversity in HLA class I and class II genes in the north Indian population are observed and several novel alleles and unique haplotypes have been identified. T1D associated with other AI diseases including AI thyroid disease in 15-30%, celiac disease in 4-9% and Addison’s disease in 0.5% detection of which is crucial to prevent morbidity related to these unrecognized diseases. There is a genetic predisposition toward T1D, which also predisposes patients to other AI diseases such as thyroid disease, celiac disease, adrenal insufficiency, vitiligo, alopecia, and gastric autoimmunity. These diseases are associated with organ specific auto antibodies like:

**Pancreatic auto Antibodies**

1. Anti Islet cell antibody (Anti Islet Cell Ab)
2. Anti Insulin antibody (Anti Insulin Ab)
3. Auto-antibodies to the 65 kD isoform of glutamic acid decarboxylase (Anti GAD Ab)
4. Auto-antibodies to Insulinoma Associated protein 2 (Anti IA2 Ab)
5. Zinc transporter autoantibody (Anti ZnT8A Ab)

**Thyroid auto Antibodies**

6. Anti-thyroid peroxidase antibody (Anti TPOAb)
7. Anti-thyroglobulin antibody (Anti TGAb)

**Celiac auto Antibody**

8. Anti-tissue transglutaminase immunoglobulin-A antibody (Anti TTGlA Ab)
Using these auto antibodies, organ specific autoimmunity may be detected before the development of clinical disease. Early detection has the potential to prevent significant morbidity related to unrecognized disease. A subset of the subjects with organ specific auto antibodies develops clinical disease. It was found that increase in number of antibodies dramatically increases the risk of developing clinical disease and those with higher antibody titers are more likely to progress to clinical disease. The frequency of screening and the follow up of patients with positive auto antibodies remain controversial, with some advocating regular screening, whereas others advocate screening in the presence of clinical symptoms. There are limited Indian studies on auto antibody positivity in pediatric population with DM. Only a few studies have evaluated more than 3 auto antibodies at a time. So more research is needed to evaluate auto antibodies directed against pancreas, thyroid gland and antibody for celiac disease in pediatric DM patients. The purpose of this study is to determine pancreatic, thyroid, celiac autoantibody positivity in Indian children with DM in Western India.

**Aims and Objective**

To evaluate for auto antibodies directed against the islet cells of the pancreas, the thyroid gland and antibody for celiac disease in patients up to 18 years diagnosed with diabetes mellitus.

**MATERIALS AND METHODS**

This is a prospective, cross-sectional, observational study carried out from November 2015 to October 2016. The study has enrolled 53 children diagnosed with diabetes mellitus up to 18 years of age, following up in pediatric outpatient as well as inpatient department. Patient’s demographic details, clinical details, family history of co morbidities and autoimmune disorders, along with laboratory data as per investigation details, family history of co morbidity, and autoimmune disorders, along with laboratory data as per investigation protocol has been collected and the data analyzed. Autoantibody profile panel subdivided under the headings of pancreatic, thyroid and celiac autoantibody. All above mentioned auto antibodies were measured by IEA i.e. immuno-enzymatic assay kits except anti-Islet cell Ab which was measured by IFA i.e. immuno-fluorescence assay kits. The tests were performed as per manufacturer’s instructions and results were compared with age related cut off values. This collected data noted and further analyzed for results.

**Investigation protocol**

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Positive</th>
<th>Negative</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Insulin</td>
<td>&gt;30 IU/mL</td>
<td>&lt;30 IU/mL</td>
<td>IFA*</td>
</tr>
<tr>
<td>Anti-ISlet</td>
<td>&gt;1.25 JDF unit</td>
<td>&lt;1.25 JDF unit</td>
<td>IFA*</td>
</tr>
<tr>
<td>Anti-GAD</td>
<td>&gt;30 IU/mL</td>
<td>&lt;30 IU/mL</td>
<td>IFA*</td>
</tr>
<tr>
<td>Anti-AIA2</td>
<td>&gt;600 IU/mL</td>
<td>&lt;600 IU/mL</td>
<td>IFA*</td>
</tr>
<tr>
<td>Anti-TPO</td>
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<td>&lt;600 IU/mL</td>
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</tr>
<tr>
<td>Anti-TG</td>
<td>&gt;1800 IU/mL</td>
<td>&lt;1800 IU/mL</td>
<td>IFA*</td>
</tr>
<tr>
<td>Anti-TTGIgA</td>
<td>&gt;30 IU/mL</td>
<td>&lt;30 IU/mL</td>
<td>IFA*</td>
</tr>
</tbody>
</table>

*JDF- Juvenile Diabetes Foundation  
*(IEA- Immuno-Enzymatic Assay)  
*(IFA-Immuno-Fluorescence Assay)  
*All above reference values same for all ages  
Total serum IgA - Normal range >50 mg/dl

**RESULTS**

Among 53 patients, 30 were females and 23 were males. The Male to Female ratio was 0.76. The children ranged in age from 1 year to 18 years. Mean age of study population was 8.54 year (SD =4.08) and median age was 9 years. Maximum number of children was in the age group of 5–10 years. Out of 53 cases, 51 were labeled as T1D and 2 cases labeled as T2D both were autoantibody negative. The association between type of diabetes and autoantibody positivity was found to be statistically significant (P value=0.033). Anti-GAD, anti TPO, anti-Islet cell, anti-Insulin, anti TG, anti TTGIgA and anti IA2 antibody positivity rates were, in that order of frequency, 28 (52.8%), 13 (24.5%), 8 (15.1%), 8 (15.1%), 7 (13.2%), 4 (7.5%), 3 (5.7%) respectively. The most common autoantibody found was anti GAD Ab with prevalence of 52.8% and least common was anti IA2 with prevalence of 5.7%. The prevalence of pancreatic autoantibody positivity was 67.9 %, thyroid autoantibody positivity 28.3%, and celiac autoantibody positivity 7.5% with 81.1% having any one of aforementioned autoantibody positive. Each of the studied autoantibody was found to have female preponderance. The association of any one of studied autoantibody positivity with gender (P=0.082) and age (P=0.187) was found to be statistically insignificant. The prevalence of at least one pancreatic autoantibody positivity (i.e. any one of anti-GAD Ab or anti Islet cell Ab or anti Insulin Ab or anti IA2 Ab) in our pediatric DM patients was 67.9 % with female preponderance but the association between pancreatic autoantibody positivity and gender was statistically insignificant (P=0.942). The prevalence of thyroid autoantibody positivity (anti TPO &/or anti TG Ab) was 28.3 % with female preponderance but the association between thyroid autoantibody positivity and gender was statistically insignificant (P=0.064). The prevalence of celiac autoantibody positivity (anti TTGIgA Ab) was 7.5 % with female preponderance but the association between celiac autoantibody positivity and gender was statistically insignificant (P=0.624). The association between any one pancreatic Ab positivity (i.e. any one of anti-GAD Ab or anti Islet cell Ab or anti Insulin Ab or anti IA2 Ab) with either anti TPO Ab, anti TG Ab or thyroid autoantibodies (anti TPO &/or anti TG Ab) positivity was statistically insignificant with respective P values (0.306),(0.667),(0.667).

The association between any two pancreatic Ab positivity (i.e. any two of anti-GAD Ab or anti Islet cell Ab or anti Insulin Ab or anti IA2 Ab) with either anti TPO Ab or anti TG Ab or thyroid autoantibodies (anti TPO &/or anti TG Ab) positivity was statistically insignificant with respective P values (0.711),(0.626),(1.000). The association between celiac Ab positivity (anti TTGIgA Ab) with either anti TPO Ab, anti TG Ab or thyroid autoantibodies (anti TPO &/or anti TG Ab) positivity was statistically insignificant with respective P values (0.249), (0.080), (0.568). The association between any one pancreatic Ab positivity (i.e. any one of anti-GAD Ab or anti Islet cell Ab or anti Insulin Ab or anti IA2 Ab) and anti TTGIgA Ab i.e. celiac Ab positivity was statistically insignificant (P value =1.000). In the study population out of 53 cases, 50 (94.3%) cases were found to have low C-peptide fasting level, 2 (3.8%) cases have high C-peptide fasting level & 1 (1.9%) was in honeymoon phase of T1D found to have normal C-peptide fasting level. Mean value of fasting C-peptide was found to be 0.50 (SD=0.88), minimum value was 0.01ng/ml & maximum was 5.60 ng/ml.
Figure 1 Gender distribution among study population

Figure 2 Age distribution among the study population

Figure 3 Gender wise distribution and association with any one of studied Ab positivity

Figure 4 Gender wise distribution and association with any one pancreatic Ab

Figure 5 Gender wise distribution and association with thyroid antibodies

Figure 6 Gender wise distribution and with coeliac antibody
CONCLUSIONS

1. Our study population from Western part of India with pediatric DM had prevalence of pancreatic autoantibody positivity 67.9%, thyroid autoantibody positivity 28.3%, and celiac autoantibody positivity 7.5% with 81.1% having any one of aforementioned autoantibody positive.

2. In this study, 81.1% of children from Western part of India with DM had at least one autoantibody positivity; this percentage might have been higher if newer autoantibody such as ZnT8 Ab had been included.

3. 3) Each of the studied autoantibody was found to have female preponderance but the difference was not statistically significant. Autoantibody positivity rate was highest in the age group of 5–10 years.

4. No correlation was found between the number of pancreatic autoantibodies positive (either one or two) and the chances of thyroid autoantibody positivity or celiac autoantibody positivity in our study.

Limitation

Our study had limitations in terms of small sample size (n=53) as compared to other similar studies.

References

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