Full Length Research Paper

Autoimmune disorders associated with type 1 diabetes mellitus in Saudi children and adolescent

Nasir A. M. Al-Jurayyan

Divisions of Endocrinology, Department of Pediatrics, College of Medicine and King Khalid, University Hospital, King Saud University, Riyadh, Saudi Arabia.

*Corresponding author email: njurayyan@gmail.com

Accepted 20 December, 2014

Abstract

Background: Patients with type 1 diabetes mellitus are at increased risk of developing other autoimmune disease. Objectives: To determine the prevalence of various autoimmune disorders in 305 patients with type 1 diabetics. Design: A retrospective, hospital based-study. Materials and Methods: The associations of other autoimmune disorders in type 1 diabetic were reviewed. Diagnosis of CD was based on positivity of screening serum, and proved by histopathological findings of intestinal biopsy specimen. Thyroid dysfunction was assessed by anti-microsomal peroxidase (TPO) and antithyroglobulin (anti-TG) antibodies coupled with diagnostic thyroid function (TSH and FT4), while for adrenal dysfunction was based on low serum cortisol and high serum ACTH. Results: The cohort includes 305 Saudi children and adolescents, 163 (53.4%) were females and 142 (46.6%) males. Thyroid dysfunction was evident in 65 (21.3%) patients, of those, 26 (8.5%) patients had evidence of overt hypothyroidism. Thirty-nine (12.8%) patients had sub-clinical hypothyroidism. Thyroid microsomal peroxidase (TPO) and thyroglobulin (TG) antibodies were done in the sera of 114 (37.4%) patients. Seventy-six (66.7%) patients were euthyroid, 20 (17.5%) patients with overt-hypothyroidism and 10 (15.8%) patients with sub-clinical hypothyroidism. Interestingly, in 16 (80%) patients with overt hypothyroidism were positive for both TPO and TG antibodies) while the majority of the euthyroid patients (93.2%) both TPO and TG antibodies were negative. Sixty-two (20.3%) patients were referred for endoscopy and biopsy. In 26 (8.5%) patients, the biopsies were abnormal. Only one patient was found to be adrenal insufficient with autoimmune polyendocrinopathy syndrome (APSI). Conclusion: The prevalence of other organ-specific disorders is high in patients with type 1 diabetes. After autoimmune thyroiditis, the second most commonly reported is celiac disease. Although, further follow-up period is needed to determine the natural history of these autoantibodies in patients with type 1 diabetes mellitus. The current strategy for screening should be reviewed.

Keywords: Autoimmune disorders, type 1 diabetes mellitus, Saudi, children, adolescent

INTRODUCTION

Diabetes mellitus, type 1, is the most common endocrinopathy to have clinical onset in childhood or adolescence, with varied pathogenesis, clinical appearance and outcome, and seriously affects patients and families life. A combination of genetic, environment and immunological factors exerts to a T-cell mediated autoimmune process targeted against insulin producing β-cells in the pancreatic islet of Langerhans (Daneman,
adrenal insufficiency. The frequency of organ specific like celiac disease, autoimmune thyroid disease, and increased risk of developing other autoimmune conditions characterized by an initial infiltration by lymphocytes and macrophages, of the organ, with impaired activity of the organ by atrophy. This progressive autoimmune process takes time, and is T-cell mediated. Antibodies against specific antigens of the involved gland are detectable in the blood before the clinical onset of the specific disease, so they represent a risk marker and their screening and follow-up allow precocious diagnosis and treatment of autoimmune related disease in genetically susceptible individuals (Allen et al., 2008; Barker, 2006; Kordonouri et al., 2009; Todd et al., 2007; Triolo et al., 2011; Tsirogianni et al., 2009; Hanukeglu et al., 2003; Kentilines et al., 1990).

The mean objective of this article is to present our experience of the various autoimmune disorders associated with type 1 diabetes mellitus, in a cohort of 305 children and adolescents at the King Khalid University Hospital, Riyadh, Saudi Arabia, between the period January 1995 and December 2012.

MATERIALS AND METHODS

This is a retrospective hospital-based study, included children and adolescents who were diagnosed and followed for type 1 diabetes mellitus, at the Pediatric Diabetic Clinic at King Khalid University Hospitals (KKUH), King Saud University, Riyadh, Saudi Arabia between the period January 1995 and December 2012. The diagnosis of type 1 diabetes mellitus was based on history of polyuria, polydipsia, and weight loss, with an elevated random blood sugar of ≥11.2 mmol/L.

Subjects were serologically screened for other associated autoimmune disorders at the time of diagnosis and annually thereafter. Serologically screening tests for celiac disease (CD), includes anti-gliadin antibody, AGA. Anti-endomysial antibodies, EMA, anti-tissue transglutaminase, tTG, antibody. Serological tests are fully-automated, except EMA test which is time consuming and operator-dependent. For serological test, also, immunoglobulin A is measured.

Positivity of one or more of these tests, the patient is referred for upper endoscopy where multiple biopsy specimens were taken. The severity of small bowel mucosal damage was reviewed by an experienced gastrointestinal pathologist and graded according to the Marsh classification from 1 to III. The diagnosis of CD is based on the revised criteria for the diagnosis of CD.

Patients were screened for thyroid dysfunction by thyroid stimulating hormone (TSH) and free thyroxine (FT4) at the time of diagnosis, and annually thereafter. These were made by method using commercially available kits. The quality control of the assay was monitored by the Middle East Extended Quality Assessment Scheme (MEEQAS) in Riyadh. Anti-thyroid microsomal and thyroglobulin antibody were estimated using haemoglutination method, and a titer of 1:100 or more was considered positive. Diagnosis of subclinical autoimmune thyroiditis was based on high levels of TSH of more than 5 IU/L associated with normal FT4, while clinical hypothyroidism (overt hypothyroidism) was associated with low FT4 levels, and/or goiter. Adrenal function was assessed at the time of diagnosis, and annually thereafter by measuring serum cortisol and adrenocorticotropic hormone (ACTH), by available commercial kits.

The study was approved by the Institutional Review Board (Ethical and Research Committee) of the College of Medicine of King Saud University, Riyadh.

RESULTS

All patients were serologically screened for celiac disease, table 1. Sixty-two (20.3%) patients were, subsequently, referred to pediatric gastroenterologist to perform upper gastrointestinal endoscopy and biopsy, being having one or two positive screening tests

In twenty-six (8.5%) patients (17 females and nine males), the biopsy results was positive for celiac disease. Their age was range between seven to 16 years (mean 11.5 years) and the duration of diabetes was 1.5 to 11.5 years (mean 5 years). The other 36 (11.8%) patients were having normal biopsies and, therefore, considered to have potential celiac disease.

Thyroid functions were abnormal in 65 (21.3%) patients. Of these, 26 (8.5%) patients had evidence of overt hypothyroidism, i.e., high TSH and low FT4 and 39 (12.8%) patients had subclinical hypothyroidism, i.e. TSH of more than 5 IU/L and normal free T4. Thyroid microsomal peroxidase (TPO) and thyroglobulin (TG) antibodies were done in the sera of 114 (37.4%) patients. Table 2, seventy-six (66.7%) patients, were euthyroid, twenty (17.5%) patients were having overt hypothyroidism, while only eighteen (15.8%) patients had subclinical hypothyroidism. Interestingly, in sixteen (80%) with overt hypothyroidism
were positive for both TPO and TG antibodies, while in the majority of euthyroid patients (93.2%) both TPO and TG antibodies were negative.

A 9-year-old girl presented with adrenal insufficiency, low serum cortisol and high adrenocorticotrophine (ACTH). Hypoparathyroidism and chronic candidiasis, autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy [APE CED], APS type 1, with AIRE gene mutation. Six months later, she developed type 1 diabetes mellitus and found to be hypothyroid, also, with positive TPO and TG antibody. She was diagnosed with celiac disease based on small bowel biopsy, a year later. She died at 14 years of age because of worsening of her autoimmune hepatitis. Otherwise, none of our patients had signs or symptoms nor biochemical evidence of adrenal insufficiency.

**DISCUSSION**

Type 1 diabetes mellitus is the most common endocrinopathy, with increasing incidence worldwide. It is now established that an increased risk of other autoimmune disease is compared to general population. Besides islet-cell autoantibodies, other antibodies against numerous non β-cell antigens have been frequently reported. Latent forms of these autoimmune-associated disease, characterized by the presence of circulating autoantibodies with mild or no symptoms, are more frequent. The frequency of organ-specific autoimmunity in patients with type 1 diabetes mellitus might be due to multiple immunological abnormalities, i.e., an imbalance in B and T lymphocytes, or tendency to react against specific antigens, or poor ability to develop immune tolerance. Early detection of antibodies and latent organ-specific dysfunction are advocated to alert physician to take appropriate actions. More than thirty percent of our type 1 diabetes are having other autoantibodies against specific organ such as the thyroid and small bowel cell (Al Jabri et al., 2013; Barker, 2006; Triolo Bet al., 2011).

Thyroid dysfunction is frequently reported in patients with type 1 diabetes mellitus, sometimes associated with celiac disease as in our series. The prevalence of thyroid autoimmunity in patients with type 1 diabetes has been reported to be two to four times more frequently than in control. In control population the prevalence of thyroid autoimmunity ranges from 2.9% to 32% which in patients with type 1 diabetes the prevalence is higher, ranging from 19 to 23.4%. A subclinical hypothyroidism has been reported up to 58% of patients with thyroid autoantibodies, confirmed by low free thyroxin and high TSH level. Overt hyperthyroidism is rarely encountered (Holl et al., 1999; Feely and Isles, 1979; Radetti et al., 1995; Lindberg et al., 1997; Kordonouri et al., 2002; Bilimoria et al., 2003; Severinski et al., 2009; Piatkowska and Szalecki, 2011; Mantovani et al., 2009; Kordonouri et al., 2002; Perros et al., 1995). Our study reported a similar prevalence.

Celiac disease, is the second most common disease, found in 62 (20.3%) patients. Twenty-six (8.5%) patients were histologically diagnosis (Revised criteria for diagnosis of celiac disease, 1990; Marsh, 1992). Al Ashwal et al and Saada et al reported a similar figures of 4.9% to 12% (Al Ashwal et al., 2003; Saada et al., 2012).

The clinical range of the disease had a wide spectrum, with differential subtypes has been described, ranging from the classic or symptomatic to asymptomatic disease. The gold standard for diagnosis is a small bowel biopsy. The findings of histological mucosal atrophy with increased number of intraepithelial infiltrate confirmed the diagnosis. The potential celiac disease is characterized by positive antibodies, but normal biopsy encountered in 36 (11.8%) patients. A higher prevalence of potential CD was found in patients with type 1 diabetes (Lindberg et al., 1997).

Once considered a rare childhood disorder, celiac disease, is now known to be a very common condition. The prevalence of the disease is dramatically increased in type 1 diabetes compared to normal population (Lindberg et al., 1997; Al Ashwal et al., 2003; Saada et al., 2012).

---

**Table 1. Serologically and biopsy results in 305 patients with Type-1 diabetes**

<table>
<thead>
<tr>
<th>Anti-gliadin</th>
<th>Anti-endomyseal</th>
<th>Anti-transglutaminase</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>-ve (243)</td>
<td>-ve (243)</td>
<td>-ve (243)</td>
<td>Normal</td>
</tr>
<tr>
<td>+ve (36)</td>
<td>+ve (30)</td>
<td>+ve (28)</td>
<td>Potential</td>
</tr>
<tr>
<td>+ve (26)</td>
<td>+ve (22)</td>
<td>+ve (25)</td>
<td>Biopsy positive</td>
</tr>
</tbody>
</table>

**Table 2. Thyroid status, and antibodies (TPO and TE) in 305 children and adolescent with type 1 DM**

<table>
<thead>
<tr>
<th>Thyroid status (No.)</th>
<th>No. of patient (%)</th>
<th>-ve antibodies</th>
<th>+ve antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (240)</td>
<td>76 (31.7%)</td>
<td>71 (93.4%)</td>
<td>5</td>
</tr>
<tr>
<td>Subclinical hypothryoidism (39)</td>
<td>18 (46.2%)</td>
<td>13 (72.2%)</td>
<td>5</td>
</tr>
<tr>
<td>Overt hypothryoidism (26)</td>
<td>20 (76.9%)</td>
<td>4 (20%)</td>
<td>16</td>
</tr>
</tbody>
</table>

TPO – thyroid-microsomal-peroxidase
TG - thyroglobulin
The mean prevalence of celiac disease in type 1 diabetes mellitus is about 8% with an extremely variable range, from 1% up to 11%, almost 10-20 folds higher than observed in normal population. Diagnosis of celiac disease usually follows the diagnosis of type 1 diabetes but in a small proportion of case, it may precede the diagnosis (Holmes, 2001).

In children and adolescents with type 1 diabetes mellitus, Addison’s disease is rarely encountered. It is an insidious, chronic disease of the adrenal cortex resulting in decrease production of glucocorticoids, mineralcorticoids, and androgen, with a concomitant increase secretion of ACTH, thus, hyperpigmentation of the skin and mucous membrane. In the majority, 80%, an autoimmune cause, either, with involvement of several organs or as an isolated condition. Correct diagnosis requires a high degree of clinical suspicion, and since the disease is a life-threatening condition several investigators recommend annual screening. Autoantibodies against 21 hydroxylase enzyme and adrenal cortex are useful marker (Lorini et al., 1996; Barker et al., 2005; Linkhari et al., 2007; Kordonouri et al., 2009; Betterie, 2002; Brewer et al., 1997; Babiker et al., 2011); Peterson et al. (1997) found a good correlation between the conventional immunofluorescent adrenal autoantibodies and 21 hydroxylase antibody technique. If present, yearly monitoring with ACTH stimulation test is performed to allow early diagnosis and prevent adrenal crisis. Risk factors for adrenal disease in patients with type 1 diabetes mellitus include a history of other autoimmunity in particular thyroid disease, and positive family history for autoimmunity. (Barker et al., 2005; Betterie, 2002; Van den Driessche et al., 2009; Thomas et al., 2004). In our series, only one patient with autoimmune polyendocrinopathy noted, APS type 1. Therefore, routine screening for Addison’s disease in children and adolescents with type 1 diabetes mellitus regardless of thyroid status does not appear warranted unless there is a strong clinical and biochemical suspicion or risk factor for Addison’s disease. This is in agreement with Babiker et al. (2011); Marks (2003)

In conclusion, the prevalence of other organ-specific disorders are higher in patients with type 1 diabetes mellitus compared to general population. After autoimmune thyroiditis, the second most commonly reported autoimmune disease is celiac disease. Although, an ongoing follow-up period will be important to determine the natural history of organ-specific auto-immunity in patient with type 1 DM. Adrenal insufficiency seems to be rare, and does not warrant frequent screening. Finally, a need to plan our strategy of screening of subjects with type 1 diabetes mellitus. to detect the other organ-specific disorders, should be reviewed.

REFERENCES


Kordonouri O, Doss D, Danne T, Dorow A, Bassir C, Gruters-Kieslich A (2002). Predictivity of thyroid autoantibodies for the development of...