Type 1 diabetes mellitus associated with autoimmune thyroid disease, celiac disease and familial Mediterranean fever: case report

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It is known that type 1 diabetes mellitus (type 1 DM) may be associated with other autoimmune diseases. Recently, a patient with an association of type 1 DM and familial Mediterranean fever (FMF) was reported in the medical literature.

A 10.5-year-old boy was brought to our clinic with complaints of polydipsia, polyuria and weight loss and was diagnosed as diabetic ketoacidosis due to autoimmune type 1 DM. Insulin therapy was started. Elevated thyroid antibodies associated with diffuse goiter and hypothyroidism led to the diagnosis of autoimmune thyroid disease (ATD), and elevated antiendomysial antibodies and abnormal intestinal biopsy findings led to the diagnosis of celiac disease (CD). L-thyroxine therapy and gluten-free diet were initiated accordingly. At the third-year of follow-up, acute attacks of fever, abdominal pain and chest pain developed. Laboratory investigations, which were normal between the attacks, revealed elevated erythrocyte sedimentation rate, fibrinogen, white blood cell count and pleural effusion on chest X-ray during the attacks. Molecular analysis for FMF revealed compound heterozygous M694I and V726A. The patient responded well to colchicine therapy started at a dose of 1.5 mg/day.

We present the second patient with type 1 DM associated with FMF who also had ATD and CD.

Key words: type 1 diabetes mellitus, familial Mediterranean fever, autoimmune thyroid disease, celiac disease.

It is known that type 1 diabetes mellitus (type 1 DM) may be associated with autoimmune diseases such as autoimmune thyroid disease (ATD), celiac disease (CD) and Addison’s disease. An association of type 1 DM and familial Mediterranean fever (FMF) has been newly reported in the medical literature.

Familial Mediterranean fever is an autosomal recessive disorder characterized by acute attacks of fever, abdominal pain, arthritis, and pleurisy recurring at different intervals. Neutrophil-mediated serosal inflammation causes polyserositis. Amyloidosis is a complication of FMF and may develop without overt attacks.

The diagnosis of FMF requires a high index of suspicion and is based on the clinical criteria of acute, reversible serosal attacks and family history, when available. The FMF gene (MEFV) was mapped on the short arm of chromosome 16. The discovery of the gene and its mutations for FMF permit genetic testing to define the diagnosis in patients with FMF. Some of FMF-related common mutations are M694V, M680I, V726A, M694I and E148Q.

We present the second patient with type 1 DM associated with FMF who also had ATD and CD.
Case Report

A 16.7-year-old male patient was being followed from the Pediatric Endocrinology Outpatient Clinic with the diagnosis of type 1 DM. He was born at term by normal vaginal delivery (birth weight 3500 g) from a healthy mother as the second child of the family. There was no consanguinity between the parents. He had first been admitted to the hospital, at the age of 10.5 years, with the complaints of polyuria, polydipsia, decreased appetite, weight loss for a few weeks, and nervousness and difficult breathing for three days. His physical examination revealed a conscious child with acidoic respiration, body weight of 35 kg (-0.12 SDS) and height of 132 cm (-1.4 SDS). Target height was 170.5 cm (-0.47 SDS). Blood glucose level was 25 mmol/L (450 mg/dl). Blood gas analysis showed a pH of 6.7 and HCO₃ 2.8 mmol/L. The diagnosis of diabetic ketoacidosis was made, and after appropriate fluid-electrolyte and insulin therapy, multiple dose (4 times daily) insulin injection treatment (0.35 U/kg/day) was started. The laboratory findings regarding autoimmune markers are seen in Table I. Human leukocyte antigens (HLA) typing was DRB1*0301, DQA1*0501, DQB1*02, DRB1*1502, DQA1*0121, DQB1*0601.

On admission, the patient also had a remarkable, grade 2b thyromegaly on physical examination. Thyroid ultrasonography revealed enlarged thyroid gland, hypoechochogenicity and no increase in vascularization. As shown in Table I, diagnosis of ATD (Hashimoto thyroiditis) was established, and L-thyroxine replacement treatment was started at a dose of 100 µg/m²/day.

The patient was under good metabolic control for DM. Investigations were performed regularly to screen for the development of associated illnesses and diabetes-related complications.

The following year, anti-gliadin and anti-endomysial antibodies were checked because of poor increase in height (3.6 cm/year) and weight and a decrease in insulin requirement. There was no complaint of diarrhea. As anti-gliadin and anti-endomysial IgA antibodies were found positive (+3) in the serum, small bowel biopsy was performed, which revealed villous atrophy. Thus, gluten sensitive enteropathy diagnosis was made at 11 years of age and gluten-free diet was started. Subsequently, his growth rate (6 cm/year) and also insulin requirement increased (0.9 U/kg/day). Meanwhile, HbA₁C level was in the upper normal range (7.5%).

The patient was followed regularly, and from 13.9 years of age, complained of a sharp back pain, penetrating to his chest while breathing. The prominent complaint was chest pain together with abdominal pain, nausea, fever, loss of appetite, and fatigue associated with the pain, lasting 1-2 days every 2-3 months. His complaints had been occurring more frequently over the last two years. He was hospitalized for further evaluation during an attack. His weight was 41.5 kg (-0.9 SDS) and height was 149 cm (-1.5 SDS) at the age of 14. He was pubertal with testes 8 ml/8 ml. Laboratory investigations, which were normal between the attacks, revealed elevated erythrocyte sedimentation rate (65 mm/hour), fibrinogen (460 mg/dl) (normal ranges: 200-400), and white blood cell (16,000/mm³) and minimal

<table>
<thead>
<tr>
<th>C-peptide nmol/L (ng/ml) (blood glucose: 25 mmol/L)</th>
<th>Results SI unit</th>
<th>Normal ranges SI unit Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.16</td>
<td>0.39-1.12</td>
</tr>
<tr>
<td>HbA₁C %</td>
<td>12.5</td>
<td>4.5-6.5</td>
</tr>
<tr>
<td>Islet cell antibody (ICA)</td>
<td>JDF</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Anti-insulin antibody (IAA) %</td>
<td>15.9</td>
<td>5-10</td>
</tr>
<tr>
<td>Anti-thyroglobulin antibody (Anti-Tg) U/ml</td>
<td>157.6</td>
<td>&lt;60</td>
</tr>
<tr>
<td>Anti-thyroid peroxidase (Anti-TPO) U/ml</td>
<td>300</td>
<td>&lt;60</td>
</tr>
<tr>
<td>Thyroxine (T₄) nmol/L (µg/dl)</td>
<td>72</td>
<td>57.9-160.9</td>
</tr>
<tr>
<td>Free T₄ (ng/dl)</td>
<td>5</td>
<td>11.4-23.1</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (TSH) mU/L (µU/ml)</td>
<td>100</td>
<td>0.27-4.2</td>
</tr>
<tr>
<td>Tri-iodothyronine (T₃) pmol/L (ng/dl)</td>
<td>768</td>
<td>1382.4-3640.3</td>
</tr>
<tr>
<td>Cortisol nmol/L (µg/dl)</td>
<td>303.4</td>
<td>137.9-689.6</td>
</tr>
</tbody>
</table>

The patient was followed regularly, and from 13.9 years of age, complained of a sharp back pain, penetrating to his chest while breathing. The prominent complaint was chest pain together with abdominal pain, nausea, fever, loss of appetite, and fatigue associated with the pain, lasting 1-2 days every 2-3 months. His complaints had been occurring more frequently over the last two years. He was hospitalized for further evaluation during an attack. His weight was 41.5 kg (-0.9 SDS) and height was 149 cm (-1.5 SDS) at the age of 14. He was pubertal with testes 8 ml/8 ml. Laboratory investigations, which were normal between the attacks, revealed elevated erythrocyte sedimentation rate (65 mm/hour), fibrinogen (460 mg/dl) (normal ranges: 200-400), and white blood cell (16,000/mm³) and minimal
pleural effusion on chest X-ray during the attack. Autoantibodies for other autoimmune diseases and connective tissue diseases were found to be negative. These findings were suggestive of FMF. Molecular analysis for FMF performed in genomic DNA extracted from the peripheral blood using polymerase chain reaction (PCR) method revealed two different point mutations: compound heterozygous M694I and V726A (Bilkent University, BilGen Laboratory, Ankara, Turkey). There was no proteinuria and daily protein excretion was 10.5 mg.

The patient responded well to colchicine therapy started at a dose of 1.5 mg/day. The pain resolved after a short time.

On his recent examination at 16.5 years of age, his weight was 66 kg (0.1 SDS) and height 171 cm (-0.4 SDS) (target height: 170.5 cm). His puberty was completed. Daily insulin requirement was 1.4 U/kg/day. Recent HbA1C level was 6.3%, thyroid hormone levels were in normal ranges, anti-thyroglobulin (Tg) was negative and anti-thyroid peroxidase (TPO) was 241.1 IU/ml. He remained on L-thyroxine therapy (125 µg/day) and colchicine without any side effects. Although there was no proteinuria, rectal biopsy was performed to check for the presence of amyloidosis at 16.6 years of age, and none was demonstrated.

Discussion

Patients with type 1 DM have an increased risk of developing other autoimmune diseases. The most common associated autoimmune disease is ATD (Hashimoto’s disease), which is reported as 7-38% among type 1 DM compared to ATD prevalence in the general population of 1-7%. There are many studies regarding an increased association of type 1 DM and CD (10,11). CD has been reported to vary from 1.7% to 8.5% among patients with type 1 DM, which is 20 times higher than that in the general population. In our patient, the association of type 1 DM, ATD and CD is an expected finding. However, the coexistence of FMF is a very rare finding, and this is only the second such patient in the literature. FMF is an autosomal recessive inflammatory disorder characterized by acute attacks of fever, abdominal pain, arthritis and pleurisy recurring at different intervals, associated with an increase in acute phase reactants. FMF is very frequent among the Jewish, Turkish, Armenian and Arab populations. The carrier frequency is as high as 1/3 to 1/5 among these populations. Neutrophil-mediated serosal inflammation causes polyserositis. The diagnosis of FMF requires a high index of suspicion and is based on the clinical criteria of acute, reversible serosal attacks and family history, when available. The disease is caused by mutations in the MEFV gene located on chromosome 16. The gene codes for a protein named “pyrin” or “marenostrin”4-6. Centola et al.12 showed MEFV was a downstream element in cytokine-induced regulatory cascade. The pyrin is a 781-aminoacid protein that is expressed in neutrophils, monocytes, and eosinophils and in fibroblasts of the skin, synovium, and peritoneum. It is an inhibitor of the inflammatory response; the mutated pyrin gene causes a decreased inhibitory function and an excess of inflammatory attacks4,12. Pyrin may also play a modulatory role in apoptosis signaling. It was found to retard the apoptotic speck protein (ASC)-induced apoptosis in neutrophils. It will be important to determine the effects of mutant forms of pyrin on ASC-induced cell death13. The discovery of the gene and its mutations permit genetic testing to define the diagnosis for FMF3-6,14. MEFV mutations can be shown in only 20-50% of patients. There are at least 26 mutations in the MEFV gene associated with FMF3. Some of the disease-related common mutations are M694V, M680I, V726A, M694I and E148Q. Our case is compound heterozygous M694I and V726A. The most common mutation in Turkey is M694V (41%), and this mutation is associated with a severe phenotype of the disease15. The most important complication of FMF is secondary amyloidosis, and it may develop without overt attacks. The most common site of deposition of amyloid in FMF is the kidney. Amyloid may also be deposited in other organs. The risk of amyloidosis is almost zero in patients with FMF who take colchicine therapy. Renal amyloidosis can cause nephrotic syndrome and renal failure in FMF3,16. In most patients with amyloidosis, the thyroid gland may be asymptomatically involved, but hypothyroidism is not a common finding17. Amyloidosis may also cause secondary diabetes mellitus18. In our patient, the thyroid disease and DM were caused by the autoimmune mechanisms.
Basu et al.\textsuperscript{19} suggested that an early low-grade inflammatory process reflected by elevated levels of prostaglandin F\textsubscript{2α} and interleukin-6 is involved in type 1 diabetes. Recently, Atabek et al.\textsuperscript{2} suggested that the activation of cytokine-induced apoptosis and decreased anti-inflammatory response may cause type 1 diabetes.

The association of type 1 DM and ATD, CD and FMF in our patient may also support that the immune dysregulation in FMF may be involved in the autoimmune mechanism that leads to type 1 diabetes. FMF should be kept in mind in the differential diagnosis of disorders associated with type 1 DM in the presence of suggestive findings.

REFERENCES