A Muslim Family with Several Members with Celiac Disease and Other Autoimmune Disorders

Yulia Treister-Goltzman · Roni Peleg

Abstract The Bedouin community of Israel is a traditional Muslim society. It is characterized by one of the highest rates of population growth in the world. The custom of intermarriage, especially among cousins or within the extended family, is very common because of the community’s tribal structure. The rate of genetic disease in this population is high. We present a Bedouin family in which the father suffers from celiac disease and Hashimoto’s disease, his daughter has celiac and Crohn’s disease, three other children have IgA deficiency, and a half uncle has Crohn’s disease. In describing this family we present the familial nature of these diseases, the age at diagnosis, the marital relationships of the family members and co-morbid diseases and medical conditions. Family doctors can develop and use genograms that can facilitate their understanding of the situation and enable them to develop plans for health promotion and disease prevention counseling in the community.

Keywords Muslim · Bedouin · Genogram · Celiac disease · Autoimmune disease

Introduction

Celiac disease is caused by intolerance to the protein component, gluten, which is found in wheat, rye and barley (oat also can contain a small amount). In celiac patients, exposure to gluten in the diet causes an inflammatory reaction directed at the mucosa of the small intestine, which can lead to mucosal atrophy [1]. The prevalence of celiac is 0.5–1 % and ranges between 0.3 and 2.4 % in different regions [2, 3]. The two primary factors involved in the development of celiac disease are a genetic predisposition and exposure to gluten [2]. Genetic predisposition plays a key role in its development. HLA-DQ2 is expressed in 90 % of celiac patients compared with 30 % in the general population, while HLA-DQ8 [3] is expressed in another 5 %. The prevalence of the disease increases to 10 % in first-degree family members of celiac patients and consanguinity rates reach as high as 75 % in monozygotic twins [2]. The disease can present at any age and its clinical presentation can range from asymptomatic patients to patients with a severe syndrome including diarrhea, abdominal distention, malabsorption, and nutritional deficits. The most common manifestation are diarrhea, weakness, flatulence, abdominal pain, short stature and reduced weight, osteoporosis, elevated hepatic transaminases, anemia and constipation. In adults there is often only a single clinical manifestation such as anemia or elevated hepatic transaminases. This can make the diagnosis difficult.

Some celiac patients are asymptomatic and diagnosed by health surveys conducted in at-risk populations. Risk factors include a family history of celiac disease, Down syndrome, type-I diabetes mellitus, autoimmune thyroiditis, and other autoimmune diseases including autoimmune liver disease, Sjogren’s disease, IgA nephropathy, Turner syndrome, iron-deficiency anemia, elevated hepatic transaminases, and advanced osteoporosis. A high prevalence of celiac disease (9 %) has been seen in patients with IgA deficiency [2, 3].

The natural course of celiac disease varies among individuals. Changes in the immune system and in the...
mucosa can develop at all stages of life and may, apparently, be reversible in certain patients [3].

The recommended serological test at the beginning of the diagnostic work-up is IgA antibodies to tissue transglutaminase (tTG), a test with a sensitivity rate of 94 % and a specificity rate of 97 %. IgA antendomysial antibodies (EMA) have a specificity rate of almost 100 % and can serve as a confirmatory test when there is a possibility of a false positive tTG tests, as in patients with type-I diabetes mellitus or other autoimmune disorders. Deamminated gliadin peptide antibodies can be used in patients with IgA deficiency [3, 4].

The role of serological testing in celiac disease is not only for diagnosis, but for monitoring adherence to treatment with a gluten-free diet [2, 3].

The definitive diagnosis of celiac disease is reached by taking small bowel biopsies during upper endoscopy. Four separate biopsies are taken because of the risk of false positive tests (normal mucosa that appears atrophic because of an incorrect biopsy taking technique), or false negative tests (due to the irregular nature of the mucosal damage in the disease [2, 3].

Treatment for celiac disease is a gluten free diet, which is attained by avoiding consumption of rye, wheat and barley. Nutritional deficiencies, such as iron, vitamin B12, folic acid and oil-based vitamins, should be corrected. Adherence to a gluten free diet can be difficult and lead to a negative effect on quality of life [2, 3].

Untreated celiac disease is associated with increased mortality because of the increased risk for malignancy, including non-Hodgkin’s lymphoma, oral, pharyngeal, esophageal and small intestinal adenocarcinoma [2, 3].

The Bedouin population of the Israeli southern Negev region is a traditional Muslim community. It is characterized by a high rate of annual natural increase at 5.3 %, among the highest in the world. For the most part the Bedouin society is conservative, preserving its values and customs. The custom of intermarriage, especially among cousins or within the extended family or the entire tribe is very common [5].

Family tree is an important tool at the disposal of the family physician. Family tree is a mean to demonstrate the varying clinical manifestations, the different co-morbid conditions, and other expressions of celiac disease as well as other autoimmune diseases among Muslim Bedouin families.

### Family Case Histories

**P.**

P., a 44-year-old man, suffers from hypothyroidism that was diagnosed following Hashimoto’s disease. Six years earlier, as part of routine testing, a mild elevation of hepatic transaminases was detected (AST 47 U/L and ALT 94 U/L) that had not been seen in earlier tests. Upon direct questioning he stated that he had suffered from post-prandial abdominal pain, sometimes accompanied by vomiting, for years.

On physical examination his height was 1.77 m, his weight was 95 kg (BMI—30.3), his blood pressure was 120/80, and his pulse rate was 70. There was no evidence of jaundice or rashes on the skin. His abdomen was non-tender without evidence of enlarged liver or spleen. The rest of the physical examination was without pathological findings. The results of relevant blood tests are shown in Table 1. The laboratory work-up included serological tests for various autoimmune diseases and for viral infections that could cause an elevation in transaminases. Serology testing for celiac disease revealed a positive test for antiendomysial antibody and tissue glutaminase (tTG). The patient was referred for upper endoscopy with biopsy that confirmed the diagnosis of celiac (moderate to severe villogous atrophy) (Fig. 2a). After the patient adhered to a gluten-free diet the transaminases returned to normal levels and the celiac serology became negative.

<table>
<thead>
<tr>
<th>Test</th>
<th>P.</th>
<th>B.</th>
<th>H.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.5</td>
<td>9.0</td>
<td>10.4</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>90.3</td>
<td>75.5</td>
<td>62.5</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>47</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>94</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.3</td>
<td>3.8</td>
<td>4.2</td>
</tr>
<tr>
<td>Iron (g/dl)</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tTG (positive &gt;30 U/ml)</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaminated gliadin peptide (positive &gt;30 U/ml)</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV antibody</td>
<td>Weakly positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA PCR</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>3.2</td>
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tender without localized rigidity; there were no abdominal masses or evidence of enlarged liver or spleen. The rest of the physical examination was without pathological findings. The results of relevant blood tests are shown in Table 1. The initial work-up for diarrhea included stool tests for bacteria and parasites that were negative.

The results of her tests showed a microcytic, hypochromic anemia, compatible with chronic illness, based on the results of iron, ferritin, and transferrin saturation levels. In addition, there was hypoalbuminemia and elevated inflammatory markers, i.e., ESR and CRP. Attempts to treat the iron deficiency with iron supplements did not resolve the anemia. Because of the continuing diarrhea and weight loss B. was treated empirically with metronidazole for a week and the diarrhea stopped for the next month. However, 1 month later the diarrhea recurred and the girl underwent further laboratory testing that showed negative tTG and EMA, but positive deaminated gliadin protein. At this point the girl underwent upper endoscopy and histology showed moderate to severe villous atrophy, characteristic of celiac disease (Fig. 2b). She also underwent colonoscopy, which demonstrated mucosal edema in the cecum and aphthous ulcers in the distal sigmoid colon and the cecum. Based on these findings she was diagnosed with concomitant celiac and Crohn’s disease. B. began a gluten-free diet together with azathioprine therapy with an improvement in the symptoms and a normalization of the blood count. When she became less adherent to the diet the tTG antibodies became positive, even though they were negative at the time of initial diagnosis. It is important to note, that the finding of aphthous ulcers in the colon is not pathognomonic for Crohn’s disease and is sometimes found in celiac disease and in microscopic colitis, so the patient is scheduled for another endoscopy with several biopsies.

H. H., a 25-year-old man, is a half-brother of P. with the same father and a different mother (see Fig. 1, family tree). At age 15 he began to suffer from abdominal pain, vomiting with blood, and a weight loss of 3 kg within a few months. On physical examination his height was 1.55 m (10th percentile) and his weight was 45 kg (5th percentile) with a BMI of 18.7. There was tenderness in the epigastrium and in the right lower abdominal quadrant without abdominal masses or evidence of enlarged liver or spleen. The rest of the physical examination was without pathological findings. The results of blood tests are shown in Table 1. The initial work-up for diarrhea included stool tests for bacteria and parasites that were negative.

The results of laboratory tests showed iron deficiency with a positive serology for *H. pylori*. At first the abdominal pain and anemia were attributed to the presence of *H.*
pylori-induced gastritis, but after successful eradication therapy H. continued to vomit. For that reason upper and lower endoscopy were performed. Duodenal biopsies demonstrated acute and chronic inflammation without villous atrophy, which was inconsistent with celiac disease. Terminal ileum biopsies showed an ulcer with acute inflammation and necrosis, and other findings that were considered to be consistent with Crohn’s disease (Fig. 2c).

Treatment was initiated with azathioprine and later on mesalazine was added. During flare-ups the patient was treated with prednisone. Over the years following the diagnosis the patient suffered from complications of Crohn’s disease including recurrent fistulae and abscesses that involved the pelvic musculature and were treated conservatively and surgically. Severe thickening of the terminal ileal wall led to obstruction of the right ureter and hydrenephrosis that necessitated the insertion of a ureteral stent. Despite treatment with infliximab, 3 years after diagnosis H. had to undergo excision of the terminal ileum and the ascending colon due to severe luminal stenosis. The surgery improved his condition and facilitated subsequent removal of the stent from the right ureter. At present the patient is in stable condition on monotherapy with azathioprine. Following the diagnosis of celiac disease in B., the other children in the family underwent serological testing for celiac disease, which was negative for the rest of the family. It is noteworthy that all the children in the family suffered from iron-deficiency anemia. Three of the five children also had IgA deficiency (Fig. 1).

Discussion

Due to the tribal structure of their population and the high rates of intermarriage, the prevalence of inherited diseases in the Bedouin population is very high. Family doctors have at their disposal important evaluation tools to monitor the genetic characteristics of specific diseases in the family and to detect new cases as soon as possible.

Celiac disease is a multifaceted disease that manifests in all age groups, with varying clinical expression and co-morbidity rates. Detection of the disease and its treatment are important to prevent complications and enhance quality of life. Celiac disease frequently co-exists with autoimmune diseases and other medical problems.

We present an Israeli Muslim Bedouin family in which the father has celiac disease and Hashimoto’s disease, one daughter has celiac disease and Crohn’s disease, three other children have IgA deficiency, and a half-uncle has Crohn’s disease. In this family description the familial character of the diseases is demonstrated along with age characteristics, intermarriage within one family, and co-morbid conditions.

Hashimoto’s disease is an autoimmune disease that has a high rate of co-morbidity with celiac disease [2, 3, 6]. Furthermore, studies have shown that strict adherence to a gluten-free diet leads to a reduction in thyroid antibody titers in addition to the disappearance of celiac antibodies from the serum [6].

The association between celiac disease and inflammatory bowel disease has been reported in the past [7–10]. This association has been attributed to identical immunopathological processes. Both celiac disease and Crohn’s disease are associated with Type 1 immunodeficiency,
which is characterized by reduced apoptosis that causes chronic inflammation [11]. B., who was diagnosed with celiac disease and Crohn’s disease at the age of 10, presents a rare case. A similarly unusual case of an 8-year-old boy who was worked-up for short stature, bloody stool and anemia, and was diagnosed with celiac disease and Crohn’s disease in early childhood, was recently reported [12].

Three other children in the family suffer from IgA deficiency, the most common primary immune deficiency. It is known to be associated with a range of autoimmune disorders including celiac disease. There is a strong association between IgA deficiency and HLA-DQ2, the gene that is found at a very high rate in celiac disease patients. The prevalence of IgA deficiency is 10–15 times higher in celiac disease patients than in the general population [13].

It is also noteworthy that all the children in the nuclear family presented here suffered from iron-deficiency anemia. This may be linked to similar eating habits among the family members or to other environmental factors, but it is also possible that other family members might have celiac disease with iron deficiency. There are reported cases of celiac disease with negative serology that are diagnosed by biopsy only. In one study 19% of patients with biopsy-proven celiac disease had a negative serological work-up and 23% had at least one negative serological test [14]. The false-negative rate increases in the population of patients with IgA deficiency [14], as diagnosed in three of the children in the family presented here. In the cases of high clinical suspicion in IgA deficient patients the recommended diagnostic strategy is checking IgG tTG, deaminated gliadin peptide and performing duodenal biopsies.

Conclusion

We present the case of a family, accompanied by its family tree, in which several members were diagnosed with celiac disease and other autoimmune disorders. They had varying clinical manifestations and ages of diagnosis. Intermarriage is very common in different societies around the world. Family doctors can use genograms to promote health and prevent diseases in these populations.

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Conflict of interest None.

References