Case Report

Anemia and celiac disease in a patient with Down syndrome

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Article received: 22-Feb-08

Abstract

Down syndrome (DS) is associated with an increased risk of celiac disease (CD) than that found in general population. An adolescent girl with DS and CD presenting with severe anaemia is reported.

A 13 year-old girl was admitted to hospital for anaemia and a 4 week-history of asthenia, anorexia, and disturbed bowel habit. Her past medical history was remarkable for hypermenorrhea and occasional vomiting. Heart rate was 106 beats/min and blood pressure 112/48 mmHg. On physical exam she was pale and a systolic murmur was heard. Blood tests depicted a severe hypochromic normocytic anaemia with haemoglobin values of 4,7 g/dL Gastrointestinal bleeding was ruled out on the basis of several image studies and a bone marrow study was also normal. Iron supplement with ferrous sulphate was prescribed. A month later she was readmitted to hospital for abdominal pain, vomiting and diarrhoea. Serum endomysium antibodies and tissue transglutaminase antibodies were found to be positive and an intestinal biopsy confirmed the diagnosis of CD. She was started on a gluten-free diet and the iron supplement was maintained. She subsequently followed a favourable clinical course with cessation of gastrointestinal symptoms and correction of the anaemia.

Several authors have suggested that people with DS should be routinely screened for CD even if they are asymptomatic. Moreover, the existence of CD should be specially considered in people with DS who present with gastrointestinal symptoms or anaemia of unclear aetiologies.

Keywords: Anaemia. Celiac disease. Down syndrome.

Introduction

Celiac disease (CD) is an immune-based bowel disease caused by permanent gluten sensitivity in those who are genetically susceptible (1). Patients with Down syndrome (DS) can have a number of gastrointestinal and immunological disorders involving the gastrointestinal (GI) tract (2). Strong evidence of a link between CD and DS, with prevalence ranging between 4 and 7% (3) has given rise to near-unanimity regarding the need to screen people with DS for CD (4). Most patients with CD have GI symptoms such as abdominal distention, intermittent diarrhea, anorexia, and failure to thrive, though this is not the case for about one third of patients with DS and CD. Moreover, those with CD have more severe anemia, lower levels of iron and calcium, and are in the lower percentiles for weight and height. Iron deficiency anemia refractory to oral iron supplements is the most frequent non-GI manifestation of CD, particularly among adults. Although anemia is a frequent finding in children

diagnosed with CD, there is little evidence of high CD rates in children with anemia (1).

The present case discusses a patient with DS who, though lacking specific GI symptoms, presented with severe anemia which eventually led to a diagnosis of CD.

Clinical Findings

A 13-year-old girl was referred to hospital by her pediatrician for anemia. Her past clinical history included an atrioventricular septal defect operated on at age 1 year, with a small asymptomatic residual interventricular defect (IVD). Onset of the presenting complaint was about four weeks prior to referral, with asthenia, anorexia and disturbed bowel habit in which loose stool alternated with normal stool. She had failed to improve with the prescribed cotrimoxazol treatment. Asthenia had become more marked in the days preceding her referral; her pediatrician had noted the paleness of her skin. Blood test results showed significant anemia, with hemoglobin at 4.7 g/dL, so the patient was immediately hospitalized. A few days before the onset of this complaint she had experienced some vomiting with dark-colored remains. Menstrual flow was reported to be heavy.

Physical examination showed a heart rate of 106 beats/min, arterial blood pressure at 112/48 mmHg, generally preserved health status, pale skin and mucosae, systolic ejection murmur in the mesocardial and pulmonary areas, and no palpable masses or enlarged viscera. No skin lesions were noted, palpable adenopathies were absent, and level of consciousness was normal. Blood workup results at admittance were as follows: hemoglobin 4.5 g/dL; MCV, 80 fl; MCH, 21.6 pg; MCHC, 26.8 g/dL; RDW, 19.8%; WBC, 6,400/mL (75%N, 18%L, 7%M); platelet count, 439,000/mL; reticulocyte index, 7.6%; RBC morphology: anisocytosis, hypochromasia and polychromasia; negative direct Coombs test; serum iron, 17 mg/dL; transferrin, 288 mg/dL; transferrin saturation, 4.6%; ferritin, 63 ng/mL; haptoglobin, 197 mg/dL; total protein, 73 g/L; albumin, 29 g/L. Serum glucose, blood chemistry, urea, creatinin, aminotransferases (AST and ALT), HDL, folic acid, vitamin B12 and coagulation tests were all normal. Myelography was ordered and was normal. Fecal occult blood test was negative. Abdominal ultrasound showed a small amount of free peritoneal fluid with no other abnormal findings. Contrast enema was normal and Tc-99m scintigraphy ruled out Meckel's diverticulum.

The patient received 2 units of packed RBCs, which raised hemoglobin to 10.8 g/dL. Iron sulfate was then prescribed and the patient released home with an initial working diagnosis of normocytic hypochromatic anemia due to probable blood loss. About one month later she was readmitted for a bout of abdominal pain, vomiting and diarrhea. Abdominal ultrasound showed mild ascites and a distended right colon with abundant fluid content. Stool culture and rotavirus antigen test were both negative. Fecal occult blood test was weakly positive. IgA endomysium antibody and IgA tissue transglutaminase antibody tests were positive. Fecal fat excretion results were normal. A gluten-free diet was established and iron sulfate treatment was continued. The patient improved clinically and laboratory results went back to normal.

Discussion

This case report shows yet again that people with DS are predisposed to CD, and highlights anemia as one of the most frequent non-GI manifestations.

CD is an autoimmune disorder triggered in genetically susceptible subjects by an environmental factor, namely gluten, the chief protein found in wheat and similar grains. It affects both adults and children, with rates ranging from 0.3% to 1% for Europeans and populations of European descent. Although the rate of diagnosis has risen, there is a sizeable pool of undiagnosed subjects (5).

A number of different factors are linked to a higher prevalence of CD, including type 1 diabetes, autoimmune thyroiditis, DS, Turner syndrome, Williams syndrome, IgA deficiency, and first-degree relatedness to a celiac patient (1).

Classically, patients with DS are liable to develop GI disorders such as duodenal atresia or Hirschprung disease. Articles published since 1975 state prevalence rates of CD for individuals with DS ranging from 4 to 17% (3). A paper by Carnicer et al. showed a minimum recorded prevalence rate of 13.6% for the catchment area of one specific hospital in Catalonia (6).

Individuals with DS are also more likely to have myeloproliferative blood disorders such as transitional myeloproliferative disorder, acute myeloid leukemia and acute lymphoblastic leukemia (4). In the case under discussion, severe anemia might have given rise to suspicions of this type of hematologic disorder, but that possibility was ruled out by normal WBC and platelet counts and a normal myelogram.

Most children with CD have GI symptoms such as diarrhea, abdominal pain, constipation, abdominal bloating, and delayed growth. A significant share

have non-GI manifestations such as herpetiform dermatitis, hypoplastic enamel of permanent teeth, osteopenia/osteoporosis, short height, delayed puberty, behavioral disorders, and iron-deficiency anemia that fails to respond to oral iron supplementation. While children with DS and CD generally do have GI symptoms, about one third lack them and present with anemia, low blood iron and calcium, and delayed growth in terms of weight and height (1). The asthenia and anorexia symptoms displayed by the patient in the present case had been ascribed to her severe anemia, but her clinical history also showed some GI symptoms in the form of intermittent diarrhea which had probably been underestimated at the time of her first hospitalization.

A definitive diagnosis of celiac disease requires a small bowel biopsy, but serum tests are used to screen patients for this procedure. Many tests are available, including IgG and IgA gliadin antibody, IgA reticulin antibody, and IgA endomysium and IgA tissue transglutaminase antibody tests. The latter two have the highest sensitivity and specificity for celiac disease. Gliadin antibody testing is no longer recommended due to its poor sensitivity and specificity (7).

Susceptibility to CD is partly linked, with a strong association, to certain allele variants of molecules DQ2 and DQ8 in the HLA class II system. The HLA-DQ2 allele is found in 90-95% of patients with CD, and most of the remainder have the HLA-DQ2 allele. As the rate of these alleles is about 30 to 40% for the general population (especially for DQ2), their absence has a very high negative predictive value. CD clearly develops through a number of factors, with DQ2 or DQ8 as an essential component. Other non-HLA genes may also be involved. In patients with DS, CD is mostly associated with DQ2, with a rate of nearly 100%. Some few individuals with DS and CD have the DQ8 allele. No association with CD has been found for any loci on chromosome 21. Hence, the reasons for the link between CD and DS and for the variable prevalence of this condition in patients with DS are still unknown (1, 7).

Diagnostic confirmation of CD routinely requires a small bowel biopsy. For children over 2 years with symptoms suggestive of CD, characteristic biopsy findings coupled with clear resolution of symptoms once diet becomes gluten-free allow a definitive diagnosis of CD with no need for subsequent biopsies (1). The specific nature of patients with DS may make the oral suction capsule biopsy procedure somewhat challenging, so endoscopy should preferably be performed under sedation, with the added advantage of enabling an inspection of the mucosa and multi-site sampling (8).

As the incidence of CD has been shown to be higher for patients with DS than for the general population, it seems sensible to screen all individuals with DS for CD (4). Universal screening has been advocated in the literature, as well as by professional bodies and clinical guidelines. Most screening procedures test for IgA endomysium antibodies and, more recently, IgA tissue transglutaminase antibodies (8). Some authors conclude that further study is needed before universal screening can be considered evidence-based (9). A recent cost-benefit analysis of CD screening in asymptomatic children with DS for prevention of lymphoma also concluded that further data were needed before this practice could be recommended (10).

Treatment for CD is a lifelong gluten-free diet, which entails avoiding all wheat-, rye- or barley-containing foods. Some clinical studies suggest that oats are well tolerated by most patients, and may improve nutritional content and enhance quality of life. Once the diagnosis has been made, patients need to be treated for their usual vitamin and mineral deficiencies (7). In the case at hand, iron supplements were necessary and essential to overcome the patient's low iron levels and anemia. Patients can greatly benefit from patient-support organizations, which provide valuable information particularly on dietary issues (such organizations include Celíacs de Catalunya, www.celiacscatalunya.org, locally, and PACE, www.celiacos.org, for all of Spain). It is very important to keep the patient's diet completely gluten-free to prevent long-term complications such as intestinal adenocarcinoma, enteropathy-associated T-cell lymphoma, and refractory celiac disease.

In conclusion, patients with DS have a higher than average predisposition to CD, which has led a number of authors and institutions to recommend routine screening for them. It is important to suspect CD strongly with these patients, particularly if they display GI symptoms, delayed growth or iron deficiency anemia, so that a relatively early diagnosis can be made and long-term complications staved off.

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