Coeliac Disease as the Cause of Resistant Sideropenic Anaemia in Children with Down's Syndrome: Case Report

Momčilo Pavlović[1], Nedeljko Radlović[2], Zoran Leković[2], Karolina Berenji[3], Zorica Stojšić[4], Vladimir Radlović[2]

[1]Paediatric Department, General Hospital, Subotica, Serbia;
[2]University Children's Hospital, Belgrade, Serbia;
[3]Institution of Public Health, Subotica, Serbia;
[4]Institute of Pathology, School of Medicine, University of Belgrade, Belgrade, Serbia

SUMMARY

Introduction Coeliac disease (CD) is a permanent intolerance of gluten, i.e. of gliadin and related proteins found in the endosperm of wheat, rye and barley. It is characterized by polygenic predisposition, autoimmune nature, predominantly asymptomatic or atypical clinical course, as well as by high prevalence in patients with Down's syndrome (DS) and some other diseases.

Outline of Cases We are presenting a girl and two boys, aged 6-7 ($\bar{X}$=6.33) years with DS and CD recognized under the feature of sideropenic anaemia resistant to oral therapy with iron. Beside mental retardation, low stature and the morphological features characteristic of DS, two patients had a congenital heart disease; one ventricular septal defect and the other atrioventricular canal. In two patients, trisomy on the 21st chromosome pair (trisomy 21) was disclosed in all cells, while one had a mosaic karyotype. All three patients had classical laboratory parameters of sideropenic anaemia: blood Hb 77-89 g/l ($\bar{X}$=81.67), HCT 0.26-0.29% ($\bar{X}$=0.28), MCV 69-80 fl ($\bar{X}$=73), MCH 24.3-30 pg ($\bar{X}$=26.77) and serum iron 2-5 µmol/L ($\bar{X}$=4.0). Beside anaemia and in one patient a mild isolated hypertransaminasemia (AST 67 U/l, ALT 62 U/l), other indicators of CD were not registered in any of the children. In addition, in all three patients, we also detected an increased level of antibodies to tissue transglutaminase (atTG) of IgA class (45-88 U/l) so that we performed endoscopic enterobiopsy in order to reliably confirm the diagnosis of CD. In all three patients, the pathohistological finding of the duodenal mucosa specimen showed mild to moderate destructive enteropathy associated with high intraepithelial lymphocyte infiltration, cryptic hyperplasia and lympho-plasmocytic infiltration of the stroma. In all three patients, the treatment with a strict gluten-free diet and iron therapy applied orally for 3-4 months resulted in blood count normalization and the correction of sideropenia. Serum level of the atTG-IgA, repeated after a 12-month diet, was also normal.

Conclusion CD should be taken into consideration in all cases of sideropenic anaemia resistant to iron oral therapy in children with DS. The diagnosis of CD implicates corresponding pathohistological confirmation, while the treatment of sideropenic anaemia and its complications, beside iron preparations, also requires compliance with a gluten-free diet.

Keywords: coeliac disease; Down's syndrome; sideropenic anaemia

INTRODUCTION

Coeliac disease (CD) is an autoimmune disease caused by gliadin intolerance and related proteins of wheat, rye and barley [1, 2]. It occurs in polygenetically predisposed persons who consume products of these cereal plants; therefore, it is classified under the group of multifactorial diseases [1]. Inherited predisposition is also supported by high variability of the disease incidence in different populations, as well as a high prevalence rate in one-egg twins (80%) and first-degree relatives (10%) [1]. In accordance with its basic nature, it is often associated with other autoimmune diseases [3]. In addition, high incidence is also recorded in persons with inherited immunoglobulin A (IgA) deficit and in patients with Down's syndrome (DS) and other chromosomal aberrations [4].

DS develops due to trisomy on the 21st chromosome pair (trisomy 21) [5, 6]. It occurs at the incidence of 1:700, thus representing the most frequent chromosomopathy and one of the major causes of mental retardation in humans [6, 7]. DS is characterized by numerous and rather typical somatic and visceral malformations, as well as by increased predisposition for autoimmune and other diseases, such as type 1 diabetes mellitus, autoimmune thyreoiditis, severe pneumonia and leukaemia [5, 7].

The association of DS and CD was first described over 30 years ago [8]. Next, it became understood that not only was CD prevalence in DS patients high, but also quite different ranging from 2.5 to 16.7% [9, 10]. Accordingly, some medical associations accepted the attitude that all DS children should undergo serological screening for CD, and thus issued corresponding recommendations and guidelines [11, 12]. However, there are authors whose experience have indicated that a strict application of such an attitude in general might not be entirely justified, i.e. that it should be more selective [13, 14].

Correspondence to:
Momčilo PAVLOVIĆ
Paediatric Department,
General Hospital, Izvorska b.b.,
24000 Subotica, Serbia
momodec@tippnet.rs

Anaemia represents a frequent finding in patients with active CD [15]. As a consequence of a negative nutritional balance and chronic inflammation, it is seen in all clinical forms of the disease [16-18]. Primarily, there is certainly the deficit of iron occurring as the consequence of anorexia, malabsorption and occult bleeding, but also the insufficiency of folic acid, vitamin B_{12} and other factors necessary for normal erythropoesis [16]. In the pathogenesis of sideropenic anaemia of the patients with active CD, a significant role is played by proinflammatory cytokines, particularly interleukin 6 (IL-6) whose activity triggers the release of the hepatic polypeptide hormone hepcidin, which affects the blockage of intestinal resorption of iron and its mobilization from iron storage [17-19]. Having in mind a wide spectre of CD manifestations, it is not rare to detect anaemia as the dominant or only sign of the disease [20]. According to investigations performed in Great Britain, CD has been confirmed in 2-3% of adults with sideropenic anaemia [21]. Accordingly, it has been recommended that every patient with sideropenic anaemia resistant to oral iron therapy should undergo serological screening for CD [21]. However, these tests, i.e. the detection of the present antibodies to tissue transglutaminase (atTG) and serum endomysium, lack absolute sensitivity and specificity, and therefore a diagnostic value, so that they are primarily used for easier recognition of asymptomatic and atypical forms. As the finding of characteristic pathohistological changes of the small bowel mucosa remains not only the "golden standard", but also the only reliable proof of CD presence, therefore, each patient with positive serological screening should also undergo enterobiopsy [11, 22, 23].

CASE REPORT

We are presenting three patients, a girl and two boys, aged 6-7 ($\overline{X}$=6.33) years, with DS and CB recognized by the feature of sideropenic anaemia resistant to oral iron therapy. Beside mental retardation, low stature and morphological characteristics of SD, we also verified a characteristic karyotype in all three children. In addition to a detailed illness history and clinical examination, with a precise measurement of body height and weight, and by comparing the obtained values in relation to standard matched values for age and gender, all the patients also underwent relevant laboratory analyses, such as blood count, serum iron concentration, hepatogram, lipidogram, total protein level and plasma albumin, screening for haemostasis, as well as the examination of stool for occult bleeding [24]. Having in mind the basic disease followed by sideropenic anaemia and occasional constipation, all the patients were also tested for the presence of autoantibodies to tissue transglutaminase atTG of IgA class above 15 U/ml was considered pathologic [21]. To assess TG, we used a commercial test based on recombinant human tissue transglutaminase as an antigen (Orgentec Diagnostics, Mainz, Germany). The diagnosis of CD was based on the criteria by the European Association of Child Gastroenterology, Hepatology and Nutrition of 1989, while the classification of the pathohistological changes of the small bowel mucosa according to the modified Marsh criteria [22, 25, 26].

First patient

A boy aged 6 years, admitted due to abdominal pain and constipation. Mosaic karyotype determined at birth. Height 93 cm (<P5; -14% in relation to mean matched values for age and gender), weight 12.5 kg (-19.90% for height). Since the third year of age, he was treated twice with oral iron preparation due to sideropenic anaemia. Red blood line on admission: (Hb) 89 g/l, haematocrit (HCT) 0.29%, medium corpuscular erythrocyte volume (MCV) 70 fl and mean corpuscular haemoglobin (MCH) 30 pg. Serum iron concentration was 5 μmol/l, and IgA atTG 88 U/ml.

Second patient

A boy aged 6 years, with phenotype and karyotype characterisitic for DS, hospitalized to explain the cause of moderately severe sideropenic anaemia dating from his second year after birth. On three occasions, he was treated with oral iron preparations, but without success. In addition, the child had a confirmed ventricular septal defect. Height 84 cm (<P5; -27.65% in relation to mean matched values for age and gender), weight 9.5 kg (-13.64% for height). On admission: Hb 79 g/l, HCT 0.26%, MCV 80 fl and MCH 24.3 pg. Serum iron concentration was 5 μmol/l, and IgA atTG 60 U/ml.

Third patient

A girl aged 7 years, with characteristic morphologic characteristics of DS, detected due to acute respiratory infection followed by high fever. Karyotype, determined immediately after birth, was trisomy on the 21st chromosome pair in all cells. Cardiological evaluation revealed a congenital heart disease of the type atrioventricular canal. On admission: height 107 cm (<P5; -11.28% in relation to mean matched values for age and gender), weight 17 kg (+5% for height). Hb 77 g/l, HCT 0.29%, MCV 69 fl and MCH 26 pg. Serum iron concentration was 2 μmol/l, and IgA atTG 45 U/ml.

Except for isolated hypertransaminasemia in the first patient (AST 67 U/l, ALT 62 U/l), other laboratory findings were normal.

To reliably confirm CD, we performed endoscopic enterobiopsy in all three patients. Specimens of the mucosa were collected from the area of the descendent duodenum, and were then immersed into a standard formalin solution and sent for pathohistological analysis. In accordance with the up-to-date recommendations, enterobiopsy was done in different areas and from each four tissue specimens were harvested. In all three patients, the histological analysis of the small bowel mucosa specimens revealed mild to moderate non-uniform destructive enteropathy followed by high intraepithelial lymphocyte infiltration, crypt hyper-

doi: 10.2298/SARH1002091P

plasia and marked lympho-plasmocytic infiltration of the stroma. Immediately after the diagnosis, all the patients were treated by a strict gluten-free diet followed by the oral correction of iron deficit in duration of 3-4 months. The applied dietetic therapeutic measures resulted in complete normalization of the haematological findings after 3 to 4 months of treatment. Identically, the control level of IgA atTG, repeated after 12 months, was normal in all three patients. The problem with constipation, however, was not solved. Therefore, additional dietetic therapeutics were undertaken, which, for the time being, gave rather modest results, which is not rare in DS patients.

DISCUSSION

CD is immunologically mediated enteropathy caused by permanent oversensitivity to gluten in genetically predisposed persons [1-4, 11]. It primarily occurs in Caucasians (0.5-1), particularly in certain groups, while in persons of other races it is considerably rarer or exceptionally rare [1-4]. The basis of the disease, as well as its key findings in its diagnostics, is characteristic inflammation of the small bowel mucosa, which withdraws after the introduction of a gluten-free diet [11, 22]. In addition to enteropathy, symptomatic or asymptomatic, the disease is also characterized by different changes involving other organs and organic systems, which sometimes can be most severe [1-4, 11]. In most cases, the disease has a long asymptomatic or clinically atypical course, while the clinical forms of the disease, particularly today, are multiply rarer [2, 3, 4]. One of frequent manifestations of CD, either classical, atypical or asymptomatic, is also sideropenic anaemia. Not rarely, it is registered as the only or basic sign of the disease [20]. The application of serological screening presents a precious method in the recognition of asymptomatic or atypical forms of the disease. However, to obtain reliable confirmation of its presence, enterobiopsy with a corresponding pathohistological finding is unavoidable [11, 21, 22, 23, 25, 27].

DS is the most frequent chromosomopathy in humans [6, 7]. It is characterized by numerous characteristics, as well as by predisposition towards different diseases, among which CD as well [9, 10, 28]. As in other cases, CD in DS can be classical, atypical and asymptomatic, and it can also be manifested by sideropenic anaemia as the only sign of the disease.

The paper presents three children, a girl and two boys, aged 6-7 years ($\overline{X}$=6.33), with DS and CD recognized under the feature of sideropenic anaemia resistant to oral iron therapy. In addition to mental retardation, low stature and other clinical features characteristic for SD, two patients had a congenital heart disease; one ventricular septal defect and the other atrioventricular canal. In two patients, trisomy on the 21st chromosome pair was found in all cells, while one patient had a mosaic karyotype. Blood Hb values were 77-89 g/l ($\overline{X}$=81.67), HCT 0.26-0.29% ($\overline{X}$=0.28), MCV 69-80 fl ($\overline{X}$=73), MCH 24.3-30 pg ($\overline{X}$=26.77), serum iron 2-5 μmol/l ($\overline{X}$=4.0). Beside sideropenic anaemia and mild isolated hypertransaminasemia (AST 67 U/l, ALT 62 U/l) in one patient, we did not register other indicators of CD in any of them. In all three patients, we also confirmed the increased level of antibodies to tissue transglutaminase (atTG) of IgA class (45-88 U/l), so that with the aim to reliably confirm the diagnosis of CD, we also performed endoscopic enterobiopsy. In all three patients, pathohistological analysis of the duodenal mucosa specimens showed mild to moderate destructive enteropathy followed by high intraepithelial lymphocyte infiltration, crypt hyperplasia and lympho-plasmocytic infiltration of the stroma. In all three patients, a strict gluten-free diet and the oral correction of iron deficit in duration of 3-4 months resulted in the normalization of blood count and ferremia. The serum level of atTG-IgA, repeated after 12 months of a strict gluten-free diet, was also normal.

This report presents an illustrative example, not only of the associated occurrence of CD and DS, but also its atypical manifestation. Thus, this should be kept in mind regarding each patient with sideropenic anaemia resistant to oral application of iron, and particularly in children with DS. The diagnosis of CD implies adequate pathohistological confirmation, while the treatment of sideropenic anaemia with its complications, beside iron preparations, also requires compliance with a gluten-free diet.

REFERENCES

1. Walker-Smith JA. Celiac disease. In: Walker AW, Durie PR, Hamilton RJ, Walker-Smith JA, Watkins JB, editors. Pediatric Gastrointestinal Disease. Hamilton: BC Decker Inc; 2000. p.727-46.
2. Mäki M. Celiac disease. In: Kleinman RE, Sanderson IR, Goulet O, Sherman PM, Mieli-Vergani G, Shneider BL, editors. Walker's Pediatric Gastrointestinal Disease. Hamilton: BC Decker Inc; 2008. p.319-27.
3. Rodrigues AF, Jenkins HR. Investigation and management of coeliac disease. Arch Dis Child. 2008; 93:251-4.
4. Farrell RJ, Kelly CP. Celiac spru. N Engl J Med. 2002; 346:180-8.
5. Bonamico M, Mariani P, Danesi HD, Crisogianni M, Failla P, Gemme G, et al. Prevalence and clinical picture of celiac disease in Italian Down syndrome patients: a multicenter study. J Pediatr Gastroenterol Nutr. 2001; 33:139-43.
6. Patton MA. Genetics. In: McIntosh N, Helms PJ, Smyth RL, editors. Forfar & Arneil's Textbook of Pediatrics. Edinburgh: Curchill Livingston; 2003. p.407-41.
7. Descartes M, Carroll AJ. Cytogenetics. In: Kliegman R, Behreman E, Jenson H, editors. Nelson Textbook of Pediatrics. Philadelphia: Saunders; 2007. p.502-17.
8. Bentley D. A case of Down's syndrome complicated by retinoblastoma and celiac disease. Pediatrics. 1975; 56:131-3.
9. Storm W. Prevalence and diagnostic significance of gliadin antibodies in children with Down syndrome. Eur J Pediatr. 1990; 149:833-4.
10. Jansson U, Johansson C. Down syndrome and celiac disease. J Pediatr Gastroenterol Nutr. 1995; 21:443-5.
11. Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, et al. Guideline for the diagnosis and treatment of celiac disease in children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2005; 40:1-19.
12. Cohen W. Health care guidelines for individuals with Down syndrome: 1999 revision. Down Synd Q. 1999; 4:1-15.

13. Swigonski NL, Kuhlenschmidt HL, Bull MJ, Downs SM. Screening for celiac disease in asymptomatic children with Down syndrome: cost-effectiveness of preventing lymphoma. Pediatrics. 2006; 118(2):594-602.
14. Pavlović M, Radlović N, Berenji K, Stojšić Z, Puleva KS Trkulja S. Down syndrome and celiac disease – when to recommend screening? Gut. 2008; 57(Suppl II):A232.
15. Fisgin T, Yarali N, Duru F, Usta B, Kara A. Hematologic manifestation of childhood celiac disease. Acta Haematol. 2004; 111:211-4.
16. Hershko C, Patz J. Ironing out the mechanism of anemia in celiac disease. Haematologica. 2008; 93(12):1761-5.
17. Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Invest. 2004; 113:1271-6.
18. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med. 2005; 352:1011-23.
19. Ganz T, Nemeth E. Hepcidin and regulation of body iron metabolism. Am J Physiol Gastrointest Liver Physiol. 2006; 290:199-203.
20. Mody RJ, Brown PI, Wechsler DS. Refractory iron deficiency anemia as the primary clinical manifestation of celiac disease. J Pediatr Hematol Oncol. 2003; 25:169-72.
21. British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia. Gut. 2000; 46(Suppl 4):1-5.
22. Walker-Smith JA, Guandalini S, Schmitz J, Schmerling DH, Visakorpi JK. Revised criteria for diagnosis of coeliac diseae. Arch Dis Child. 1990; 65:909-11.
23. AGA Institute. AGA Institute medical position statement on the diagnosis and management of celiac disease. Gastroenterology. 2006; 131(6):1977-80.
24. Needlman RD. Growth and development. In: Bermasn RE, Kliegman RM, Arvin AM, editors. Nelson Textbook of Pediatrics. Philadelphia: WB Saunders Comp; 1996. p.30-72.
25. Radlović N. Coeliac disease in children – modern diagnostic approach. Srp Arh Celok Lek. 2008; 136(Suppl 2):152-7.
26. Marsh MN. Gluten, major histocompatibility complex, and the small bowel. A molecular and immunobiological approach to the spectrum of gluten sensitivity ("celiac sprue"). Gastroenterology. 1992; 102:330-54.
27. Fraser JS, Ciclitira PJ. Pathogenesis of celiac disease: implications for treatment. World J Gastroenterol. 2001; 7(6):772-6.
28. Henderson A, Lynch S, Wilkinson S. Adults with Down's syndrome: the prevalence of complications and health care in the community. Br J Gen Pract. 2007; 57(534):50-5.

Целијачна болест као узрок резистентне сидеропенијске анемије код деце са Дауновим синдромом – приказ три болесника

Момчило Павловић[1], Недељко Радловић[2], Зоран Лековић[2], Каролина Берењи[3], Зорица Стојшић[4], Владимир Радловић[2]

[1]Дечје одељење, Општа болница, Суботица, Србија;
[2]Универзитетска дечја клиника, Београд, Србија;
[3]Завод за јавно здравље, Суботица, Србија;
[4]Институт за патологију Медицински факултет, Универзитет у Београду, Београд, Србија

КРАТАК САДРЖАЈ

Увод Целијачна болест је трајни облик неподношења глутена, односно глијадина и сродних протеина који се налазе у ендосперму пшенице, ражи и јечма. Одликују је полигенска предиспозиција, аутоимуна природа, нетипични клинички ток углавном без симптома и висока преваленција код болесника са Дауновим синдромом и још неким обољењима.

Приказ болесника Приказујемо девојчицу и два дечака узраста од шест до седам година (просечно 6,33 године) са Дауновим синдромом и целијачном болешћу препознатом под сликом сидеропенијске анемије резистентне на оралну терапију гвожђем. Поред менталне ретардације, ниског раста и морфолошких обележја типичних за Даунов синдром, два болесника су имала урођену срчануману (један вентрикуларни септални дефект, а други атриовентрикуларни канал). Код два болесника тризомија 21. пара хромозома је нађена у свим ћелијама, док је код једног кариотип био типа мозаика. Код сва ти болесника забележени су класични лабораторијски показатељи сидеропенијске анемије: *Hb* крви 77-89 *g/l* ($\bar{X}$=81,67 *g/l*), *HCT* 0,26-0,29% ($\bar{X}$=0,28%), *MCV* 69-80 *fl* ($\bar{X}$=73 *fl*), *MCH* 24,3-30 *pg* ($\bar{X}$=26,77 *pg*) и гвожђе у серуму 2-5 *μmol/l* ($\bar{X}$=4,0 *μmol/l*). Осим анемије и код једног болесника благе изоловане хипертрансаминаземије (*AST* 67 *U/l*, *ALT* 62 *U/l*), ни код једног од њих нису забележени други показатељи целијачне болести. Такође, код сва три болесника је утврђен и повишен ниво антитела на ткивну трансглутаминазу (*atTG*) *IgA* класе (45-88 *U/l*), те им је, ради поуздане дијагнозе целијачне болести, урађена ендоскопска ентеробиопсија. Патохистолошком анализом узорака дуоденалне слузокоже у сва три случаја установљена је блажа до умерена деструктивна ентеропатија праћена високом интраепителном лимфоцитном инфилтрацијом, хиперплазијом крипти и лимфо-плазмоцитном инфилтрацијом строме. Уз стриктну дијету без глутена и оралну примену гвожђа током три-четири месеца, код сва три болесника крвна слика се нормализовала, а сидеропенија кориговала. Ниво *atTG IgA* класе у серуму након годину дана дијете такође је био нормалан.

Закључак Целијачну болест треба имати у виду у свим случајевима сидеропенијске анемије резистентне на оралну терапију гвожђем код детета са Дауновим синдромом. Дијагноза целијачне болести подразумева одговарајућу патохистолошку потврду, док лечење сидеропенијске анемије, као њене компликације, поред препарата гвожђа, захтева и доследну примену дијете без глутена.

Кључне речи: целијачна болест; Даунов синдром; сидеропенијска анемија

Примљен • Received: 19/02/2009 **Прихваћен • Accepted:** 27/03/2009