COELIAC DISEASE

# The coexistence of Down syndrome and a triad consisting of: coeliac disease, insulin dependent diabetes mellitus and congenital hypothyroidism

**Kamil K Hozyasz, Beata Pyrzak and Marta Szymanska**

The incidence of immune mediated diseases and hormonal disturbances is increased in people with Down syndrome. However, there are only three published reports of the coexistence of thyroid disorder, insulin dependent diabetes mellitus and coeliac disease in children with Down syndrome. Here we describe a young male with Down syndrome who was diagnosed with congenital hypothyroidism, diabetes mellitus, and coeliac disease. The role of serological screening for coeliac disease in children with Down syndrome is discussed.

## Introduction

Coeliac disease (CD) is a chronic, immune mediated disorder characterised by permanent intolerance to gluten, which is present in wheat, barley, and rye[1]. The classic form of CD includes malabsorption, diarrhoea, and weight loss. However, the clinical picture of the disease varies widely from life-threatening conditions to cases that are asymptomatic. Coeliac disease is also associated with many other autoimmune disorders[1-3].

Previously perceived as a relatively rare condition, recent population-based screening studies have shown that the prevalence of coeliac disease is high (e.g. 1-10 patients per 1000 individuals)[3]. The first stage of screening for CD is to determine the presence of serological markers. The gold standard for the diagnosis of a gluten-dependent enteropathy depends upon biopsy of the small bowel[3].

Down syndrome is the most common chromosome anomaly recognised in humans. In 1975 Bentley reported, for the first time, the occurrence of coeliac disease in a young male with Down syndrome[4]. Since then it has been estimated that 3.2% to 16.9% of children with Down syndrome have CD[5,6].

Several studies have shown an increased incidence of both insulin dependent diabetes mellitus (IDDM) and thyroid disorders in CD patients [2,7], as well as in Down syndrome cases[8,9]. Furthermore, coeliac disease and thyroid disorders are now recognised as important concerns in Down syndrome clinical care[9].

In the present study, the authors report a patient with coexisting Down syndrome, coeliac disease, hypothyroidism, and insulin dependent diabetes mellitus.

## Patient description

A young male with Down syndrome, born weighing 3400g, from the third twin pregnancy in his family (his twin sister was born without any chromosomal abnormalities). Newborn blood spot thyroid stimulating hormone (TSH) screening detected an elevated hormone level 119,1 mIU/L; (Norm: <15 mIU/L). Endocrinological investigations at birth confirmed congenital hypothyroidism (free T3 0,57 pmol/L; Norm: 2,4 – 5,7 pmol/L and free T4 <0,08 ng/dL; Norm: 0,62 – 1,63 ng/dL) and treatment with thyroxine was initiated. The patient was not breast-fed. Gluten was introduced into the diet around the ninth month. At the age of 19 months the boy showed symptoms of polyuria and polydipsia. At the same time, IDDM was diagnosed and regular insulin therapy was initiated. No clinical features suggesting enteropathy were observed.

Department of Paediatrics, Institute of Mother and Child, Kasprzaka 17a, 01-211 Warsaw, Poland

**Correspondence to** Kamil K. Hozyasz, MD • email: kamil.hozyasz@imid.med.pl

doi:10.3104/case-studies.2062

| Patient (number) | Age of mother at birth (years) | Sex | Weight at birth (g) | Age at diagnosis of coeliac disease (years) | Signs and symptoms suggesting coeliac disease | Age of diagnosis of IDDM (years) | Other endocrinal disturbances | Country of origin |
|---|---|---|---|---|---|---|---|---|
| 1 | 43 | F | no data | 17 | bouts of diarrhoea, loss in bodyweight | 19 | Graves' disease, secondary amenorrhoea | Switzerland[10] |
| 2 | 27 | M | 2.900 | 8 | flatulence, abdominal pain | 3 | autoimmunological hypothyroidism | Italy[11] |
| 3 | no data | M | no data | 16 | no* | 16 | autoimmunological Hashimoto thyroiditis | Turkey[12] |
| 4 | 36 | M | 3.400 | 4 | no* | 2 | congenital hypothyroidism | Poland |

* Coeliac disease diagnosed due to screening programme

Table 1 | **Main characteristics of described patients with Down syndrome and coexisting coeliac disease-IDDM thyroid disorder triad**

He was screened for coeliac disease, as are other children with insulin dependent diabetes mellitus (IDDM) with poor glycaemic control. His serum was positive for the following antibodies: IgA antiendomysial (IgA EMA; titre of 1:160), IgG antiendomysial (IgG EMA; 1:80), IgA tissue transglutaminase (IgA tTG; 750,3AU/mL, Norm: 0-20AU/mL), IgA antireticulin (IgA ARA; 1:50), IgG antireticulin (IgG ARA; 1:5); and negative for IgG tissue transglutaminase (IgG tTG) and IgA antigliadin (IgA AGA). Histological examination of the duodenal mucosa demonstrated total villous atrophy, with crypt hyperplasia, an increased number of intraepithelial lymphocytes and lamina propria inflammation, confirming the diagnosis of CD. The serological antibodies disappeared after exclusion of gluten from the diet. The treatment of coeliac disease with gluten-free diet improved glycaemic control in the patient.

## Discussion

This patient is the first described case of Down syndrome coexisting with congenital hypothyroidism, Coeliac disease, and insulin dependent diabetes mellitus.

Congenital hypothyroidism has been reported to occur much more frequently in newborns with Down syndrome than in the general population[8,9]. Patients with Down syndrome who demonstrate the coexistence of the CD-IDDM-thyroid disorder triad, display very diverse clinical symptoms[10-12], (see TABLE 1) and not all patients display clinical signs of coeliac disease.

Considering that both gastroduodenoscopy and small bowel capsule biopsy are invasive procedures, prior screening of individuals at risk of coeliac disease should be performed by serological testing. IgAEMA and IgA tTG are reported to be the most sensitive and specific serological markers in coeliac patients without immunoglobulin A (IgA) deficiency[13]. IgA deficiency can give false negative results for IgA EMA and IgA tTG (total IgA levels or IgG EMA/IgG tTG must be measured simultaneously). In the presented patient, both markers reached high values. IgA AGA and IgG AGA are less specific immunological markers of coeliac disease in patients with Down syndrome[6,13].

Recently, Swigonski et al.[14] recommend that asymptomatic children with Down syndrome should not be screened for coeliac disease. It is difficult to accept this opinion. In the general population, the rate of asymptomatic to symptomatic CD cases is up to 8:1[3,17]. It is therefore no surprise that some examinations displaying clinical and growth characteristics of individuals with Down syndrome do not distinguish between children with and without coeliac disease[15]. The subtle symptoms of CD can overlap with the natural history of Down syndrome[6,9]. Both children with coeliac disease as well as those with Down syndrome tend to have constipation, diarrhoea, and short stature. Furthermore, children with Down syndrome may be less able to articulate their complaints. Even asymptomatic coeliac disease can cause both immunological deregulation and nutritional deficiencies[3,16,17]. The combination of immunological disorders, like CD and IDDM, may affect the functioning of the immune system[18]. It should be noted that early diagnosis and treatment may reduce the mortality risk in patients with coeliac disease[19]. In some patients with thyroid disorders, the diagnosis of coeliac disease and elimination of gluten from the diet may lead to increased efficiency of hormonal therapy[2]. Some, but not all studies have demonstrated that the treatment of patients with IDDM and coexisting CD with a strict gluten-free diet improves glycaemic control[7,20].

## Conclusion

There are no uniform recommendations for coeliac disease screening in children with Down syndrome[9]. As the disease could develop with age, the proposed periodic screening for CD of all children with Down syndrome[6,20], including those not displaying signs suggesting the coexistence of CD, is worthy of notice.


1. Sollid LM, Jabri B. Is celiac disease an autoimmune disorder? *Current Opinion in Immunology*. 2005:17(6);595-600. doi: 10.1016/j.col.2005.09.015
2. Sategna-Guidetti C, Volta U, Ciacci C, Usai P, Carlino A, De Franceschi L, Camera A, Pelli A, Brossa C. Prevalence of thyroid disorders in untreated adult celiac disease patients and effect of gluten withdrawal: an Italian multicenter study. *American Journal of Gastroenterology*. 2001:96(3);751-757.
3. Chand N, Mihas AA. Celiac disease: current concepts in diagnosis and treatment. *Journal of Clinical Gastroenterology*. 2006:40(1);3-14.
4. Bentley D. A case of Down's syndrome complicated by retinoblastoma and celiac disease. *Pediatrics*. 1975:56(1);131-133.
5. Jansson U. Johansson C. Down syndrome and celiac disease. *Journal of Pediatric Gastroenterology and Nutrition*. 1995:21(4);443-445.
6. Mackey J, Treem WR, Worley G, Boney A, Hart P, Kishnani PS. Frequency of celiac disease in individuals with Down syndrome in the United States. *Clinical Pediatrics*. 2001:40(5);249-252.
7. Hansen D, Brock-Jacobsen B, Lund E, Bjorn C, Hansen LP, Nielsen C, Fenger C, Lillevang ST, Husby S. Clinical benefit of a gluten-free diet in type I diabetic children with screening-detected celiac disease: a population-based screening study with 2 years' follow-up. *Diabetes Care*. 2006:29(11);2452-2456. doi: 10.2337/dc06-0990
8. Cutler AT, Benezra-Obeiter R, Brink SJ. Thyroid function in young children with Down syndrome. *American Journal of Diseases of Childhood*. 1986:140(5);479-483.
9. Cohen WI. Current dilemmas in Down syndrome clinical care: celiac disease, thyroid disorders, and atlanto-axial instability. *American Journal of Medical Genetics Part C (Seminars in Medical Genetics)*. 2006:142C(3);141-148. doi: 10.1002/ajmg.c.30102
10. Ruch W, Schurmann K, Gordon P, Burgin-Wolff A, Girard J. Coexistent coeliac disease, Graves' disease and diabetes mellitus type 1 in a patient with Down syndrome. *European Journal of Pediatrics*. 1985:144(1);89-90.
11. Rosso C, Cecere G, Concolino D, Baserga M. Diabete, ipotiroidismo e celiachia nella sindrome di Down. *Minerva Pediatrica*. 1997:49(10);483-485.
12. Kinik ST, Ozcay F, Varan B. Type I diabetes mellitus, Hashimoto's thyroiditis and celiac disease in an adolescent with Down syndrome. *Pediatrics International*. 2006:48(4);433-435. doi: 10.1111/j.1442-200X.2006.02238.x
13. Hansson T, Dahlbom I, Rogberg S, Nyberg B-I, Dahlstrom J, Anneren G, Klareskog L, Dannaeus A. Antitissue transglutaminase and antithyroid autoantibodies in children with Down syndrome and celiac disease. *Journal of Pediatric Gastroenterology and Nutrition*. 2005:40(2);170-174.
14. Swigonski NL, Kuhlenschmidt HL, Bull MJ, Corkins MR, Downs SM. Screening for celiac disease in asymptomatic children with Down syndrome: cost-effectiveness of preventing lymphoma. *Pediatrics*. 2006:118(2);594-602. doi: 10.1542/peds.2005-2123
15. Book L, Hart A, Black J, Feolo M, Zone JJ, Neuhausen SL. Prevalence and clinical characteristics of celiac disease in Downs syndrome in a U.S. study. *American Journal of Medical Genetics*. 2001:98(1);70-74. doi: 10.1002/1096-8628(20010101)98:1<70::AID-AJMG1002>3.0.CO;2-G
16. Brar P, Kwon GY, Egbuna II, Holleran S, Ramakrishnan R, Bhagat G, Green PH. Lack of correlation of degree of villous atrophy with severity of clinical presentation of coeliac disease. *Digestive Liver Disease*. 2007:39(1);26-29.
17. Zimmer K-P. Klinische Bedeutung nichtklassischer Zoliakieformen. *Deutches Ärzteblatt*. 2001:98(49);A3285-A3292. http://www.aerzteblatt.de/v4/archiv/pdf.asp?id=29756
18. Nilsson L, Kivling A, Jalmelid M, Magnusson KF, Faresjo M. Combinations of common chronic paediatric diseases deviate the immune response in diverging directions. *Clinical Experimental Immunology*. 2006:146(3);433-442.
19. Peters U, Askling J, Gridley G, Ekbom A, Linet M. Causes of death in patients with celiac disease in a population-based Swedish cohort. *Archives of Internal Medicine*. 2003:163(13);1566-1572.
20. Sciberras C, Vella C, Grech V. The prevalence of coeliac disease in Down's syndrome in Malta. *Annals of Tropical Paediatrics*. 2004:24(1);81-83. doi: 10.1179/027249304225013268


Received: 2 October 2007; Accepted subject to revision: 9 October 2007; Revised version accepted: February 2009; Published online: April 2010