

# Physiologic hypercortisolism at onset of celiac disease in a girl

## A case report

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### Abstract

**Rationale:** Celiac disease (CD) is an autoimmune disorder induced by dietary gluten in genetically predisposed subjects. Activation of the hypothalamic-pituitary-axis (HPA) can occur in patients with CD; however, this condition has never been described in overweight/obese CD children.

**Patient concerns:** A 12-year-old girl with CD was admitted with mild acanthosis nigricans of the armpits, groin and neck. Recently, extra fat appeared around the neck, and moon face was observed. The abdomen was globular and meteoric, treatable and not aching. She weighed 64 kilos (75°–97° percentile) and was 146 centimeters tall (3°–25° percentile) with a body mass index of 30 kg/mq<sup>2</sup>. Laboratory tests revealed hypertriglyceridemia and positive anti-transglutaminase IgA. Cortisoluria was determined. Serum ACTH was normal.

**Diagnoses:** This paper reports a case of a girl with CD in which both obesity and activation of HPA activity were noted.

**Interventions:** During follow-up, anti-transglutaminase IgA increased to 201.5 UI/mL. The patient was positive for anti-endomysium antibodies, and the HLA DQ2 haplotype was identified, confirming a diagnosis of CD.

**Outcomes:** Despite a gluten-free diet, obesity and hyperadrenalism persisted, and anti-transglutaminase antibodies remained elevated. In addition, high cortisoluria persisted. A high-dose suppression dexamethasone test (8 mg) produced negative results with a morning cortisol value of 1 ng/mL, suggesting the diagnosis of pseudo-Cushing's syndrome.

**Lessons:** This case highlights that the first manifestation of CD could be being overweight, and this finding seems to support the need to prescribe laboratory tests for CD not only to children with failure to thrive, as commonly recommended, but also to those with increased body weight.

**Abbreviations:** BMI = body mass index, CD = celiac disease, GFD = gluten-free die, HPA = hypothalamic-pituitary-axis.

**Keywords:** celiac disease, Cushing's syndrome, gluten-free diet, overweight, pseudocushing syndrome

## 1. Introduction

Celiac disease (CD) is an autoimmune disorder induced by dietary gluten in genetically predisposed subjects.<sup>[1]</sup> CD was initially thought to be a gastrointestinal disease of young children characterized by severe chronic diarrhea and significant failure to thrive depending on intestinal malabsorption (i.e., classic CD). Over time, particularly when serologic tests for CD became available, it was revealed that CD could occur at any age and be

asymptomatic (i.e., silent CD) or associated with multiple extraintestinal clinical problems, including autoimmune, endocrine, and neurological diseases.<sup>[2]</sup> Moreover, CD is associated with overweight or obese individuals (i.e., atypical CD).<sup>[3]</sup> At presentation, overweight/obesity was diagnosed in 8.8%–20.8% of children in various retrospective studies.<sup>[4–10]</sup> Moreover, in some cases, the introduction of gluten-free diet (GFD) was not followed as expected by a progressive normalization of the body weight but by an increase in body mass index (BMI). In the study by Valletta et al,<sup>[7]</sup> after initiation of GFD, 21% and 4% of the studied patients were classified as overweight and obese, respectively.

Depending on the degree and duration of weight gain, overweight and obesity can progressively cause and/or exacerbate a great number of co-morbidities, including type 2 diabetes mellitus, hypertension and cardiovascular diseases, dyslipidemia, liver dysfunction, respiratory and musculoskeletal disorders, subfertility, psychosocial problems, and certain types of cancer.<sup>[11]</sup> Moreover, some studies indicate activation of the hypothalamic-pituitary-axis (HPA) can occur, potentially lead to the development of physiologic (i.e., non-neoplastic) hypercortisolism (formerly named pseudo-Cushing's syndrome).<sup>[12]</sup> However, these conditions were never described in overweight/obese CD children. This study reports a case of a girl with CD in which both obesity and HPA activity were noted.

Editor: N/A.

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:36(e12160)

Received: 26 April 2018 / Accepted: 8 August 2018

<http://dx.doi.org/10.1097/MD.00000000000012160>

## 2. Case

### 2.1. Presenting concerns

A 12-year-old girl was admitted to the Santa Maria Hospital of Terni for weight gain and purple striae on the abdomen and thighs. No significant disease occurred in the previous years. She exhibited regular development except for being overweight since the early infancy. Her maternal grandparents had a history of adult-onset type 2 diabetes mellitus, and the remaining family history was not significant. She was born at a weight of 3090 g and was weaned at the age of 10 months. At 6 years of age, hypercholesterolemia was first identified (total cholesterol 217 mg/dL, HDL cholesterol 259 mg/dL). In the previous 2 months, additional weight gain of 6 kg was observed in the absence of dietary changes with a deposition of fat at the neck base. She had not reached menarche yet and had a Tanner P3B3 pubertal status.

Management of this case was approved by the Ethics Committee of Ospedale Santa Maria of Terni, Italy. Written informed consent was obtained from the parents of the patient and the patient.

### 2.2. Clinical findings

At physical evaluation, general conditions were good. Mild acanthosis nigricans of the armpits, groin, and neck were noted. Extra fat recently appeared around the neck, and moon face was observed.

She had abundant subcutaneous tissue and a mild hirsutism. The abdomen was globular and meteoric, treatable, and not aching. She weighed 64 kg (75<sup>o</sup>–97<sup>o</sup> percentile) and was 146 cm tall (3<sup>o</sup>–25<sup>o</sup> percentile) with a BMI of 30 kg/mq<sup>2</sup>. Her waist circumference was 90 cm, and she had an excess weight of 25.2 kg (+64.4%) calculated based on an ideal weight of 39.1 kg. Blood pressure was normal (100/70 mm Hg).

### 2.3. Diagnostic focus and assessment

At first evaluation, full blood count was within the normal range except for slight leukocytosis (13,000 leukocytes/mm<sup>3</sup>) and hypertriglyceridemia (total cholesterol of 218 mg/dL, with an HDL fraction of 56 mg/dL, an LDL fraction of 108 mg/dL, and triglycerides of 268 mg/dL). Fasting glycemia was normal (93 mg/dL). In addition, liver transaminases (SGOT 22 UI/L, SGPT 24 UI/L), electrolytes (Na mEq/L, K 3.8 mEq/L, Cl 199 mEq/L), creatine-phosphokinases (104 UI/L), pseudocholinesterasis (6692 U/L), thyroid profile (FT4 1.14 ng/dL, TSH 2.81 μU/mL), and ferritin (27 ng/mL) were normal.

At the screening for CD, total IgA levels were 188 mg/dL, and antitransglutaminase IgA was 62.10 UA/mL (normal values, <4 UA/mL). Abdominal ultrasound results were normal. Using the glucose load curve, hyperinsulinism was identified with a basal insulin of 26 μL and conserved glucose tolerance. For the physical characteristics of moon face and striae rubra, cortisoluria was determined and resulted in a 24-hour value of 463 μg/24 h (normal range, 20.9–292.3 μg/24 h). Serum ACTH was normal (24.5 pg/mL) as assessed by two determinations.

### 2.4. Therapeutic focus and assessment

At the 1-month follow-up visit, antitransglutaminase IgA was increased to 201.5 UI/mL. The patient was positive for antiendomysium antibodies, and the HLA DQ2 haplotype was identified, confirming a diagnosis of CD and sparing the gut

biopsy according to the European Society of Pediatric Gastroenterology, Hepatology and Nutrition 2012 criteria.<sup>[9]</sup>

### 2.5. Follow-up and outcomes

At the 6-month follow-up after GFD, her weight was 70.5 kg, and her height was 148 cm with a BMI of 32 kg/mq<sup>2</sup>. Serum IgA levels were reduced but still high (104.7 UI/mL). Abdominal ultrasound was normal.

At the 1-year follow-up, obesity and hyperadrenalism persisted with a weight of 71 kg, height of 151 cm and a waist circumference of 91 cm. Mild fatty liver disease and fatty degeneration of the pancreatic tail were observed via ultrasound. Antitransglutaminase antibodies persisted at high levels (74 UI/mL). However, the interview with the girl's mother revealed that some traces of gluten could not be excluded from the foods from the school canteen. Cortisoluria persisted at high levels. A high-dose suppression dexamethasone (8 mg) test was performed, revealing a negative result with a morning cortisol level of 1 ng/mL, excluding adrenal hyperplasia, pituitary adenoma or ectopic ACTH production. Overall results were suggestive of pseudo-Cushing's syndrome.

### 2.6. Timeline

Clinical findings and laboratory data upon admission confirmed our suspicion of CD associated with a pseudo-Cushing's syndrome. Follow-up at 6 months and 1 year after the beginning of GFD confirmed the positive outcome.

## 3. Discussion

Overweight/obesity was previously reported in CD patients, particularly in older children and adults. However, these conditions are rarely noted as isolated manifestations. To explain increased body weight, the so-called compensatory hypothesis, that is, the increased absorption of nutrients by the distal intestinal segments not damaged by the autoimmune process, has been proposed.<sup>[13]</sup> Overweight/obesity has been ascribed to an overcompensation phenomenon, a condition similar to that occurring after surgical removal of a upper portion of the small intestine. The compensatory tract of the intestine increases with increasing age.<sup>[3]</sup> This phenomenon potentially explains why CD in younger infants generally presents with failure to thrive, whereas overweight/obesity is diagnosed in older children, adolescents and adults. The case reported here suggests that being overweight can be the first manifestation of CD and underscores the need to prescribe laboratory tests for CD not only to children with failure to thrive, as commonly recommended,<sup>[14]</sup> but also to those with increased body weight.

As also evidenced by this case, in overweight/obese children with CD, GFD does not assure normalization of body weight. In contrast, initiation of GFD can have a paradoxical effect and lead to a further increase in BMI. The negative impact of GFD is mainly ascribed to the poor palatability of the GFD that can lead to consumption of greater amounts of hyperproteic and hyperlipidemic foods with increased caloric intake.<sup>[15,16]</sup> This finding indicates that particular attention should be given to the composition of GFD prescribed to children with CD to avoid an undesirable increase in caloric intake.

Regarding the girl described herein, however, overweight/obesity were accompanied by physiologic (non-neoplastic) hypercortisolism (formerly named pseudo-Cushing's syndrome),

a condition that may cause some of the clinical features of the classic Cushing's syndrome and in this case was the most important clinical manifestation of CD. Physiologic (non-neoplastic) hypercortisolism is a relatively rare condition that has been mainly reported in adults suffering from diseases that can activate the HPA axis through psychological, inflammatory, and chemical stressors.<sup>[17]</sup>

However, hypercortisolism has been described also in other clinical conditions, such as uncontrolled diabetes, chronic intense exercise, pregnancy and obesity.<sup>[17]</sup> In patients with increased body weight, an increase in metabolic clearance of cortisol has been described.<sup>[18,19]</sup> This increased clearance is thought to stimulate HPA activity, leading to hypercortisolism.<sup>[20,21]</sup> Moreover, overweight/obesity is frequently associated with metabolic syndrome, a condition in which activation of the HPA axis has been demonstrated.

Constantinopoulos et al<sup>[22]</sup> reported that baseline serum cortisol and urinary free cortisol were significantly increased in obese adult patients with metabolic syndrome compared with those without metabolic syndrome and normal subjects. In the case reported herein, only three of the International Diabetes Federation criteria for the definition of metabolic syndrome in children aged 10 to 16 years were evidenced, including waist circumference >90th percentile and hypertriglyceridemia (>150 mg/dL) and hypercholesterolemia (281 mg/dL).<sup>[23]</sup> In contrast, blood pressure and serum glucose concentrations were within normal limits. However, no consensus exists regarding the number of parameters to use for the definition of metabolic syndrome in pediatric patients.<sup>[23]</sup> Moreover, the girl had a family history of type 2 diabetes mellitus. In addition, waist circumference >90th percentile is considered essential to define metabolic syndrome in children aged 6 to 10 years.<sup>[24]</sup> It seems therefore possible that the increased in body weight caused several metabolic problems that subsequently activated hypercortisolism.

When our patient was admitted to the hospital, she was significantly overweight with some of the classic signs of Cushing's syndrome, such as moon face, deposition of fat around the neck and purple striae on the abdomen. The differentiation of classic Cushing's syndrome from physiologic (non-neoplastic) hypercortisolism was possible on the basis of the results of cortisoluria and single serum cortisol value at midnight followed by an overnight high dosage dexamethasone test. A single cortisol value at midnight followed by overnight high-dosage dexamethasone test is acceptable for a confirmation and diagnostic differentiation between pituitary and adrenal causes of hypercortisolemia.

#### 4. Conclusion

Physiologic hypercortisolism is typically a transient disease that is resolved after treatment of the casual condition. In this case, despite GFD, hypercortisolism did not disappear, and we confirmed with further tests that CD can be associated with hyperadrenalism and with a diagnosis of pseudo-Cushing's syndrome. Thus, in presence of significant obesity, laboratory tests for CD should be recommended.

#### 5. Patients' parents' perspective

We are very grateful to the pediatricians for the diagnostic and therapeutic approach, which was associated with a favorable clinical evolution.

#### 6. Informed consent

The patients' parents provided their written informed consent for the publication of this study and the patient signed to confirm her consent.

#### Author contributions

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