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Parathyroid adenoma with coeliac disease: primary or quaternary hyperparathyroidism?

Gruczolak przytarczyc i choroba trzewna: pierwotna czy czwartorzędowa nadczynność przytarczyc?

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Abstract

Coeliac disease is a gluten-sensitive enteropathy of varying severity. Osteomalacia and hypocalcaemia can result from malabsorption of vitamin D and calcium, which, in turn, can lead to secondary hyperparathyroidism. If coeliac disease remains untreated for long, tertiary hyperparathyroidism can also develop through autonomy of the parathyroid glands via chronic stimulation. Primary hyperparathyroidism also has been reported in some cases of coeliac disease. We report the case of an adolescent with coeliac disease presenting with severe hypercalcaemia from a parathyroid adenoma. A 14 year-old girl was admitted to our department for delayed puberty and growth retardation. Laboratory examination revealed iron deficiency anaemia, low 25OH vitamin D level (7 ng/ml), high parathyroid hormone level (PTH) (955 pg/ml), and hypercalcaemia (13.4 mg/dl). Endoscopic biopsy was compatible with gluten enteropathy. Endomysium antibody was positive. A gluten-free diet was started. Her calcium returned to normal after excision of the parathyroid adenoma. After four months of the gluten-free diet, she began to mature, and puberty began with development of breasts and axillary-pubic hair growth. It has been suggested that autonomous four-gland hyperplasia or tertiary hyperparathyroidism may progress to adenoma formation, and that this should be termed "quaternary hyperparathyroidism". More studies are required to explain the relationship between coeliac disease and hyperparathyroidism. **(Pol J Endocrinol 2012; 63 (1): 56–58)**

Key words: *coeliac disease, parathyroid adenoma, gluten intolerance*

Streszczenie

Choroba trzewna jest enteropatią glutenowrażliwą o różnym stopniu ciężkości. W wyniku zaburzeń wchłaniania witaminy D i wapnia może dojść do osteomalacji i hipokalcemii, a to z kolei może prowadzić do wtórnej nadczynności przytarczyc. Jeśli choroba trzewna pozostaje nieleczona przez długi czas, rozwija się trzeciorzędowa nadczynność przytarczyc spowodowana autonomizacją przewlekle stymulowanych gruczołów. Hiperparatyroidyzm pierwotny opisywano również u pacjentów z chorobą trzewną. Autorzy omawiają przypadek nastolatki z chorobą trzewną, u której występowały objawy ciężkiej hiperkalcemi wywołanej gruczolakiem przytarczyc. Dziewczynkę w wieku 14 lat przyjęto na oddział autorów z powodu opóźnionego dojrzewania płciowego i zahamowania wzrostu. Badania laboratoryjne wykazały niedokrwistość z niedoboru żelaza, niskie stężenie witaminy 25OH-D3 (7 ng/ml), wysokie stężenie parathormonu (PTH) (955 pg/ml) i hiperkalcemię (13,4 mg/dl). Obraz preparatu z biopsji endoskopowej odpowiadał enteropatii glutenowej. Wykazano obecność przeciwciał przeciw *endomysium*. Zalecono dietę bezglutenową. Po usunięciu gruczolaka przytarczyc stężenie wapnia wróciło do normy. Po 4 miesiącach stosowania przez chorą diety bezglutenowej rozpoczęło się u niej dojrzewanie płciowe (powiększyły się gruczoły piersiowe i pojawiło się owłosienie łonowe). Sugerowano, że w przypadku autonomicznej hiperplazji czterech przytarczyc lub hiperparatyroidyzmu trzeciorzędowego może nastąpić progresja do gruczolaka przytarczyc i że taki stan należy określić mianem „hipertyroidyzmu czwartorzędowego". Potrzebne są dalsze badania w celu wyjaśnienia zależności między chorobą trzewną i nadczynnością przytarczyc. **(Endokrynol Pol 2012; 63 (1): 56–58)**

Słowa kluczowe: *choroba trzewna, gruczolak przytarczyc, nietolerancja glutenu*

Introduction

Coeliac disease (CD), a gluten-sensitive enteropathy of varying severity, affects millions of people wordwide [1] and is one of the commonest autoimmune diseases in children [1, 2]. Its clinical manifestations can vary by age: whereas infants and young children might have diarrhoea, abdominal distension, or failure to thrive, adults might also display anaemia, osteoporosis, osteomalacia, neurological symptoms, growth retardation, or delayed puberty [1–4]. Osteomalacia and hypocalcaemia result from malabsorption of vitamin D and calcium, which in turn can cause secondary hyperparathyroidism. In patients with persistently untreated CD, tertiary hyperparathyroidism can also develop through autonomy of the parathyroid glands with chronic stimulation [5]. Primary hyperparathyroidism has also been reported to accompany CD in some cases [6–9]. We report the case

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of an adolescent with CD who presented with severe hypercalcaemia because of a parathyroid adenoma.

Case report

A 14 year-old girl was admitted to our department for delayed puberty and growth retardation. She was 125 cm tall and weighed 28.5 kg, which meant that she was below the third percentile of growth for her age. She was not menstruating, and secondary sex characteristics (axillary and pubic hair and breasts) were absent. Wrist radiography was consistent with a skeletal age of 7–8 years.

Laboratory examination revealed iron-deficiency anaemia, a low 25-hydroxy vitamin D level, an elevated parathyroid hormone level (PTH), hypercalcaemia, hypogonadotropic hypogonadism, normal levels of growth hormone, and a low insulin-like growth factor 1 (IGF-1) level (Table I).

We performed an upper gastrointestinal endoscopy to assess possible explanations for the malabsorption. The duodenal bulb was found to be oedematous and atrophic. Endoscopic biopsy was compatible with total villous atrophy, crypt hyperplasia, intraepithelial lymphocyte infiltration, oedema, and lymphocyte and plasma-cell infiltration of the lamina propria (Figure 1). Endomysial antibody testing was positive. The diagnosis of CD was made, and she was started on a gluten-free diet.

Because of the hypercalcaemia and hyperparathyroidism that were present despite her severe vitamin D deficiency, we performed neck ultrasonography. Testing revealed a 10.7 × 5.4 mm hypoechoic lesion in the lower right lobe of the thyroid. The thyroid parenchyma was otherwise homogeneous. Sestamibi parathyroid scintigraphy was then performed, which revealed a parathyroid adenoma. She underwent parathyroidectomy, immediately after which her calcium level had fallen to 8.8 mg/dl and the PTH level had decreased to 12.3 pg/ml.

Table I. *Laboratory results*

Tabela I. *Wyniki badań laboratoryjnych*

Test	Result	Normal range
Serum calcium [mg/dl]	13.4	(8.2–10.6)
Serum phosphate [mg/dl]	4	(2.5–4.5)
Serum parathyroid hormone [pg/ml]	955	(11.1–79.5)
Serum alkaline phosphatase [IU/l]	1,052	(70–290)
Serum 25-hydroxy vitamin D [ng/ml]	7	(10–100)
24-h urinary calcium [mg/d]	230	(100–300)
Serum albumin [g/dl]	4.3	(3.2–4.8)
Follicle-stimulating hormone [mIU/ml]	0.29	(0.68–6.7)
Luteinising hormone [mIU/ml]	0.1	(0.03–3))
Oestradiol [pg/ml]	5.32	< 15
Cortisol [μg/dl]	17.8	(6.2–19.4)
Growth hormone [ng/ml]	6.67	(0.01–5.22)
Insulin-like growth factor-1 [ng/ml]	26.2	111–551
Thyroid-stimulating hormone [IU/l]	1.79	(0.35–5.5)
Free thyroxine [ng/dl]	1.24	(0.89–1.76)
Haemoglobin [g/dl]	10.4	(11.5–17)
Serum iron [ug/dl]]	14	(50–70)
Total iron-binding capacity [ug/dl]	327	(222–428)
Serum ferritin [ng/ml]	3	(10–291)

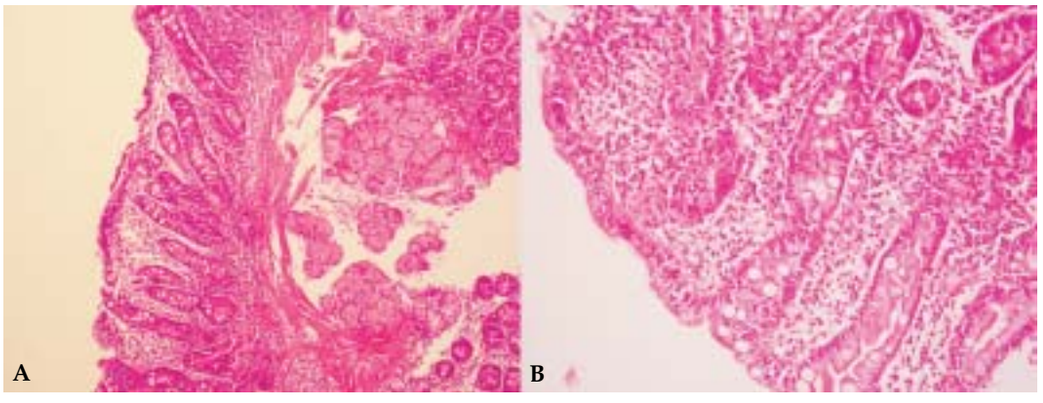

Figure 1AB. *Photomicrographs of haematoxylin and eosin-stained (H&E) slide preparation of endoscopic biopsy showing total villous atrophy, crypt hyperplasia, intraepithelial lymphocyte infiltration, oedema, and lymphocyte and plasma-cell infiltration of the lamina propria (A; H&E × 10, B; H&E × 20)*

Rycina 1AB. *Mikroskopowy obraz preparatu z biopsji endoskopowej [barwienie hematoksyliną-eozyną (HE)]. Widoczny całkowity zanik kosmków jelitowych, przerost krypt, śródnabłonkowe nacieki limfocytarne, obrzęk i naciek z limfocytów i komórek plazmatycznych w blaszce właściwej błony śluzowej (A; HE × 10, B; HE × 20)*

After four months of the gluten-free diet, she had reached 132 cm in height and weighed 34 kg. She had entered Tanner Stage 2 of development, and had begun to grow axillary and pubic hair.

Discussion

The classical form of CD, which is diagnosed most commonly between six and 18 months of age, is characterised by symptoms of intestinal malabsorption resulting from villous atrophy. The atypical form is characterised by structural abnormalities in the small bowel mucosa, minor gastrointestinal symptoms, and systemic signs and symptoms such as osteoporosis, peripheral neuropathy, anaemia, and infertility. In the latent form, the structures of the intestinal mucosa are normal, but serology testing is positive, and extraintestinal signs and symptoms may or may not be present [1, 4]. Regardless of the form, injury to the small intestine mucosa results in malabsorption, which in turn can cause vitamin and iron deficiencies associated with osteoporosis, neurological disorders, and other sequelae [1, 4]. Withdrawal of dietary gluten usually results in clinical and pathological improvement in most patients within a few weeks [10].

Our patient presented with short stature, delayed puberty, iron deficiency anaemia, and vitamin D deficiency. Her CD was diagnosed at a relatively late age and included extraintestinal manifestations. Although the pathogenesis of CD-associated short stature remains unclear, impaired growth in children with the disease results mainly from nutritional deficits and involvement of the growth hormone/IGF-1 axis. A gluten-free diet frequently results in marked improvement in linear growth, especially during the first year [11–13], as noted in our patient. In addition, some patients with CD show resistance to growth hormone as suggested by normal or elevated growth hormone levels and low IGF-1 levels [12]. This was also true in our patient.

In CD, malabsorption of calcium and/or vitamin D and endogenous foecal calcium losses can lead to low serum calcium levels. This stimulates secretion of PTH, which limits renal calcium excretion, increases the release of calcium from bones, and increases intestinal absorption of calcium through conversion of 25-hydroxy vitamin D to its active form (1,25-dihydroxyvitamin D) [12, 13]. As a result, secondary hyperparathyroidism is often present in patients with CD [14]. Long-lasting secondary hyperparathyroidism in patients with CD can become autonomous, a situation commonly called "tertiary hyperparathyroidism". In such cases, patients have hypercalcaemia and high PTH levels, as in primary hyperparathyroidism, but hyperplasia of the four parathyroid glands is the most typical morphological feature [5, 7, 13]. In contrast, isolated adenomas can be detected only rarely in these patients (~5% of cases) [15].

Some patients have CD with primary hyperparathyroidism [6–9, 16]. A relationship might exist between CD and primary hyperparathyroidism, perhaps attributable either to an autoimmune base or to tertiary hyperparathyroidism [7]. However, the loss of the suppressive effects of vitamin D might itself lead to expression of different proto-oncogenes, resulting in formation of an adenoma [16]. Given that adenomas form through a process entirely different from that of parathyroid hyperplasia, both autonomous parathyroid hyperplasia and tertiary hyperparathyroidism progressing to adenoma formation might be more accurately termed "quaternary hyperparathyroidism" [16].

In conclusion, persistent vitamin D deficiency alters the metabolism of parathyroid gland cells, either as autonomous, four-gland hyperplasia or adenomas. Our patient had a parathyroid adenoma accompanying severe vitamin D deficiency resulting from CD. Further studies are needed to examine the relationships between primary hyperparathyroidism, CD, and tertiary and/or "quaternary hyperparathyroidism".

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