Eur J Pediatr (2006) 165:897–903
DOI 10.1007/s00431-006-0182-4

ORIGINAL PAPER

Growth hormone impaired secretion and antipituitary antibodies in patients with coeliac disease and poor catch-up growth after a long gluten-free diet period: a causal association?

Lorenzo Iughetti · Annamaria De Bellis · Barbara Predieri · Antonio Bizzarro · Michele De Simone · Fiorella Balli · Antonio Bellastella · Sergio Bernasconi

Received: 7 February 2006 / Revised: 5 May 2006 / Accepted: 9 May 2006 / Published online: 3 August 2006

Abstract
Introduction Coeliac disease (CD) is usually associated with impaired growth in children. A gluten-free diet (GFD) induces a catch-up growth with the recovery of height in about 2 years.
Aim and discussion The lack of the height improvement has been related to growth hormone (GH) secretion impairment. CD is an autoimmune disease often associated with other endocrine and non-endocrine autoimmune disease. The aim of this study was to evaluate antipituitary autoantibodies (APA) and antihypothalamus autoantibodies in CD children with poor clinical response to a GFD and growth hormone deficiency (GHD). We diagnosed CD on the basis of specific antibodies and endoscopic biopsies in 130 patients aged 1–15 years. Seven CD children, without catch-up growth after at least 12-months GFD, were tested for GH secretion and, in five out of seven patients, the diagnosis of GHD was made in the absence of metabolic and systemic diseases.
Results APA and antihypothalamus antibodies were detected by the indirect immunofluorescence method in the seven CD children without catch-up growth factor and in 25 CD children without growth impairment matched for sex and age, and in 58 healthy children as control groups. APA resulted positive at high titres in four out of five CD-GHD patients and were also positive at low titres (<1:8) in three of only CD children and in two out of 58 controls. Hypothalamic-pituitary magnetic resonance imaging (MRI) was normal in all patients except in one with cystic pineal. APA have been previously detected not only in adults with GHD, but also in idiopathic GHD children, suggesting the occurrence of an autoimmune hypophysitis in these patients.
Conclusion In our study, the presence of APA in CD children without catch-up growth after GFD seems to be able to identify an autoimmune form of hypophysitis involving the somatotrophs cells.

Keywords Antipituitary antibodies · Coeliac disease · Gluten-free diet · Catch-up growth · Idiopathic growth hormone deficiency

Abbreviations

ACTH	Corticotropin
AGA	Antigliadin autoantibodies
APA	Antipituitary autoantibodies
ARA	Antireticulin autoantibodies
BMI	Body mass index
CD	Coeliac disease

L. Iughetti (✉) · B. Predieri · F. Balli
Department of Pediatrics,
University of Modena and Reggio Emilia,
Via del Pozzo, 71,
41.100 Modena, Italy
e-mail: iughetti.lorenzo@unimore.it

A. De Bellis · A. Bellastella
Department of Clinical and Experimental Medicine and Surgery,
Chair of Endocrinology, Second University of Naples,
80.131 Naples, Italy

A. Bizzarro
Department of Clinical and Experimental Medicine and Surgery,
Chair of Immunology and Allergology,
Second University of Naples,
80.131 Naples, Italy

M. De Simone
Department of Pediatrics, University of L'Aquila,
67.100 L'Aquila, Italy

S. Bernasconi
Department of Pediatrics, University of Parma,
43.100 Parma, Italy

E_2	Estradiol
EMA	Antiendomysial autoantibodies
FITC	Fluorescein isothiocyanate
FSH	Follicle-stimulating hormone
F-T_3	Free triiodothyronine
F-T_4	Free thyroxine
GFD	Gluten-free diet
GH	Growth hormone
GHD	Growth hormone deficiency
GHRH	Growth hormone releasing hormone
Ig	Immunoglobulin
IGF-1	Insulin-like growth factor 1
IGF-BP3	IGF-binding protein 3
LH	Luteinising hormone
MRI	Magnetic resonance imaging
PRL	Prolactin
T	Testosterone
T1DM	Type 1 diabetes mellitus
TH	Target height
TSH	Thyroid-stimulating hormone
tTG	Antitransglutaminase autoantibodies

Introduction

Coeliac disease (CD) is a permanent, genetically determined intolerance to gluten that results in entheropathy and frequent malabsorption in children that may impair final statural growth [4, 7, 8, 27, 31, 32, 43, 46]. In fact, after starting a gluten-free diet (GFD), a significant increase in height and weight velocity has been evidenced [5, 7, 11, 13, 21, 22, 30], with weight reaching full catch-up growth in the first year of GFD and height reaching the expected centile after about 2 years [1, 42, 45]. However, even if in CD patients linear growth retardation is probably caused by nutritional deficiency, it has been reported that, in some patients with a GFD, the expected catch-up growth does not occur. The lack of a significant improvement of height has been related to the presence of growth hormone (GH) secretion impairment, as recently evidenced [6].

CD is considered an organ-specific autoimmune disease because of the specific autoantibodies, proven biopsy [33, 36, 44] and the common association with other autoimmune diseases, such as type 1 diabetes mellitus (T1DM) or thyroiditis and these latter associations seem to be related to gluten exposure [28, 51].

Recently, it has been supposed that, in three CD patients poorly responding to a GFD, an autoimmune involvement of the pituitary gland could coexist [10]; moreover, antipituitary antibodies (APA) have been detected in adults and in children with idiopathic growth hormone deficiency (GHD), indicating an autoimmune hypophysitis in these patients [16, 18].

The aim of this study was to investigate not only the occurrence of GHD, but also the presence of APA and antihypothalamus antibodies in CD patients with poor clinical response to a GFD.

Patients and methods

Patients

From 1999 to 2004 at the Pediatric Clinic of the University of Modena and Reggio Emilia, 130 patients [59 males, 71 females, age 5.67±3.60 years, height 0.32±1.25 SDS, body mass index (BMI) 16.4±2.33 kg/m^2, target height (TH) 0.14±0.66 SDS] were diagnosed as being affected by CD. In all patients, the diagnosis of CD was made on the basis of the presence of antigliadin (AGA), antiendomysial (EMA) and antitransglutaminase (tTG) antibodies and the subsequent endoscopic examination of the upper gastrointestinal tract with at least four biopsies of the distal duodenal mucosa, according to the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) criteria [52].

Growth velocity was determined every 12 months in all children. They were monitored by a diet record and meeting with a dietician in addition to the absence of sera EMA after a long period (≥12 months) of GFD.

The CD children showing no catch-up growth after at least a 12-month GFD period were evaluated in order to exclude a possible GHD. Moreover, APA and antihypothalamus antibodies were also detected in the seven CD children without catch-up growth factor and in 25 CD children without growth impairment (height 0.35±1.03 SDS, BMI 15.9±2.54 kg/m^2) matched for sex and age, and in 58 healthy children as control groups.

Methods

The patients with poor catch-up growth were submitted to endocrinological investigation by measuring basal serum GH, insulin-like growth factor (IGF-1), IGF-binding protein 3 (IGF-BP3), free triiodothyronine (F-T_3), free thyroxine (F-T_4), thyroid-stimulating hormone (TSH), prolactin (PRL), cortisol, corticotropin (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E_2, female) or testosterone (T, male) and performing immunological assays for AGA, EMA, tTG, antithyroid, APA and antihypothalamus antibodies.

Moreover, in different days, arginine (0.5 g/kg iv) and L-dopa (500 mg/1.73 m^2 orally) tests were performed in all of the seven children with poor growth and GH was evaluated on blood samples obtained after 30, 60, 90 and 120 min.

The bone age was determined on the basis of roentgenograms of the left hand and wrist according to the method of Greulich and Pyle [26].

The diagnosis of GHD was established on the basis of the following criteria: short stature (height below the 3rd centile of Tanner's growth charts); decreased growth velocity (below the 25th centile for age); delayed skeletal maturation (bone age/chronological age<0.7) according to Greulich and Pyle's *Atlas* [26]; blunted GH response (<10 μg/L) to two different pharmacological tests; absence of other endocrine, metabolic and systemic causes of short stature.

Hormonal assays GH, IGF-1, IGF-BP3, F-T_3, F-T_4, TSH, PRL, cortisol, ACTH, LH, FSH, E_2 or T were measured using a commercial time-resolved fluoroimmunoassay.

Immunological assays APA were detected by an immunofluorescence method on cryostat sections of young baboon pituitary and hypothalamus glands, as previously described [14, 16, 17, 19, 20]. In particular, fluorescein isothiocyanate-conjugated goat antihuman immunoglobulin (Ig) sera were used to detect the presence of APA and antihypothalamus antibodies, respectively, and then positive serum samples were tested with fluorescein isothiocyanate goat antihuman IgG, IgM and IgA sera separately. All of the sera were evaluated blindly by fluorescence microscope. The levels of APA and antibodies to hypothalamus were considered positive starting at dilution 1:2 and were expressed as the end-point dilution titre.

EMA were detected by indirect immunofluorescence on sections of human umbilical cord (Antiendomysium HUC, Eurospital, Trieste, Italy). The antigen-antibody complex is visualised by a fluorescence microscope with the aid of fluorescein-labelled antibodies. The test was considered positive when the fluorescence was observed around the smooth muscle fibres in the tunica media.

IgA-tTG antibodies were detected using a sandwich type enzyme immunoassay with human recombinant tTG antigen as the substrate (Eu-tTG IgA Umana; Eurospital, Trieste, Italy). The dynamic range of the system ranged between 0 and 20 arbitrary units (AU). Values <7 AU/ml were considered negative and values ≥7 AU/ml were considered positive according to the manufacturer's instructions.

AGA-IgA and AGA-IgG were determined using a fluorescence enzyme immunoassay performed on microplates coated with the alpha-fraction of gliadin from wheat gluten (α-Gliatest IgA and α-Gliatest IgG; Eurospital, Trieste, Italy). The results are expressed in AU. AGA-IgA values above 1.8 AU/ml and AGA-IgG values above 4 AU/ml were considered positive according to the manufacturer's instructions.

Neuroradiological investigation Magnetic resonance imaging (MRI) of the hypothalamus and pituitary region was performed in all patients.

Results

Seven out of 130 patients exhibited the above-mentioned criteria demonstrating poor catch-up growth (Table 1) and were submitted to endocrinological evaluation. All children showed similar byoptical findings. None of these subjects presented anaemia, hypoproteinaemia and diarrhoea. Five of these seven patients (patient numbers I–V) showed blunted GH response to the different stimuli for meeting all of the criteria for the diagnosis of GHD (Table 2).

Patient number VII showed a blunted GH response to arginine, but refused to perform the second test and dropped out from follow-up. No other endocrinological alterations were revealed, in particular, TSH and PRL levels were in the normal range.

Four out of the five patients with blunted GH responses (patient numbers I, II, IV and V) resulted positive at high titres (>1:8) for APA (two of them were positive also for antibodies to hypothalamus). APA were also positive at low titers (<1:8) in three out of 25 (12%) of only CD children and in two out of 58 (3.4%) controls (Table 2, Fig. 1). None of the only CD children and no control child showed the presence of antihypothalamus antibodies.

Finally, none of the children showed significant alterations of the hypothalamic-pituitary region at MRI, except for one (patient number V, Table 2), who showed findings supporting a cystic pineal.

Discussion

In the diagnostic approach of children with short stature, CD must be excluded by the measurement of specific antibodies, even if the subjects did not show gastrointestinal symptoms. Indeed, the detection of EMA and/or tTG can lead to the identification of atypical forms in which short stature may be the only symptom.

In the majority of CD patients, the linear growth retardation has been related to nutritional deficiency. This nutritional hypothesis is considered to have been overlooked; in fact, recently, it has been suggested that a systemic autoimmune inflammatory reaction involving a possible role of TNF-alfa could have a negative interference in growth [29, 35]. However, in some CD children, it has been reported that a pituitary dysfunction can occur.

In the past, an insufficient GH response to hypoglycaemia has been reported to occur in coeliac children, disappearing after the institution of a GFD [13, 49]. In 69% of children with active CD, a plasma GH peak has been observed as being 2SD below the mean [49]. Moreover, a low IGF-1 level has been evidenced in coeliac children unrelated to GHD and resistant to GH therapy, with normalisation only under a GFD [4, 34].

Table 1 Clinical characteristics of patients at the diagnosis of coeliac disease (CD) and growth hormone deficiency (GHD) after ≥12 months of gluten-free diet (GFD) (M=male; F=female; PH=pubic hair; B=breast; G=genital)

	Patient I	Patient II	Patient III	Patient IV	Patient V	Patient VI	Patient VII
Sex	M	M	M	F	M	F	F
Age at CD diagnosis, y	7.6	7.1	11.8	10.5	9	6	11.9
Height at CD diagnosis, SDS	−1.96	−0.9	−1.41	−1.48	−1.12	−1.42	−1.58
Target height, SDS	−0.44	0.32	−0.23	0.46	−1.01	−0.85	−0.43
Age at the time of endocrinological evaluation, y	8.6	11	14.4	12.5	14	11.6	13
Bone age at the time of endocrinological evaluation, y	5.5	10	12	10.5	13	10.5	11.5
Height at the time of endocrinological evaluation after ≥12 months of GFD, SDS	−1.86	−1.88	−2.39	−2.25	−2.45	−2.33	−1.87
Growth velocity at the time of endocrinological evaluation after ≥12 months of GFD, cm/y (SDS)	4.5 (−1.39)	3.4 (−2.36)	2.5 (−1.34)	4.9 (−3.07)	5.8 (−2.55)	2.5 (−4.92)	5.2 (−0.99)
Pubertal stage at the time of endocrinological evaluation after ≥12 months of GFD	PH1-G1	PH1-G1	PH2-G2	PH2-B2	PH3-G2	PH1-B2	PH3-B3
Testicular volume at the time of endocrinological evaluation after ≥12 months of GFD, ml	2–2	4–4	4–4	/	8–10	/	/

A study involving 21 children (mean age 4.5 years), suspected to be affected by CD, demonstrated that the IGF-1 level rose significantly ($P<0.01$) in 10 of them after submission to a GFD, but then it significantly decreased when they underwent challenge with gluten and it was re-established to a normal level when returning to GFD [53].

An hypothalamic-pituitary involvement consisting in a marked reduction of some circulating thyroid hormones and an enhanced response of TSH to the administration of thyrotropin-releasing hormone (TRH) has been observed in active CD [24, 48]. It has been suggested that this could be due to the direct action of circulating gluten peptides [14, 23] entering the central nervous system and having endorphin-like properties [54].

In untreated coeliac adults, it has been recently demonstrated an impaired hypothalamic control of GH secretion [41]; GH did not respond to L-dopa administration, but it responded to GH-releasing hormone (GHRH), probably due to an abnormal brain monoamine tone, and responded paradoxically to TRH [48]. This condition was previously described in other chronic diseases, such as severe liver disease, anorexia nervosa, mental depression and TIDM [9, 12, 37, 38, 40].

The hypothesis that autoimmunity could involve the pituitary gland was reported about 40 years ago and has been confirmed by autoptical studies [2, 15, 25, 39]. More recently, some morphological findings on hypothalamic-pituitary MRI have been used to confirm this diagnosis [15]. Moreover, hyperprolactinaemia has been shown in patients with lymphocytic hypophysitis and MRI alterations [20, 47], and it has been related to stalk compression resulting in decreased dopamine to anterior pituitary; in agreement with the absence of pituitary MRI alterations, the PRL levels of our patients were in the normal range.

The autoimmune pituitary involvement has been hypothesised by the presence of APA in GHD patients, even if the nature and the significance of APA are still discussed [2, 15]. However, the presence of APA at high titres could explain some cases of apparently idiopathic GHD as soon as the detection of antihypothalamus antibodies is correlat-

Table 2 Endocrinological, immune and neuroradiological characteristics of patients at the diagnosis of GHD and after ≥12 months of GFD

	Patient I	Patient II	Patient III	Patient IV	Patient V	Patient VI	Patient VII
F-T4, ng/dL	0.99	1.28	1.00	0.99	1.04	1.21	1.02
TSH, mUI/L	1.5	2.7	4.2	2.9	3.2	3.6	2.4
PRL, ng/ml	6	8.2	7.4	5	11	9.3	6.2
IGF-1, ng/mL	76.6	128.8	144.0	142.9	285.0	153.0	230.0
GH, μg/L (peak after L-dopa)	7.0	7.6	2.7	8.9	5.9	10.8	Not determined
GH, μg/L (peak after arginine)	7.2	7.3	4.0	9.4	8.1	5.0	0.3
TTG	Absent	Absent	Absent	Absent	Absent	Absent	Absent
EMA	Absent	Absent	Absent	Absent	Absent	Absent	Absent
APA	1/32	1/64	Absent	1/64	Absent	Absent	Absent
Anti-hypothalamus antibodies	Absent	Absent	Absent	1/32	1/16	Absent	Absent
Pituitary/hypothalamus MRI	Normal	Normal	Normal	Normal	Cystic pineal	Normal	Normal

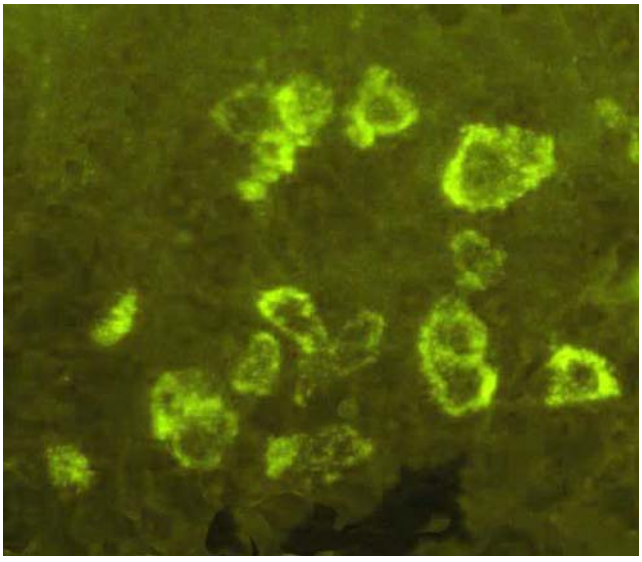

Fig. 1 Antipituitary antibodies (APA) and antihypothalamus antibodies detected by the immunofluorescence method

ed with infundibulo-neurohypophysitis [16, 20]. It has been suggested that the high titres of APA are good markers of the pituitary impairment in autoimmune endocrine disease patients [15, 16].

In our patients, the presence of APA and antihypothalamus antibodies in GHD and CD patients suggests an associated autoimmune involvement in a context of autoimmune polyendocrine syndrome (APS) [3].

The development of autoimmune conditions in CD is related to the age at diagnosis. It was demonstrated that, in CD patients who had started a GFD at the age of 10 years or more, the frequency of autoimmune disorders was significantly increased with respect to the controls. In this way, it has been suggested that the presence of other autoimmune diseases in CD patients depends on the time of exposure to gluten and that an early diagnosis and treatment of CD might protect against the development of autoimmune conditions [50].

Even if the autoimmune origin of the GHD in our patients is not further supported by MRI, the absence of pituitary enlargement or other neuroradiological signs might be related to the short duration of the disease. In fact, the cases reported in the literature with MRI alteration are, in general, performed on adult subjects. The golden diagnostic tool to confirm the occurrence of lymphocytic hypophysitis in our patients should be pituitary biopsy, but it was not possible to perform this because of ethical problems. On the other hand, it has been previously stressed that APA are very suggestive for the diagnosis of autoimmune hypophysitis, despite the normal MRI in patients with idiopathic hypopituitarism [2, 15, 16, 39].

Our results, showing either the presence of APA in the sera of some children with CD and/or impaired GH response to the stimuli, strongly support the assumption that GH secretion should be evaluated in coeliac patients showing no catch-up growth after a consistent period of GFD. The presence of antihypothalamus antibodies in two patients (patient numbers IV and V in Table 2) with GHD in the absence of diabetes insipidus needs some commenting. It could indicate that these antibodies are directed against the hypothalamic structures regulating GH secretion and release more than the vasopressin (AVP) secreting cells. This seems to be also confirmed by the occurrence of GH secretion impairment in one of the two patients (patient number V of Table 2) positive for antihypothalamus but not for APA.

Moreover, one out of the five CD children with GH impairment did not show positivity for APA, exhibiting the lowest GH response and having a very impaired auxological response to GFD; this case could be considered as idiopathic GHD and could exclude an autoimmune origin of GHD. However, a subsequent pituitary involvement could occur, suggesting a periodical evaluation of APA/antihypothalamus antibodies in this patients.

In conclusion, the occurrence of an autoimmune mechanism as the cause of GH impairment in some CD patients might be hypothesised from our study, suggesting that the autoimmune hypophysitis may be much more frequent than previously considered not only in adults [15–17] but also in children [18]. In this connection, to look for antipituitary and antihypothalamus antibodies in the sera of children with CD, especially in whom GFD did not improve the growth significantly, could help to find out an autoimmune subclinical GHD.

Further longitudinal studies are in progress to validate this hypothesis.

References

1. Barr DG, Shmerling DH, Prader A (1972) Catch-up growth in malnutrition, studied in celiac disease after institution of gluten-free diet. Pediatr Res 6(5):21–27
2. Bellastella A, Bizzarro A, Coronella C, Bellastella G, Sinisi AA, De Bellis A (2003) Lymphocytic hypophysitis: a rare or underestimated disease? Eur J Endocrinol 149(5):363–376
3. Betterle C, Dalpra C, Greggio N, Volpato M, Zanchetta R (2001) Autoimmunity in isolated Addison's disease and in polyglandular autoimmune diseases type1, 2 and 4. Ann Endocrinol 62(2): 193–201
4. Bonamico M, Scirè G, Mariani A, Pasquino M, Triglione P, Scaccia S, Ballati G, Boscherini B (1992) Short stature as the primary manifestation of monosymptomatic celiac disease. J Pediatr Gastroenterol Nutr 14(1):12–16
5. Bosio L, Barera G, Mistura L, Sassi G, Bianchi C (1990) Growth acceleration and final height after treatment for delayed diagnosis of celiac disease. J Pediatr Gastroentrol Nutr 11(3):324–329
6. Bozzola M, Giovenale D, Bozzola E, Meazza C, Martinetti M, Tinelli C, Corazza GR (2005) Growth hormone deficiency and

coeliac disease: an unusual association? Clin Endocrinol 62 (3):372–375
7. Cacciari E, Salardi S, Lazzari R, Cicognani A, Collina A, Pirazzoli P, Tassoni P, Biasco G, Corazza GR, Cassio A (1983) Short stature and celiac disease: a relationship to consider even in patients with no gastrointestinal tract symptoms. J Pediatr 103 (5):708–711
8. Cacciari E, Salardi S, Volta U, Biasco G, Lazzari R, Corazza GR, Feliciani M, Cicognani A, Partesotti S, Azzaroni D, Tassoni P, Pirazzoli P, Bianchi FB, Pisi E (1985) Can antigliadin antibody detect symptomless coeliac disease in children with short stature? Lancet 1(8444):1469–1471
9. Ceda GP, Speroni G, Dall'Aglio E, Valenti G, Butturini U (1982) Non-specific growth hormone responses to thyrotropin-releasing hormone in insulin-dependent diabetes: sex- and age-related pituitary responsiveness. J Clin Endocrinol Metab 55 (1):170–174
10. Collin P, Hakanen M, Salmi J, Maki M, Kaukinen K (2001) Autoimmune hypopituitarism in patients with coeliac disease: symptoms confusingly similar. Scand J Gastroenterol 36(5): 558–560
11. Damen GM, Boersma B, Wit JM, Heymans HSA (1994) Catch-up growth in 60 children with coeliac disease. J Pediatr Gastroenterol Nutr 19(4):394–400
12. Dasmahapatra A, Urdanivia E, Cohen MP (1981) Growth hormone response to thyrotropin-releasing hormone in diabetes. J Clin Endocrinol Metab 52(5):859–862
13. Day G, Evans K, Wharton B (1973) Abnormalities of insulin and growth hormone secretion in children with celiac disease. Arch Dis Child 48(1):41–46
14. De Bellis A, Bizzarro A, Amoresano Paglionico V, Di Martino S, Criscuolo T, Sinisi AA, Lombardi G, Bellastella A (1994) Detection of vasopressin cell antibodies in some patients with autoimmune endocrine disease without overt diabetes insipidus. Clin Endocrinol 40(2):173–177
15. De Bellis A, Bizzarro A, Bellastella A (2005) Pituitary antibodies and lymphocytic hypophysitis. Best Pract Res Clin Endocrinol Metab 19(1):67–84
16. De Bellis A, Bizzarro A, Conte M, Perrino S, Coronella C, Solimeno S, Sinisi AM, Stile LA, Pisano G, Bellastella A (2003) Antipituitary antibodies in adults with apparently idiopathic growth hormone deficiency and in adults with autoimmune endocrine diseases. J Clin Endocrinol Metab 88(2):650–654
17. De Bellis A, Bizzarro A, Perrino S, Coronella C, Conte M, Pasquali D, Sinisi AA, Betterle C, Bellastella A (2005) Characterization of antipituitary antibodies targeting pituitary hormone-secreting cells in idiopathic growth hormone deficiency and autoimmune endocrine diseases. Clin Endocrinol 63(1):45–49
18. De Bellis A, Salerno M, Conte M, Coronella C, Tirelli G, Battaglia M, Esposito V, Ruocco G, Bellastella G, Bizzarro A, Bellastella A (2006) Antipituitary antibodies recognizing GH-producing cells in children with idiopathic growth hormone deficiency and in children with idiopathic short stature. J Clin Endocrinol Metab (in press) DOI 10.1210/jc.2006-0040
19. De Bellis A, Colao A, Bizzarro A, Di Salle F, Coronella C, Solimeno S, Vetrano A, Pivonello R, Pisano G, Lombardi G, Bellastella A (2002) Longitudinal study of vasopressin-cell antibodies and of hypothalamic-pituitary region on magnetic resonance imaging in patients with autoimmune and idiopathic complete central diabetes insipidus. J Clin Endocrinol Metab 87 (8):3825–3829
20. De Bellis A, Bizzarro A, Pivonello R, Lombardi G, Bellastella A (2005) Prolactin and autoimmunity. Pituitary 8(1):25–30
21. De Luca F, Astori M, Pandullo E, Sferlazzas C, Arrigo T, Sindoni A, Magazzù G (1998) Effects of a gluten-free diet on catch-up growth and height prognosis in coeliac children with growth retardation recognized after the age of 5 years. Eur J Pediatr 147 (2):188–191
22. Exner GU, Sacher M, Shmerling DH, Prader A (1978) Growth retardation and bone mineral status in children with coeliac disease recognized after the age of 3 years. Helv Paediatr Acta 33 (6):497–507
23. Farthing MJG, Rees LH, Edwards CRW, Dawson AM (1983) Male gonadal function in coeliac disease: 2. Sex hormones. Gut 24(2):127–135
24. Farthing MJG, Rees LH, Edwards CRW, Byfield PGH, Himsworth RL, Dawson AM (1982) Thyroid hormones and the regulation of thyroid function in men with coeliac disease. Clin Endocrinol 16 (6):525–535
25. Goudie RB, Pinkerton PH (1962) Anterior hypophysitis and Hashimoto's diseases in a young woman. J Pathol Bacteriol (Lond) 83:584–585
26. Greulich WW, Pyle SI (1959) Radiographic atlas of skeletal development of the hand and wrist, 2nd edn. Stanford University Press, Stanford, California
27. Groll A, Candy DCA, Preece MA, Tanner JM (1980) Short stature as the primary manifestation of coeliac disease. Lancet 2 (8204):1097–1099
28. Iughetti L, Bulgarelli S, Forese S, Lorini R, Balli F, Bernasconi S (2003) Endocrine aspects of coeliac disease. J Pediatr Endocrinol Metab 16(6):805–818
29. Jelinkova L, Tuckova L, Cinova J, Flegelova Z, Tlaskalova-Hogenova H (2004) Gliadin stimulates human monocytes to production of IL-8 and TNF-alpha through a mechanism involving NF-kappaB. FEBS Lett 571(1–3):81–85
30. Karberg J, Henter JI, Tassin E, Lindblad BS (1988) Longitudinal analysis of infantile growth in children with coeliac disease. Acta Pediatr Scand 77(4):516–524
31. Knudtzon J, Fluge G, Aksnes L (1991) Routine measurements of gluten antibodies in children of short stature. J Pediatr Gastroenterol Nutr 12(2):190–194
32. Kumar PJ, Walker-Smith J, Milla P, Harris G, Colyer J, Halliday R (1988) The teenage coeliac: follow up of 102 patients. Arch Dis Child 63(8):916–920
33. Lahat N, Ben-Nun A, Kinarti E, Lerner A (1995) T cell receptor repertoire in the peripheral blood and intestinal mucosa of coeliac patients. Clin Exp Immunol 101(3):422–427
34. Lecornu M, David L, Francois R (1978) Low serum somatomedin activity in celiac disease. A misleading aspect in growth failure from asymptomatic celiac disease. Helv Paediatr Acta 33(6): 509–516
35. Leon F, Sanchez L, Camarero C, Roy G (2005) Cytokine production by intestinal intraepithelial lymphocyte subsets in celiac disease. Dig Dis Sci 50(3):593–600
36. Lerner A, Kumar V, Iancu TC (1994) Immunological diagnosis of childhood coeliac disease: comparison between antigliadin antireticulin and antiendomysial antibody. Clin Exp Immunol 95 (1):78–82
37. Maeda K, Kato Y, Ohgo S, Chihara K, Yoshimoto Y, Yamaguchi N, Kuromaru S, Imura H (1975) Growth hormone and prolactin release after injection of thyrotropin-releasing hormone in patients with depression. J Clin Endocrinol Metab 40(3):501–505
38. Maeda K, Kato Y, Yamaguchi N, Chihara K, Ohgo S (1976) Growth hormone release following thyrotropin-releasing hormone injection into patients with anorexia nervosa. Acta Endocrinol (Copenh) 81(1):1–8
39. Mauerhoff T, Mirakian R, Bottazzo GF (1987) Autoimmunity and the pituitary. In: Doniach D, Bottazzo GF (eds) Endocrine and other organ-oriented autoimmune disorders. Bailliere's clinical immunology and allergy 1, Saunders, London, pp 217–235
40. Panerai AE, Salerno F, Manneschi M, Cocchi D, Muller EE (1977) Growth hormone and prolactin responses to thyrotropin-

releasing hormone in patients with severe liver disease. J Clin Endocrinol Metab 45(1):134–140
41. Peracchi M, Molteni N, Cantalamessa L, Bardella MT, Peracchi G, Orsatti A, Faggioli P, Bianchi PA (1992) Abnormal growth hormone responsiveness to stimuli in women with active celiac sprue. Am J Gastroenterol 87(5):580–583
42. Prader A, Shmerling D, Zachman M, Biro Z (1969) Catch-up growth in coeliac disease. Acta Paediatr Scand 58:311–319
43. Rosenbach Y, Dinari G, Zahavi I, Nitzan M (1986) Short stature as the major manifestation of celiac disease in older children. Clin Pediatr 25(1):13–16
44. Rosenberg R-WMC, Montzaris GZ, Jewell DP (1992) The immunology of coeliac disease. In: Branski D, Rozen P, Kagnoff MF (eds) Gluten-sensitive enteropathy. Frontiers of gastrointestinal research, vol 19. Karger, Basel, Switzerland, pp 29–43
45. Shmerling D, Prader A, Zachmann M (1968) The effect of dietary treatment on growth in celiac disease. In: McCance RA, Widdowson EM (eds) Calorie deficiencies and protein deficiencies. Churchill, London, p 159
46. Stenhammar L, Fallstrom SP, Jansson G, Jansson U, Lindberg T (1986) Coeliac disease in children of short stature without gastrointestinal symptoms. Eur J Pediatr 145(3):185–186
47. Unluhizarci K, Bayram F, Colak R, Ozturk F, Selcuklu A, Durak AC, Kelestimur F (2001) Distinct radiological and clinical appearance of lymphocytic hypophysitis. J Clin Endocrinol Metab 86(5):1861–1864
48. Vanderschueren-Lodeweyckx M, Eggermont E, Cornette C, Beckers C, Malvaux P, Eeckels R (1977) Decreased serum thyroid hormone levels and increased TSH response to TRH in infants with coeliac disease. Clin Endocrinol 6(5):361–367
49. Vanderschueren-Lodeweyckx M, Wolter R, Molla A, Eggermont E, Eeckels R (1973) Plasma growth hormone in coeliac disease. Helv Paediatr Acta 28(4):349–357
50. Ventura A, Magazzù G, Greco L for The SIGEP Study Group for Autoimmune Disorders in Celiac Disease: D'Andrea N, Lambertini A, Zaniboni G, Pensabene L, Guandalini S, Marani M, Miano A, Caruselli C, Mostaccio L, Bertolani P, Balli F, Ciccarelli G, Guariso G, Cataldo F, Chiaravalloti G, Ughi C, Martelossi S, Torre G (1999) Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. Gastroenterology 117(2):297–303
51. Ventura A, Magazzù G, Greco L, Coordinators of the SIGEP Group: Balli F, Bertolani P, Caruselli C, Cataldo F, Chiaravalloti G, Ciccarelli G, D'Andrea N, Greco L, Guariso G, Lambertini A, Marani M, Martelossi S, Miano A, Mostaccio L, Pensabene L, Romano C, Torre G, Ughi C, Zaniboni G (1997) Autoimmune disorders in coeliac disease: relationship with duration of exposure to gluten. J Pediatr Gastroenterol Nutr 24:463
52. Walker-Smith JA, Guandalini S, Schmitz J, Shmerling DH, Visakorpi JK (1990) Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. Arch Dis Child 65 (8):909–911
53. Weile B, Krasilnikoff PA, Giwercman A, Skakkebaek NE (1994) Insulin-like growth factor-I in celiac disease. J Pediatr Gastroentrol Nutr 19(4):391–393
54. Zioudrou C, Sreaty RA, Klee WA (1979) Opioid peptides derived from food proteins. The exorphins. J Biol Chem 254(7): 2446–2449