CLINICAL CASE

Common variable immunodeficiency, insulin-dependent diabetes mellitus and celiac disease

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SUMMARY

Common variable immunodeficiency is a disorder characterised by hypogammaglobulinemia with B-lymphocytes in peripheral blood and repeated infections. We report a child with a diagnosis of diabetes mellitus and celiac disease during lactation, and in whom common variable immunodeficiency was diagnosed at the age of 5. During evolution of the disease he presented multiple respiratory infections in spite of substitution therapy with gamma globulins. He presented pulmonary fibrosis with a pulmonary volume reduced, and a spirometric restrictive patron. Immunologically, he presents reduction in CD4 lymphoid population. He expresses the alleles DQ2 A1 0501 and B1 which are strongly associated with susceptibility to insulin - dependent diabetes mellitus and celiac disease, but don't express antigens HLA class II DR3 and DR4 that are more frequent in these entities.

The main disease and all the complications had affected his curve pondostatural.

Key words: Common variable immunodeficiency. Diabetes mellitus. Celiac disease. Hypogammaglobulinemia. Autoimmunity.

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INTRODUCTION

Common variable immunodeficiency is a heterogeneous group of immunological deficiency syndromes. The onset of symptoms may occur at any moment, but are most frequent in the second and third decades of life. CVID is characterized by hypogammaglobulinemia with normal or slightly reduced circulating B lymphocytes in peripheral blood, altered humoral response, and repeated bacterial infections. In 30% of cases there is a numerical or functional alteration of T lymphocytes (1-3). In addition to these alterations, associations with autoimmune diseases such as systemic lupus erythematosis, rheumatoid arthritis, autoimmune hemolytic anemia, thrombocytopenia and endocrinopathies are common in these patients (1-3).

The interest of this clinical case lies in the coexistence in the same child of three associated diseases: common variable immunodeficiency, diabetes mellitus type I, and celiac disease.

CLINICAL CASE

16-year-old male patient, in whom common variable immunodeficiency was diagnosed at our service at the age of five years. *Family history* of first-degree consanguinity of parents; father with diabetes type II, sister with selective deficit of IgA and two *first cousins on his father's side* with diabetes mellitus type I. *Personal history:* first consulted at age of one month for bacterial sepsis of gastrointestinal origin and malabsorption syndrome. At nine months diabetes mellitus type I was diagnosed, and insulin therapy initiated.

The boy has presented multiple infections throughout his life, (acute gastroenteritis, febrile syndromes) and decompensations of the

diabetes mellitus. Malabsorption syndrome persists. At age of 20 months was admitted to hospital for weight and height deficit and for study of suspected celiac disease. During this hospitalization, *Giardia lamblia* infection and hypogammaglobulinemia were detected, the latter interpreted as secondary to protein loss via the gut. Discharged from hospital a gluten-free diet was prescribed. At the age of 3 years 10 months hospitalized for acute lymphocyte meningitis, which remitted without complications.

At the age of 4 years the diagnosis of celiac disease was confirmed after the third intestinal biopsy. Markers (antibodies IgA, IgG for gliadin and IgG for endomysium) were negative.

At the age of 5 years the child was referred to the immunoallergy service for hypogammaglobulinemia.

Complementary tests performed were:

Serum immunoglobulin levels: IgG 46 mg/dl, IgA < 1.1 mg/dl, IgM 17 mg/dl, secretory IgA in saliva 3.1 mg/dl. *Anti-rubeola antibodies.* IgG (+) IgM (-). *Lymphoid populations:* CD3: 73%, CD4: 48%, CD8: 23%. Total B-lymphocytes: 15%. Delayed hypersensitivity (skin tests): Tetanus, Diphtheria and Tuberculin (+++) Streptococcus, Trichophyton and Proteus (-). HIV Serology (-), Blood group O (+), *Isohemagglutinins* negative; antinuclear and antiDNA antibodies, negatives.

Histocompatibility antigens: HLA DR3 and DR4 negatives, HLA DQ2, DQA1 0501 and DQB1 0201 positives.

At this point, diagnosis of *common variable immunodeficiency* was made, and treatment with intravenous gamma globulin (300 mg/kg/month) initiated.

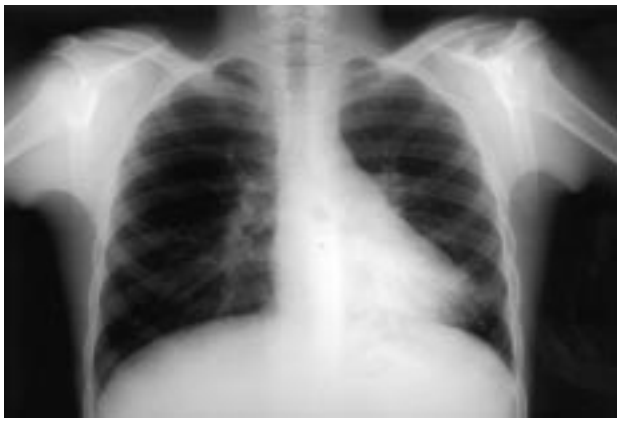
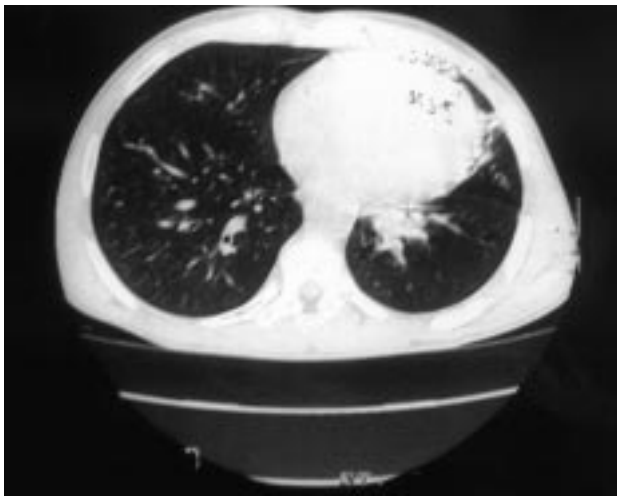
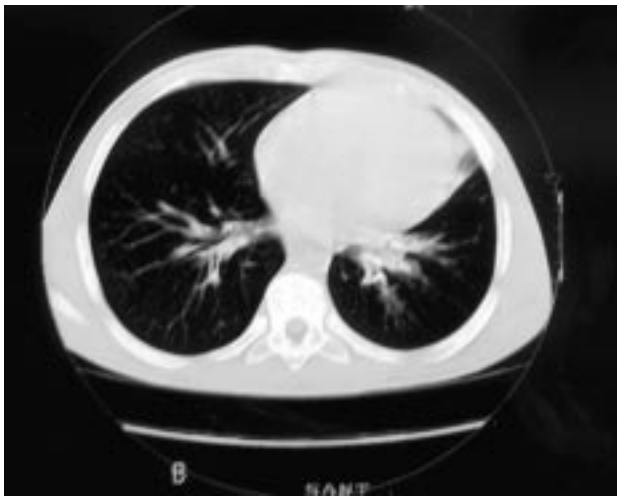


Figure 1.—Torax radiography: persistent peribronchitis in right branch and left retrocardiac.

Evolution: immunological markers of celiac disease are still negative. The subject remains on gluten-free diet. Thyroid function hormones are normal and antithyroid antibodies negative. He has presented multiple decompensations of his diabetes mellitus and also multiple respiratory processes and in the last four years chest X-rays show persistent retrocardiac infiltrate (Fig. 1). Chest tomography revealed bronchiectasis of the lingula (Figs. 2 and 3). Spirometry controls present a persistent restrictive pattern. Currently receiving intravenous gamma globulin (600 mg/kg/month) to maintain IgG levels above 400 mg/dl (Fig. 4). A progressive reduction of the CD4 lymphoid population and a total absence of IgA and IgM has been observed (tables I and II). The pondostatural curve has been affected with a desacceleration in growth rate. Now his height is - 2 standard *rom* (Fig. 5).





Figures 2 and 3.—Lung's scanner show bilateral diffuse bronchiectasis.

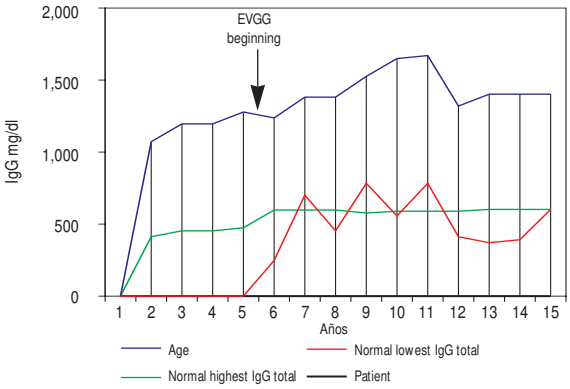


Figure 4.—Evolution of IgG serum levels.

Table II

Evolution of immunoglobulin levels (mg/dl)

Age	IgG	IgA	IgM	IgG1	IgG2	IgG3	IgG4
20 m	355	14.2	66.7				
5 a	46	< 1.1	17	45	< 4	31	5.1
6 a	283	Absent	11.2	237	120	8	5
7 a	688	3.6	8.3	419	530	absent	Absent
8 a	501	Absent	8.3	100	275	5	2
9 a	807	Absent	13.8	338	401	absent	11.6
10 a	578	Absent	absent	293	336	absent	8.3
11 a	831	Absent	absent	361	521	absent	11.9
12 a	466	Absent	absent	217	221	absent	4.1
13 a	400	Absent	absent	233	235	absent	5.7
14 a	432	Absent	absent	163	162	2	5
15 a	442	Absent	absent	180	201	2	6
16 a	670	Absent	Absent	354	212	4	15

DISCUSSION

According to the WHO, the term *Common Variable Immunodeficiency* describes a poorly defined syndrome characterized by the defective formation of antibodies and a variable pattern of humoral and cellular immune alteration. Diagnosis is based on the exclusion of other causes of humoral immune defect (4).

Common variable immunodeficiency (CVID) is not frequently diagnosed in the first decade of life. Although it is a heterogeneous syndrome which may appear at any age it is most frequently described after the second and third decades of life. A small group of patients with CVID have a positive family history of isolated IgA deficit (1, 2), as was the case in our subject, whose sister presents IgA deficit.

Ninety-five percent of patients with insulin-dependent diabetes express the antigens HLA class II DR3 and DR4 (5-7) and more than 90% of patients with celiac disease express HLA DR3 (8). Although our patient presented these two entities, these HLA antigens were negative; however, he expressed the alleles DQ2 A1 0501 and B1 0201 which are also strongly associated with susceptibility to insulin-dependent diabetes mellitus (6) and with celiac disease (8, 9). Entities such as celiac disease and diabetes mellitus share the same HLA antigens, and as these diseases are more frequent in CVID patients it is surprising that we have not found other reports in the literature of the three diseases in the same patient. The 25-year review of the association of immunodeficiency and celiac disease by Heneghan and Stevens (10) found only a single case of CVID and celiachia in 604 patients with diagnosed celiac disease. There is also a report of an adult patient with a diagnosis of CVID and gluten sensitive enteropathy (11).

The association of insulin-dependent diabetes with CVID has been documented on a number of occasions (5, 12, 13) and Kuijpers, et al (14) reported an 8-year-old patient who also presented chronic autoimmune neutropenia associated with an autoimmune hematological disorder. Other associations have been described with autoimmune endocrinopathology, insulin-dependent diabetes mellitus and this immunodeficiency by Wong, et al, in a patient with acquired perforating dermatosis, pancreatic insufficiency and common variable immunodeficiency and also with pernicious anemia and growth hormone deficiency (15).

Our patient presents a reduction in the CD4 lymphocyte subpopulation, which has been described both in CVID patients and in insulin-dependent diabetics. A reduction in CD4 lymphocyte subpopulation has been reported in patients with diabetes mellitus and CVID (1, 5).

In spite of substitutive treatment with gamma globulins, patients with CVID present chronic

Table I

Levels of Lymphoid Populations

Age	LB%	LT%	LT4%	LT8%	T4/T8
5 a	18	62	41	28	1.4
6 a	15	45	25	12	2
8 a	18	62	42	38	1.11
9 a	13	79	39	43	0.90
10 a	10	84	54	32	1.69
12 a	12	75	33	47	0.70
14 a	11	76	37	44	0.84
15 a	14	73	34	42	0.81

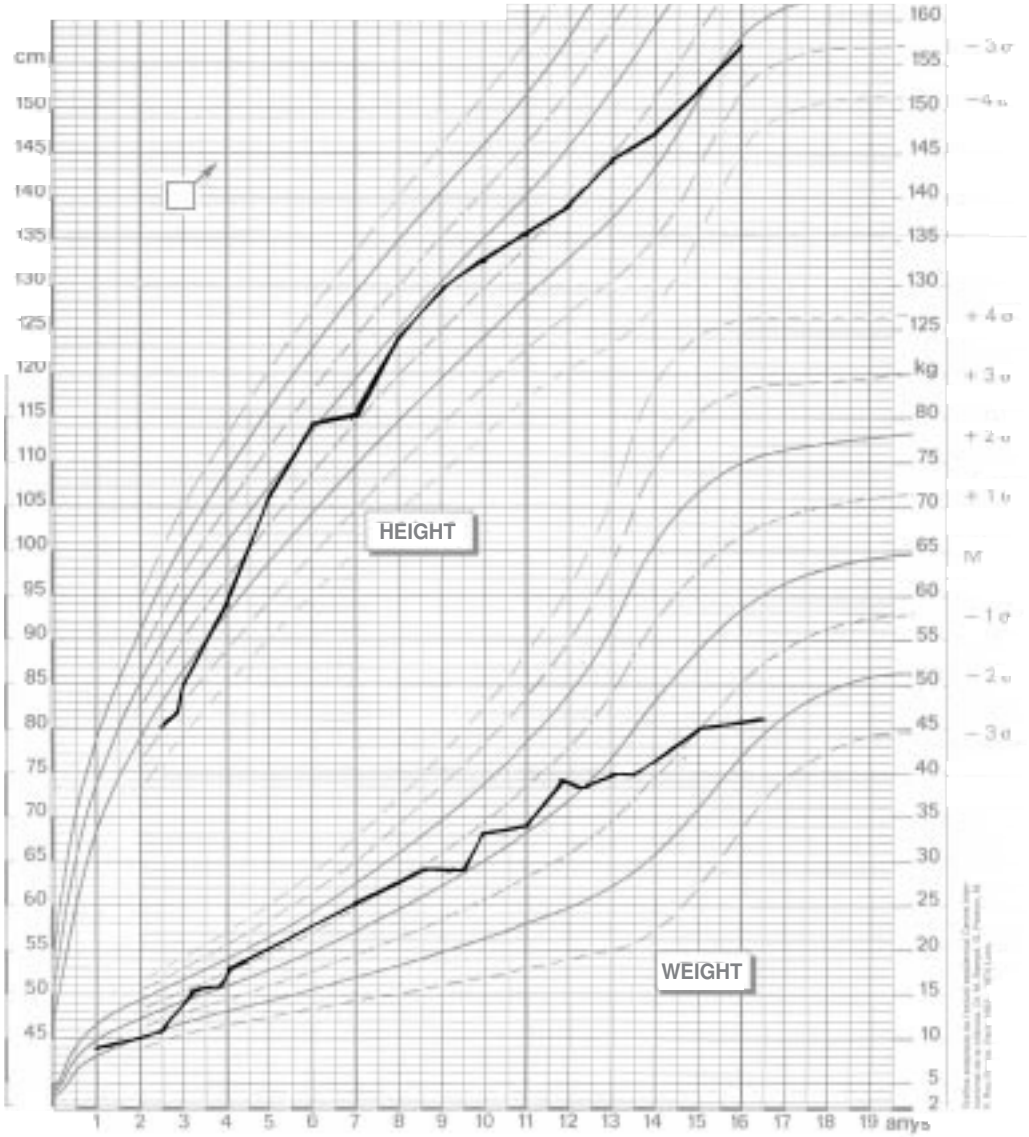


Figure 5.—Patient's auxometry show a desacceleration in the growth velocity and in the weight.

sinopulmonary infections and chronic pulmonary disease (1, 2, 16).

CONCLUSIONS

1. Common variable immunodeficiency in our patient is associated with celiachia and Diabetes mellitus type I.
2. The immunological pattern was a quantitative and qualitative alteration of the humoral response, with hypogammaglobulinemia of the three types (IgG, IgM and IgA), absence of isohemagglutinins, and alteration in the cell response reflected by an altered delayed hypersensitivity skin test; CD4 lymphocyte population reduced.
3. The infectious processes have affected mainly the respiratory tract, both upper and lower, in spite of substitutive treatment with intravenous gamma globulin.
4. The evolution of the diabetes mellitus has been poor due to the multiple decompensations.

RESUMEN

La inmunodeficiencia común variable es un trastorno caracterizado por hipogammaglobulinemia con linfocitos B en sangre periférica e infecciones de repetición. Describimos un niño diagnosticado a la edad de cinco años de inmunodeficiencia común variable que de lactante se diagnosticó diabetes mellitus y enfermedad celíaca. Ha presentado durante su evolu-

ción múltiples infecciones respiratorias a pesar de la terapia de sustitución con gammaglobulinas. Inmunológicamente ha presentado disminución de la población linfoide CD4. Expresa los alelos DQ2 A1 0501 y B1 los cuales están fuertemente asociados con susceptibilidad a diabetes mellitus insulinodependiente y enfermedad celíaca, pero no expresa los alelos que más frecuentemente se describen en esta asociación HLA clase II DR3 y DR4. Su crecimiento pondoestatural se ha visto afectado debido a su enfermedad de base y a todas las complicaciones secundarias.

Palabras clave: Inmunodeficiencia común variable. Diabetes mellitus. Enfermedad celíaca. Hipogammaglobulina. Autoinmunidad.

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