Hashimoto’s thyroiditis, hypoparathyroidism and coeliac disease: lessons from a rare association

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Abstract
We present the case of a 36 years old woman, affected by euthyroid Hashimoto’s thyroiditis (HT) from the age of 20. She reported the following symptoms for three years: weight reduction, abdominal pain, alternate constipation and diarrhoea, tiredness, paresthesias and cramps. Biochemical evaluation revealed low iron levels (21 ug/dl, with microcytic anemia) and hypocalcemia (6.6 mg/dl), first attributed to coeliac disease (EMA IgG, AGA IgG-A and tTG IgA positivity; Marsh-Oberhuber 3a/3b type at duodenal biopsy). TSH, PTH and 25-OHD3 were in the normal range. Although the patient was on a gluten-free diet for the second year, cramps persisted and facial spasms and tetanic crises appeared. One year later she came to our attention with severe hypocalcemia (Ca 5.1 mg/dl, Ca++ 0.6 nmol/L) and low PTH (2.5 pg/ml). A diagnosis of primary hypoparathyroidism was made and conventional treatment was started. In the following months, symptomatic hypocalcemia persisted (6.7 mg/dl, Ca++ 0.7 nmol/L), despite the gradual increase of calcium and calcitriol supplements. Gastro-intestinal re-evaluation demonstrated gluten contamination, so as to hypothesize that the scarce dietary compliance had caused persistent malabsorption and had made the hypocalcemia difficult to manage. The observation of these three disorders coexisting in a single patient, never reported by the literature, warns us about the virtually unlimited possibilities of autoimmune disease clustering. Clinicians should be aware of the increased risk of developing additional AIDs in patients with one autoimmune disorder.

Key-Words: Autoimmune disorder, Hypoparathyroidism, Hashimoto thyroiditis, Coeliac disease

Introduction
Autoimmune diseases (AIDs) represent a heterogeneous group of disorders that affect specific target organs or multiple organ systems, due to the loss of immunological tolerance to self-antigens [1-3]. These conditions share common genetic background and immunopathogenic mechanisms, which explain the clinical similarities they have among them as well as their familial segregation and clustering with each other [3]. Despite their pathogenesis is not fully
understood yet, AIDs are deemed to be multifactorial diseases, in which environmental and existential factors trigger the development of the immune response against self-antigens in genetically susceptible individuals [1-3]. Several genes involved in immunological pathways, like HLA and T-cell regulatory genes, confer generalized susceptibility to autoimmunity, while other genes exert either predisposing or protective effects for particular types of disease in a tissue-specific fashion [1,4,5]. Besides the genetic and epigenetic factors, autoimmune disorders may also share common existential and environmental factors potentially involved in the development and progression of the disease, such as age, sex, improved hygiene and vitamin D deficiency, whose role in autoimmunity is intensely debated at present [2, 6].

It is well known that patients with a single AID have an increased risk of developing other AIDs over time [4-5]. The association of specific AIDs amounts to autoimmune polyglandular syndromes (APSs). APSs (types 1, 2, 3 and 4) represent a heterogeneous group of rare diseases characterized by autoimmune activity against more than one endocrine organs, although non-endocrine organs can be affected, with variable onset and phenotype [7]. The two major APSs, namely APS1 and APS2, both have adrenal insufficiency (Addison's disease) as a prominent component, while the APS3 has an autoimmune thyroid disease as a leading feature and the APS4 include a variety of other associated disorders [7]. In particular, APS1 is defined by the presence of ≥ 2 of the following: Addison disease, chronic mucocutaneous candidiasis and hypoparathyroidism (HypoPTH) [7,8]. APS1 has a strong genetic component since it is almost always inherited in an autosomal recessive manner linked to mutation of the AIRE (Autoimmune Regulator) gene on chromosome 21, it usually occurs in sibling and begins in childhood [7,8]. Herein, we report the case of a 36 year-old woman with the unusual association of three AIDs, namely Hashimoto's thyroiditis (HT), celiac disease and HypoPTH.

Case Report.

A 36 years-old woman, affected by euthyroid HT from the age of 20, was referred to our Division reporting the following symptoms for three years: weight reduction, abdominal distention and pain, alternate constipation and diarrhoea, tiredness, paresthesias and cramps. Her family history was positive for cardiovascular diseases (both parents, hypertension) and metabolic diseases (mother, diabetes mellitus 2). Two years ago, biochemical evaluation had revealed low iron levels (21 ug/dl, with microcytic anemia) and hypocalcemia (6.6 mg/dl), first attributed to malabsorption. TSH was in the normal range (3.49 uIU/ml; n.v. 0.4-4.0), as well as were PTH (41.39 pg/ml, n.v.15-75) and 25-OH-D3 (40.64 ng/ml; >30). With suspicion to coeliac disease (CD), serum levels of antigliadin (AGA) IgG-A, anti-endomisium (EMA) IgG-A, and anti-tissue
transglutaminase (tTG) IgA had been measured and found to be elevated (AGA IgA 654 RU/ml and IgG 93 IU/l, nv <12; EMA IgG positive; Ttg IgA >200 RU/mL, nv <10). The patients had undergone endoscopy and jejunal biopsy, that showed severe villous atrophy, increased intraepithelial lymphocytes and a lamina propria infiltrate of mixed inflammatory cells. Biopsy confirmed diagnosis of CD (Marsh-Oberhuber 3a/3b type) and gluten-free diet was initiated finally. Although the patient was on a gluten-free diet for the second year, cramps persisted and facial spasms and tetanic crises appeared. One year later she came to our attention with severe hypocalcemia (Ca 5.1 mg/dl, Ca++ 0.6 nmol/L, P 6.4 mg/dl). PTH was low (2.5 pg/ml). (Table 1).

Her past medical history was negative for previous thyroid surgery or radiation exposure, haematological, renal or other chronic diseases. Physical examination revealed positive Chvostek and Trousseau signs. No skin or mucus membrane abnormalities were noted, including normal hair with no hair loss, no vitiligo, or mucucutaneous candidiasis, nor nails alterations. Also no evidence of spondyloarthropathy was noted. Ophthalmological assessment was normal with no cataract and no any fundus abnormalities, as was neurological evaluation. Abdominal ultrasound revealed no nephrocalcinosis or nephrolithiasis. Urinary calcium was mildly elevated. There was no clinical and biochemical evidence of hypoadrenalism (Table 1) nor specific Ab positivity (adrenal cortex-Ab and anti-21OH-Ab).

Since her family and personal history was negative for any syndromic and/or genetic disorder causing chronic refractory hypocalcemia, a diagnosis of primary autoimmune HypoPTH was postulated and conventional treatment with calcium and calcitriol supplements was started, accordingly to currently guidelines [9].

**Table 1.** Serum and urinary biochemical data of our patient at admittance.

<table>
<thead>
<tr>
<th>Analyte (unit of measure)</th>
<th>Patient’s value*</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcemia (mg/dl)</td>
<td>5.1</td>
<td>8.2–10.4</td>
</tr>
<tr>
<td>Ionized calcemia (mg/dl)</td>
<td>0.6</td>
<td>1.10-1.30</td>
</tr>
<tr>
<td>Phosphatemia (mg/dl)</td>
<td>6.4</td>
<td>2.8–4.5</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>137</td>
<td>130-148</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.7</td>
<td>3.5-5.2</td>
</tr>
<tr>
<td>Magnesium (mg/dl)</td>
<td>1.7</td>
<td>1.6-2.3</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.7</td>
<td>0.5-1.4</td>
</tr>
<tr>
<td>Urea nitrogen (mg/dl)</td>
<td>28</td>
<td>10-50</td>
</tr>
<tr>
<td>Total proteins g/dl</td>
<td>6.9</td>
<td>6-8.2</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>2.5</td>
<td>12-62</td>
</tr>
<tr>
<td>1,25 OH-vitamin D (ng/ml)</td>
<td>40.8</td>
<td>&gt;30</td>
</tr>
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In the following months, symptomatic hypocalcemia persisted (6.7 mg/dl, Ca++ 0.7 nmol/L), despite the gradual increase of calcium and calcitriol supplements. Laboratory analyses indicated mild anaemia (haemoglobin 11.4 g/dL, iron 33 ug/dl, ferritin 5.4 ng/mL; n.v. 11-206), and gastrointestinal re-evaluation demonstrated gluten contamination, so as to hypothesize that the scarce dietary compliance had caused persistent malabsorption and had made the hypocalcemia difficult to manage.

**Discussion.**

Herein, we report the unusual association on three endocrine and non-endocrine AIDs, namely HT, CD and HypoPTH, as a paradigmatic example of coexistence and mutual interference between autoimmune disorders. HT, the most common autoimmune thyroid disease at any age, is often associated with other AIDs [2, 3]. A recent study of our group has focused on the association between HT and non-thyroidal AIDs, showing that the prevalence of autoimmune comorbidities increases with age and occurs most frequently in adult females. Also this article highlighted the association between HT and CD, either in pediatric/adolescence or adult age [10]. These data are in line with evidence from the literature showing a strong association between CD and HT, to the extent that a routine screening for CD has been widely proposed in patients with autoimmune thyroid disease [3, 10-12]. On the contrary, autoimmune HypoPTH is a rare disease and, when coexisting with other AIDs, it usually occurs in the context of the APS1, with the classical triad including also chronic mucocutaneous candidiasis and adrenocortical failure [7,8].

Herein we have reported the unusual occurrence of HypoPTH in association with HT and CD. To the best of our knowledge, the present is the second case reported in the literature of such an
association of autoimmune diseases. Prior to us, Silva and Souza reported on a 50 year-old woman with autoimmune hypothyroidism of difficult compensation, associated with anemia, hypocalcemia with a previous episode of tetany, hypomagnesemia, psychologic alterations and important weight loss [13]. However, the clinical case was mainly focused on the difficult compensation of hypothyroidism due to undiagnosed CD. The case of our patient is the first one described where the association of HT and CD is complicated by the further presence and difficult therapeutic correction of HypoPTH. The complex autoimmune diathesis of our patient is clinically relevant for diagnostic management and therapeutic approach. Indeed, in our patient the diagnosis of HypoPTH has been delayed, because at first evaluation the paucisymptomatic hypocalcemia associated with classic presentation of malabsorption (weight reduction, diarrhoea, low iron levels) was related to recently diagnosed CD and the inappropriate normal PTH values for calcium levels were not considered. Furthermore, once diagnosed, the medical treatment of HypoPTH was obstructed by patient’s scarce compliance to gluten-free diet and persistent malabsorption.

The observation of these three disorders coexisting in a single patient, never reported by the literature, warns us about the virtually unlimited possibilities of autoimmune disease clustering; moreover, we can notice reciprocal interferences between CD and HypoPTH in controlling hypocalcemia, worsened by coeliac disease-related malabsorption, that on the other hand would be successfully overcome by a regular gluten-free diet. The presented case shows that there is a need for continuous surveillance for the development of other AIDs in predisposed patients that have already been diagnosed with an AD. In many cases, the presence of one AD may lead to the discovery of other autoimmune conditions, also improving therapeutic approach, as in our patient.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

References