Autoimmune thyroid diseases in children and adolescents with Maturity Onset Diabetes of the Young

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Background

The relationship between Type 1 diabetes mellitus (T1DM) and autoimmune thyroid disease (ATD) in the pediatric age has been described in the literature. The prevalence of thyroid autoantibodies in children with T1DM ranges from 3% to 50% in different countries and populations, which is significantly higher than in the general population (range, 1% to 4%). In adults, various studies have shown a high prevalence of thyroid disorders, including a higher prevalence of ATD, also in patients with T2DM (12%–23%) compared to the non- diabetic population. To the best of our knowledge, the relationship between thyropathies and other forms of diabetes, such as monogenic diabetes has not been investigated.

Maturity-onset diabetes of the young (MODY) is a collection of different forms of monogenic diabetes with an autosomal dominant mode of inheritance spanning up to two or more generations. The gene mutations result in disordered glucose sensing and insulin secretion leading to the development of hyperglycemia. The onset of MODY occurs during childhood, adolescence, or in adulthood, but it is more common before 25 years of age and it accounts for 2–5% of all diabetic forms in young patients.

The aim of our study was to assess the prevalence of ATD in children and adolescents with MODY type 2 (MODY2) compared to patients with T1DM and a control group, in order to define the usefulness of careful follow-up of the thyroid autoimmunity .

Patients and methods

We recruited 23 children and adolescents with MODY2 (11F/12M;13.5±5.3 yr) and 166 patients with T1DM (80F/86M; 14.0±4.7 yr) from the Pediatric Endocrinology and Diabetology Unit of the Fondazione IRCCS Policlinico San Matteo.

The control group consisted of 62 age-matched healthy subjects (34F/28M).

The thyroid evaluation consisted of a clinical evaluation, measurement of basal serum TSH, free T3, free T4 and anti-thyrotropin receptor antibodies (TRAb), anti-thyroid peroxidase antibodies (TPOAb) and anti-thyroglobulin antibodies (TGAb) as well as thyroid ultrasonography.

ATD diagnosis was based on the finding of one or more positive thyroid autoantibodies and a characteristic thyroid ultrasound lacking homogeneity, with a hypogenic or mixed echopattern. To detect the presence of celiac disease, as an associated autoimmune disease, patients were checked for anti-transglutaminase antibodies (tTG-IgA) and anti-endomysial antibodies (EMA-IgA) together with anti-transglutaminase antibodies (Ttg-IgG) in case of IgA deficiency.

To consider the impact of a familial predisposition on the development of ATD, a family history of autoimmune thyroid disorders was collected (only first-degree relatives were considered significant).

Results

ATD was diagnosed in 15 patients with T1DM (10.5%; 9F/6M), in four with MODY2 (17.4%; 4F) and finally in one control subject (1.6%, 1F). A significantly higher ATD prevalence was detected in T1DM and MODY2 compared to controls (p=0.02), without differences between T1DM and MODY2 (p=0.26). The mean age at ATD diagnosis was 12.4±3.3 yrs. in subjects with MODY2 and 13.7±2.1 yrs. in T1DM (p=0.7). There were no gender differences in the prevelance of ATD in T1DM (p=0.42); on the contrary, in patients with MODY2 a higher prevalence was noted in females (p=0.04).

Thyroid function in the euthyroid range was detected in all subjects with MODY2. Patients with T1DM exhibited subclinical hypothyroidism in four cases (p=0.52; 3F/1M; all were treated with L-thyroxine). Hyperthyroidism was detected in two males (p=1.0). ATD was associated with celiac disease in two patients with T1DM and in no subjects with MODY2 (p=1.0).

None of the patients with MODY2 and five subjects with T1DM (p=0.53) had a positive family history of autoimmune thyroid disease (Hashimoto's thyroiditis).

Conclusions

Autoimmune thyroiditis is known as the most common disorder associated with T1DM. ATD and T1DM have a common genetic background and similar pathogenesis so it is possible to observe them both in the same individual or family. For the first time, we report the increased prevalence of ATD in patients with MODY2 as compared with a control group. Additionally, we noted an increased ATD occurance in females. No association with celiac disease or positive family history were detected in this population.

MODY is a genetic form of diabetes related to mutations in at least 13 genes. MODY2 results from mutations in the glucokinase gene. This form of diabetes is not usually related to the presence of autoimmunity and a laboratory evaluation reveals negative pancreatic autoantibodies for T1DM, although in a limited number of reports autoantibody positivity has been described [9]. Thyroid disorders in MODY2 have not been previously reported and the exact cause of the association between MODY2 and ATD has not been fully elucidated.

Despite the negative family history of ATD in subjects with MODY2, the role of genetic factors should be considered.. However, these genetic factors do not fully explain the host's predisposition to ATD, and environmental factors such as infection, chemicals, and nutrition may play a role in the ATD pathogenic process.The mechanisms underlying the effects of genetic and environmental factors on the immune system and immune balance are not well understood. The literature proposes that genes and environmental factors may interact to produce a synergistic effect, triggering endocrinopathies like ATD through epigenetic modulation. The role of ATD-causing epigenetic mechanisms, including changes in DNA methylation, covalent modifications of histone tails, and gene silencing mediated by non-coding RNA molecules, should all be considered in the association between MODY2 and ATD.

Clinical observational studies with large numbers of MODY2 patients are mandatory to confirm the results observed here and further research in this field is needed to achieve a better understanding of the networks involved in ATD pathogenesis. However, the increased prevalence of ATD in patients with MODY2, supports the recommendation of a careful follow-up for all children and adolescents with this disorder in order to assess the presence of thyroid autoimmunity.

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Diabetes and insulin

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