The Autoimmunity’s Footprint in Pediatrics: Type 1 Diabetes, Coeliac Disease, Thyroiditis

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\textbf{ABSTRACT}

Pediatric autoimmune diseases are generally rare and when they occur, they might represent a diagnosis and treatment challenge. Many pediatric systemic autoimmune diseases are different from adults’ diseases, thus turning into a special problem for the physicians and researchers attending the children affected by these diseases. The most frequent autoimmune diseases of children and teenagers are represented by type 1 diabetes mellitus, thyroid disease and coeliac disease. Type 1 diabetes mellitus is the most frequent chronic endocrine-metabolic disease of the child, affecting each race and nationality; its incidence is increasing annually, acquiring a “pandemic” character. Coeliac disease appears more frequently in patients with diabetes mellitus rather than in general population (9% versus 2%) and in 10% of all thyroiditis cases there is an association with type 1 diabetes comparing to 6% on the general population. The family members of children with diabetes are also susceptible of presenting manifestations of certain autoimmune diseases comparing to the general population.

We shall present three cases of patients diagnosed with type 1 diabetes mellitus from an early age, with their disease becoming associated with coeliac disease, thyroiditis and even vitiligo over time. It should be mentioned that in one case, the same autoimmune manifestations were also identified in the father.

\textbf{Keywords:} children, type 1 diabetes, autoimmunity, coeliac disease, thyroiditis

\section*{INTRODUCTION}

Pediatric autoimmune diseases are generally rare and when they occur, they might represent a diagnosis and treatment challenge. Many pediatric systemic autoimmune diseases are different from adults’ diseases, thus turning into a special problem for the physicians and researchers attending the children affected by these diseases.

Autoimmune disorders appear when the own immune system attacks and destroys the healthy tissue. Over 80 types of autoimmune diseases are quoted by specialized publications, but the precise cause of autoimmune disorders is still unknown (1). They may occur more frequently in people who have a genetic predisposition to autoimmune diseases. An autoimmune disorder might affect one or several types of organs or tissues, which means that a person/patient may suffer from several autoimmune diseases at the same time (2).
Type 1 diabetes mellitus is the most frequent endocrine-metabolic disease of children and teenagers. Its incidence is increasing annually for each population, regardless of race and nationality. Type 1 diabetes mellitus results from the autoimmune destruction of insulin-producing beta cells at the pancreas level; this disease is basically a complex genetic disorder expressed by an increased frequency in families where there are relatives suffering from type 1 diabetes mellitus and other autoimmune diseases (3, 4). The inheritance of this genetic tare in the presence of certain environment triggers leads to the identification of insulin producing cells (pancreatic B) as “non-self” and then to their destruction by auto-antibodies. The most frequent autoantibodies associated to diabetes mellitus are the islet cell antibodies (ICA), insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD65), molecules associated to protein tyrosine phosphatase IA-2 (ICA 512) and IA-2SS (phogrin) and/or Zinc transporter 8 (ZnT 8) (50). GAD and ZnT8A antibodies are associated to thyroid autoimmunity (52). The family members of children with diabetes are more likely to be susceptible of having antibodies and manifestations of certain autoimmune diseases compared to general population (54-56).

Studies reported in the specialized literature show that the risk of pediatric patients developing diabetes mellitus is 5 to 6% when the father has type 1 diabetes and 3 to 4% when the mother has it (3). It is considered that a part of the mother’s chromosomal material or the DNA becomes inactivated when passed to the children, thus leading to the risk’s percentage difference of acquiring the disease for the child. In case a brother has type 1 diabetes, the risk is 5–6%; however, the risk increases when the brother shows major complex of histocompatibility (MHC) identical haplotypes. In case of monozygotes where one suffers from type 1 diabetes mellitus, the other one’s risk to develop the disease is considered to be of approximately 40%, but recent research suggests that the percentage could be much higher (3, 4).

After decades of research and thousands of reports, HLA remains by far the strongest predictor of type 1 diabetes risk. “HLA” does not refer to one single genetic locus, but to an area of the genome which includes genes codifying three classical HLA II antigens and three classical HLA I antigens as well as a series of other genes whose products might influence susceptibility. Gene polymorphisms besides those within the HLA area, especially genes for insulin and PTPN22 genes (protein tyrosine phosphatase gene), also influence susceptibility for type 1 diabetes but in a smaller percent than the classical HLA loci. Thus, the genes known to be affecting T1D susceptibility may be grouped in three general categories: immune function, insulin expression and β-cellular function. Besides HLA, the locus with the highest susceptibility is the insulin gene itself, when insulin expression levels are affected. Other loci are involved in the β cell function (3).

It is a known fact that type 1 diabetes mellitus is associated with a series of other autoimmune diseases; the strongest association is with celiac disease; hypothyroidism or Hashimoto disease; Graves disease or hyperthyroidism; Addison disease or adrenal insufficiency and pernicious anemia, and rheumatoid arthritis (4).

The celiac disease is associated to type 1 diabetes mellitus in 4 up to 9% of all cases, but for 60-70% of asymptomatic cases (“Silent celiac disease”). Children with type 1 diabetes mellitus have an increased risk of celiac disease in the first 10 years of diabetes evolution (14). Both celiac disease and type 1 diabetes are two genetic disorders based on similar genes (DQ2 and DQ8). Both of them are immuno-regulated and associated to other autoimmune diseases of autoimmune thyroid and rheumatoid arthritis type. Approximately 3.5–10% of people suffering from celiac disease develop type 1 diabetes mellitus and vice versa. Celiac disease or type 1 diabetes mellitus screening is recommended for persons already diagnosed with one of the two autoimmune disorders. When individuals suffer from both diseases, type 1 diabetes mellitus is most commonly diagnosed first; the speculated motivation is that the diabetes symptoms are more obvious and therefore it is easier to be diagnosed than celiac disease (5-13).

Patients with type 1 diabetes mellitus and undiagnosed celiac disease may present unstable glucose values, reduced need of insulin, delayed gastric emptying, weight loss, growth retardation (for children) and reduced bone density. Some diabetic patients with newly diagnosed celiac disease may present different symptoms: hypoglycemic disorders, increased need of insulin and hemoglobin A1C increased values (glycosyla-
The autoimmune thyroid disease is frequent in the general population and its prevalence increases with age. In children with type 1 diabetes mellitus, autoimmune thyroid disease is one of the most frequent associations of autoimmune diseases. Autoimmune thyroiditis associated to type 1 diabetes mellitus is also clinically silent but it may progress either as thyroid disease with obvious or subclinical hypothyroidism, or with hyperthyroidism (44). Thyroid dysfunction may affect the control of diabetes mellitus. Autoimmune thyroid disease is easier detected by measuring the circulating antibodies against thyroid peroxidase (anti-TPO Ab) and thyroglobulin (anti-Tg Ab) (36). Autoimmune thyroiditis associated to type 1 diabetes mellitus may have two clinical forms: hypothyroidism and hyperthyroidism.

The primary or subclinical hypothyroidism due to autoimmune thyroiditis occurs in approximately 3-8% of the young adults with type 1 diabetes mellitus (57, 58), with an incidence between 0.3 and 1.1 in 100 children and teenagers with diabetes per year (44, 45). Anti-thyroid antibodies may be detected in up to 29% of all patients with type 1 diabetes mellitus throughout the first years of illness (51, 58), and they are highly predictive for the hypothyroidism development, with a risk of approximately 25% (58, 60). Anti-thyroid antibodies are more frequent in girls than in boys, most of the times during pubertal maturation (58), and they can be associated to aging and long duration of diabetes (58, 60). Hypothyroidism is accompanied by a series of anomalies in plasma lipid metabolism, triglycerides, low density lipoproteins (LDL), cholesterol presenting high values. The clinical features may include the presence of a painless goiter, weight gain, delayed growth, fatigue, lethargy, cold intolerance, bradycardia (57) and a poor glycemic control. Hypothyroidism is confirmed by demonstrating a low free thyroxine and a high concentration of TSH. The presence of compensated hypothyroidism may be detected in a person with a moderately increased TSH but a normal level of free thyroxine.

Hyperthyroidism within autoimmune thyroiditis is usually associated with exacerbation of glucose control and increase of insulin necessary by gluconeogenesis increase at hepatic level, fast glucose absorption at gastro-intestinal level and increase of insulin resistance until occurrence of diabetic ketoacidosis. Hyperthyroidism is less frequent than hypothyroidism in association with type 1 diabetes mellitus, with a prevalence of 3-6% in diabetic children (58), and remaining more frequent than in general population. Hyperthyroidism should be considered in case there is an unexplained difficulty in maintaining glycemic control, weight loss despite a normal appetite, agitation, tachycardia, tremor, heat intolerance, thyroid enlargement or specific eye symptoms. The diagnosis of autoimmune thyroiditis with hyperthyroidism is established based on anti-receptor TSH antibodies (TR Ab), TSH dosage when it is low and increased T3.

Considering the high prevalence of autoimmune thyroiditis, the thyroid dysfunction in patients with type 1 DZ and the effects of thyroid disorders on their metabolic control, there is a general agreement regarding the diabetic patients’ screening for thyroid antibodies and dysfunction. Despite this fact, there is still no consensus regarding the screening of autoimmune thyroiditis and thyroid function in patients with type 1 DZ (49).

**CASE 1**

Patient S. A.-M. diagnosed with type 1 diabetes mellitus at the age of 1 year and 3 months. The onset included the diabetic ketoacidosis (pH 7.22; bicarbonate 6 mmol/L; base excess (BE) 21.9 mmol/L), glyceria 566 mg/dL, glycosuria, ketonuria, HbA1c 12.5%. The patient’s
evolution in the following eight years was favorable, with an average HbA1c of 8% in this period. At the age of nine, upon the annual evaluation, the patient presents Ig A type Ac anti-transglutaminase 150 U/mL (normal values < 10 U/mL) and Ig A anti-gliadin antibody 30 U/mL (normal values 0-20 U/mL); this is the reason why a duodenal biopsy is decided. The histopathological result indicated Marsh III stage celiac disease. Gluten-free diet is initiated (partially observed by the patient) for two years, leading to a poor glycemic balance (HbA1c 9-10%). Also at that time (at the age of 11), the appearance of vitiligo areas is noted, especially on the neck and dorsum of the hands, and the evaluation of thyroid function – TSH 9.9 µU/mL (normal values: 0.6–4.84 µU/mL), FT4 18.9 (normal values 12.5–21.5 pmol/L), ATPO 496 UI/mL – showed significant values for an autoimmune thyroiditis in the subclinical hypothyroidism stage.

Thus, within 10 years from diabetes onset, the patient presents the association of three autoimmune diseases: celiac disease, vitiligo, and thyroiditis.

The family medical history is very important: the father was diagnosed with type 1 diabetes mellitus, two years before the little girl’s diagnosis (at the age of 26), by associating the same autoimmune diseases as his daughter, namely vitiligo, celiac disease, fast onset thyroiditis and unfavorable evolution of the diabetes mellitus, which led to the occurrence of diabetes mellitus major complications; therefore, at the age of 42 he is a candidate for kidney transplant.

CASE 2

The patient M. A-M. D, diagnosed with diabetes mellitus at the age of 1 year and 7 months. The onset was also accompanied by diabetic ketoacidosis (pH 7.24, BE 22 mmol/L, bicarbonate 10 mmol/L) glycemia 468 mg/dL, glycosuria, ketonuria, HbA1c 11.6%. The glycemic balance was unstable (the patient presented hypo- – hyperglycemia) in the first four years, due to an extreme appetite, which led to the occurrence of a poor nutritional condition associated to mental disorders (psychomotor agitation, negativism) at the age of six. At the same time, the Ac anti-gliadin and anti-transglutaminase positivity was detected, and this is the reason why duodenal biopsy was performed. The histopathologic diagnosis indicated Marsh III stage celiac disease. Initially, the gluten-free diet was not fully observed, the glycemic balance continued to be unstable with high daily hypo/hyperglycemic values, which led to the occurrence of a significant microalbuminuria (287 microg/dL) for an early diabetic nephropathy at the age of 10. At the same age, the ATPO,TSH and fT4 values lead to the Hashimoto autoimmune thyroiditis diagnosis confirmed by thyroid ultrasound, which describes a thyroid with a reduced echogenicity, several homogeneous nodular hypoechoic images with dimensions of up to 4 mm and hypoechoic layers disposed throughout the entire thyroid.

Within the evolution, gluten-free diet is initiated, which is fully observed this time, the treatment of thyroid dysfunction with L-thyroxine as well as of early diabetic nephropathy with Captopril leading to the normalization of glycemic balance, weight status and microalbuminuria negativity.

CASE 3

C.A. diagnosed with type 1 diabetes at the age of 10, ketoacidosis onset, good glycemic control until the age of 14 years (6–6.5%), after that followed by cognitive disorders with extremely poor school results, behavioral (agitation, nervousness, smoking) and dietary disorders (alcohol consumption and failure in observing the carbohydrate quantity and quality) with the occurrence of frequent, medium and severe hypoglycemia (3–4 episodes per year) that required hospitalization. During these hospitalizations, significant weight loss and unresponsive tachycardia to the beta-blocker treatment were determined; this is the reason why thyroid function investigations were performed, which subsequently revealed highly reduced TSH and highly increased T3; thus, Graves disease was diagnosed and treatment with Thyroxol was initiated.

Regarding the family medical history, the mother is also diagnosed with chronic autoimmune thyroiditis with hyperfunction (Graves disease).

DISCUSSION

It is an already known fact that autoimmune diseases affect a substantial percentage of the
population, thus providing a wide subject for the future scientific researches concerning the discovery of methods by which these diseases may be detected, prevented and even healed. An equally well known fact until now is that certain autoimmune diseases do not “appear” alone but in association with others; in this regard, the most common combination is of type 1 diabetes mellitus with thyroid diseases, followed by the association of type 1 diabetes with celiac disease.

Patients diagnosed with celiac disease require the observance of a strict free gluten diet throughout their entire lives in order to prevent acute (malabsorption, diarrhea, folic acid deficiency, iron deficiency, growth retardation) and chronic complications (intestinal lymphoma, osteoporosis, autoimmune diseases, infertility, death) (61-63). Gluten exclusion associated to a diet imposed by diabetes mellitus lead to an unstable/poor glycemic balance, with an accelerated onset of diabetes mellitus chronic complications (see the presentation of the second case complicated with diabetic nephropathy). Thus, unfortunately, failure to observe a gluten-free diet in a patient with diabetes mellitus and celiac disease is a very common situation. The purpose of a gluten-free is to achieve and maintain a proper glycemic balance, normal blood pressure, normal lipid profile and a proper body weight. The maintenance of a constant glycemic control is essential to reduce both micro- and macro-vascular complications of type 1 diabetes mellitus (64, 65). This is why patients’ counseling and education on carbohydrate quantity and quality is important (66). But gluten-free diet might be an obstacle, given that many gluten-free foods provide a high glycemic index. Therefore, the association of celiac disease in a person with diabetes may influence the prognosis of a diabetic patient regarding the onset of long term complications (see the presentation of the first case – the rapid onset of severe chronic complications in the patient’s father).

The relation between thyroid disorders and diabetes mellitus is characterized by a complex interaction. Hyperthyroidism modifies the glycemic control in diabetic subjects; also, it may increase and accelerate diabetic retinopathy, while hypothyroidism may increase susceptibility to severe hypoglycemia, complicating diabetes mellitus management with the early occurrence of neuropsychiatric complications (see the presentation of the third case).

**CONCLUSION**

Type 1 diabetes as an autoimmune disease associated with other autoimmune diseases. The early determination of associated autoimmune diseases in the absence of clinical symptoms requires regular screening (annually), starting with the first year after diabetes onset. Family aggregation of autoimmune diseases requires the examination of all family members. Type 1 diabetes and management of its complication for short and long term depends on early diagnosis and treatment of the associated autoimmune diseases.

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