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Frequency of Autoimmune Diseases Associated with Type 1 Diabetes Mellitus in Children and Adolescents in Albania

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1. Abstract

1.1. Background: Type 1 diabetes mellitus (T1D) is the most common chronic autoimmune metabolic and endocrinological disease of children and adolescents. Children and adolescents with T1D are at increased risk of developing other autoimmune diseases; more often autoimmune thyroiditis followed by celiac disease and other conditions, which significantly affect the clinical management of the disease, metabolism and quality of life, especially in the pediatric age. The aim of this study was to evaluate the frequency of autoimmune diseases associated with T1D in children and adolescents in Albania.

1.2. Methods: During 1 January 2010 to 31 December 2014, 152 children aged <15 years old and newly diagnosed with T1D in the premises of University Hospital Center "Mother Theresa" in Tirana, Albania, were included in the study. T1D was diagnosed according to WHO criteria. Basic sociodemographic information as well as data on concomitant autoimmune conditions were retrieved through patients' clinical records and interviews with parents. Binary logistic regression was used to evaluate the factors associated with the presence of autoimmune disorders among T1D children.

1.3. Results: More than half of pediatric patients were males (52%), about 60.5% were less than 10 years old and 75% resided in urban areas. Positive family history was noticed in 30.9% of cases. The prevalence of any autoimmune disorder among T1D children was 25.7%, significantly higher among females and those with family history for both T1D and T2D. The most common autoimmune disorder at the moment of T1D diagnosis was Hashimoto's thyroiditis (11.8%), followed by subclinical hypothyroidism (3.3%) and celiac disease (2.6%). Females were significantly 2.42 times more likely to have autoimmune disorders compared to males, whereas children with family history for both T1D and T2D were 7.5 time more likely to have an autoimmune disorder compared to children with no family history, but this association had borderline significance (P=0.086).

1.4. Conclusion: The present study evidenced a relatively high prevalence of concomitant autoimmune disorders among children newly diagnosed with T1D in Albania. Because of the negative effects of undiagnosed autoimmune disorders on the health, well-being and quality of life of T1D children, these children need to be screened about concomitant autoimmune disorders at the moment of T1D diagnosis and during the course of diabetes.

2. Introduction

Diabetes Mellitus Type 1 (T1D) is the most common metabolic and endocrinological disease of an autoimmune nature in children and adolescents which is caused by absolute insulin deficiency as a result of the destruction of insulin-producing pancreatic β-cells [1]. Children and adolescents with T1D are at increased risk of developing accompanying OR manifesting other autoimmune diseases compared to healthy children [2, 3]. This is related to the genetic predisposition which, under the influence of environmental factors, induces a specific immune response leading to the development of these diseases. Numerous studies have pointed out the genetic basis of the coincidence of T1D and other autoimmune diseases [4]. The association of different autoimmune diseases in the same individual is explained by the fact that they have a common

genetic background as demonstrated by concordance in monozygotic twins (85%) and family aggregation [5].

The autoimmune process that develops in pancreatic beta cells can also affect other organs resulting in the development of specific endocrine autoimmune diseases or various non-endocrine tissues and organs leading to the development of non-endocrine autoimmune diseases [6]. The appearance or development of other autoimmune diseases in patients with T1D increases morbidity and mortality and impairs the quality of life of the affected indidivuals [4, 7]. The autoimmune diseases that most often accompany T1D are: autoimmune thyroid disease (SAT) (15-30%), celiac disease (CD) (4-9%), autoimmune atrophic gastritis/pernicious anemia (5-10%), vitiligo (2-10%) and Addison's disease -it (0.5%) 2,3]. Autoimmune diseases that less frequently accompany T1D in children and adolescents are autoimmune hepatitis, Autoimmune Polyglandular Syndrome (APS), and primary ovarian insufficiency. Autoimmune diseases appear in genetically predisposed individuals and are inherited as complex genetic traits.

Type 1 diabetes (T1D) and autoimmune thyroid disease (SAT) are the most frequent chronic autoimmune diseases worldwide [8]. The incidence of SAT in patients with T1D is 2-4 times more frequent (ranging from 19-23.4%) than in the general population (ranging from 2.9 to 3.2%) [9]. The frequency of SAT in the diabetic population varies depending on age, sex, ethnic origin and increases with the duration of the disease. Risk factors for the development of SAT in children and adolescents with type 1 diabetes are almost similar to the adult population, and include gender, duration of diabetes, ethnic origin, presence and persistence of anti-beta cell antibodies (anti-GAD), age of the patient at the moment of diabetes diagnosis [10, 11] and the presence of specific HLA subtypes [9], among others.

Celiac disease (CD) is an immune-mediated chronic polygenic systemic autoimmune disease of the digestive tract that occurs in genetically predisposed individuals. CD is characterized by a specific serum antibody response induced by gliadin, an alcohol-soluble fraction of the gluten protein commonly found in grains such as wheat, rye, and barley. CD is a very common disease in children; CD prevalence has increased significantly, becoming a global public health concern. In Finland, it is seen in 1 case per 99 school-aged children [12], in Italy 1 in 106 cases [13]. CD is diagnosed in 1-5.5% of the pediatric population, with the lowest incidence in Japan and the highest in the Saharan population [14]. The overall incidence and prevalence of T1D and CD is quite diverse across the world and is increasing rapidly [15-17]. CD is the most common autoimmune disease after autoimmune thyroiditis in children with T1D, with an incidence of 0.6 - 16.4% [18] and an average prevalence of 8% [19-21]. For the first time the association between CD and T1D was described in the 1960s [22]. The prevalence of CD is higher in children and adolescents with T1D compared to the general population, varying significantly from 1%-11.1% (average 8%), with an incidence of about 8 in 1000 patients per year [23-26] or 10-20 times higher compared to 0.5% of the general pediatric population [27-34]. The prevalence of CD in T1D patients is similar in the United States, Europe, Canada and Asia, although a study in Sweden reported a higher prevalence of 9% [35]. Predisposing risk factors for the development of CD in patients with T1D are female gender, young age at diagnosis and duration of T1D [18, 27], race, duration of exposure to gluten, co-existence of autoimmune thyroid disease [25,27,36-38], infections at a young age [39], carrying genotypic characteristics or specific alleles similar to T1D [40], etc.

The American Diabetes Association (ADA) [41] and ISPAD [42] recommend that children with T1D should be screened and monitored in order to ensure early diagnosis and treatment of concomitant autoimmune diseases in genetically predisposed individuals [43] in order to prevent significant complications related to undiagnosed disease. The frequency of organ-specific autoimmunity in patients with T1D may be due to multiple immunological abnormalities [44]. Early recognition and treatment of these diseases is very important in order to prevent significant complications as they significantly affect the clinical management of the disease, metabolism, growth, bone health, fertility, quality of life of patients, especially in pediatric age [45].

The information related to autoimmune diseases accompanying T1D in children in Albania is rather scarce. In this context, the current study aimed to document the frequency of autoimmune diseases and related factors among children with T1D in Albania.

3. Methods

3.1. Study Type

This is a case series study involving children diagnosed with type 1 diabetes mellitus in the premises of the Endocrinology and Diabetes Service, at the University Hospital Center "Mother Teresa", Tirana (QSUT), during the period 2010-2014.

3.2. Study Population

During January 1, 2010 – December 31, 2014 a total of 166 children were newly diagnosed with type 1 diabetes mellitus; among these 152 children (79 males and 73 females) met the inclusion criteria (age <15 years old) whereas 3 children were >15 years old at the moment of diagnosis and 11 children were previously diagnosed with T1D and were, therefore, excluded from the study. Thus, the final study population comprised 152 children newly diagnosed with T1D in our practice.

3.3. Data Collection

The clinical records of children as well as interviews with their parents were used as a source to retrieve the needed data and information. Basic socio-demographic data included sex, age at the moment of diagnosis and place of residence. The presence of concomitant autoimmune diseases was based on laboratory examination and measurement of the level of antibodies specific to certain

autoimmune disorders such as autoantibodies associated with T1D (insulin autoantibodies (IAA), IA2, glutamic acid decarboxylase antibodies (GADA) and antithyroid antibodies (Anti TPO) and C-peptide. Information on various other parameters was also collected, including family history for T1D, presence of specific signs and symptoms and other laboratory parameters.

The diagnosis of diabetes mellitus type 1 was determined based on clinical data and laboratory examinations according to WHO criteria (1). The date of onset of diabetes was defined as the date of the first insulin injection.

3.4. Statistical Analysis

Absolute numbers and corresponding percentages were used to describe the categorical data. Mean value and standard deviation was used to describe numerical data.

The square hi test was used to compare categorical variables, or the Fisher's exact test in case of 2x2 tables.

Binary Logistic Regression test was used to evaluate the associations between the presence of autoimmune disorders and the independent variables.

In all cases, the associations between the variables were considered significant if the value of the statistical significance was ≤0.05 (or ≤5%).

All statistical analyzes were performed through the Statistical Package for Social Sciences, version 26 (IBM SPSS Statistics for Windows, version 26) software program.

4. Results

In this study there were included 152 children with type 1 diabetes mellitus (T1D). About half of participants were males (52%). The mean age pediatric patients at the time of diagnosis was 8.3 years ± 3.6 years, with 20.4% of patients being 0-4 years old, 40.1% 5-9 years old and 39.5% 5-9 years old at the moment of diagnosis. Three quarters of T1D pediatric patients included in this study resided in urban areas. About 3 out of 10 T1D children had a positive family history for diabetes: 28.3% of children had a positive history for either T1D or T2D whereas 2.6% had a positive family history for both T1D and T2D (Table 1).

The total prevalence of autoimmune disorders among T1D pediatric children included in the study was 25.7% (Table 2). At the moment of diagnosis, the prevalence of Hashimoto's thyroiditis, celiac disease and subclinical hypothyroidism was 11.8%, 2.6% and 3.3%, respectively, whereas after T1D diagnosis the prevalence of Hashimoto's thyroiditis was 3.3% and the prevalence of celiac disease was 5.2%.

Table 3 shows the distribution of autoimmune disorders by pediatric patients' sex. The prevalence of autoimmune disorders appears to be significantly higher among females (34.2%) compared to males (17.7%). There were no significant age or place of residence differences in the prevalence of autoimmune diseases among T1D children. On the other hand, the prevalence of autoimmune disorders was significantly higher among T1D children with a positive family history for both T1D and T2D (75%) compared to children with positive history for either T1D or T2D (14%) or children without family history for T1D or T2D (28.6%).

Table 4 shows the association of the presence of autoimmune disorders with the characteristics of T1D children. Female T1D children were significantly 2.42 more likely to have autoimmune disorders compared to male children. On the other hand, a positive family history for both T1D and T2D increased the likelihood of autoimmune disorders by 7.5-fold, but this association did not reach statistical significance (P=0.086). Age and place or residence were not significantly associated with the presence of autoimmune disorders among T1D children.

Table 1: Basic socio-demographic data of children with T1D in the study

Variable	Absolute number	Frequency (%)
Total	*152*	*100*
Gender		
Male	79	52
Female	73	48
Age group		
0-4 years	31	20.4
5-9 aged	61	40.1
10-14 years	60	39.5
Residence		
Urban	114	75
Rural	38	25
Family history for T1D or T2D		
No history	105	69.1
History for T1D or T2D	43	28.3
History for both T1D and T2D	4	2.6

Table 2: Autoimune disorders among T1D pediatric patients

Variable	Absolute number	Frequency (%)
Autoimune disorders among all T1D children		
No	113	74.3
Yes	39	25.7
Autoimune disorders at the moment of T1D diagnosis		
Hashimoto's thyroiditis	18	11.8
Celiac disease	4	2.6
Subclinical hypothyroidism	5	3.3
No	125	82.2
Autoimune disorders after T1D diagnosis		
Hashimoto's thyroiditis	5	3.3
Celiac disease	8	5.2
No	139	91.5

Table 3: Autoimmune diseases by sex among T1D pediatric patients

Variable	Presence of autoimmune disorders		P-value †
	No	Yes	
Sex			
Male	65 (82.3) *	14 (17.7)	**0.026**
Female	48 (65.8)	25 (34.2)	
Age group			
0-4 years	26 (83.9)	5 (16.1)	0.293
5-9 aged	42 (68.9)	19 (31.1)	
10-14 years	45 (75.0)	15 (25.0)	
Place of residence			
Urban	85 (74.6)	29 (25.4)	1
Rural	28 (73.7)	10 (26.3)	
Family history for T1D or T2D			
No history	75 (71.4)	30 (28.6)	**0.013**
History for T1D or T2D	37 (86.0)	6 (14.0)	
History for both T1D and T2D	1 (25.0)	3 (75.0)	

*Absolute number and row percentage.

†P-value according to chi square test (Fisher's Exact Test for 2x2 tables).

Table 4: The association between presence of autoimmune disorders with selected independent variables among T1D children – Odds ratios (OR) from Binary Logistic Regression

Variable	OR *	95% CI §		P-value
		Lower limit	Upper limit	
Sex				
Male	1.00 (reference)	-	-	**0.022**
Female	2.42	1.14	5.14	
Age group				0.303 (2)†
0-4 years	1.00 (reference)	-	-	-
5-9 aged	2.35	0.78	7.07	0.127
10-14 years	1.73	0.56	5.32	0.336
Place of residence				
Urban	1.00 (reference)	-	-	0.915
Rural	1.05	0.45	2.42	
Family history for T1D or T2D				**0.032 (2)**
No history	1.00 (reference)	-	-	-
History for T1D or T2D	0.41	0.16	1.06	0.066
History for both T1D and T2D	7.5	0.75	74.989	0.086

* Odds Ratio (OR) of the presence of autoimmune disorders among T1D children versus no autoimmune disorders, according to Binary Logistic Regression.

§95% (95% CI) Confidence Interval for OR.

†Overall P-value according to Binary Logistic Regression and degrees of freeedom (in parantheses).

5. Discussion

The present study for the first-time generated data related to the frequency of autoimmune diseases in pediatric patients with type 1 diabetes mellitus in Albania as well as the factors related to them, thus helping to elucidate these phenomena in this small Balkan country. The findings from this study suggested that the overall prevalence of autoimmune comorbidities in T1D pediatric patients was quite high, 25.7%. The prevalence of concomitant autoimmune diseases was significantly higher among girls than among boys, and increased in patients with a family history of T1D and T2D, but there were no significant age-related or residence-related differences.

The high prevalence of concomitant autoimmune diseases in children with T1D has also been reported by other studies in the in-

ternational arena. For example, a study among 68 children with T1D in Brazil reported that the prevalence of celiac disease (based on the presence of anti-tTG IGA antibodies) was 7.4%, 11.8% of them were positive for anti-thyroid peroxidase antibodies, 11.8% were positive for anti-thyroglobulin antibodies and 5.9% were positive for anti-GAD [46]. Internationally, the prevalence of thyroid-related autoimmune diseases varies between 20% and 30% [28, 47, 48]. Similarly, to our study, the prevalence of concomitant autoimmune disorders is higher among girls with T1D than among boys with T1D [49, 50]. In our study the 11.8% prevalence of Hashimoto's thyroiditis in children with T1D is completely similar to the prevalence of the presence of antibodies against thyroid peroxidase evidenced in another international study [46]. The higher prevalence of celiac disease in children with T1D has also been reported in the international literature; in general, type 1 diabetes mellitus is diagnosed before celiac disease and only 10-25% of celiac disease cases are diagnosed before type 1 diabetes mellitus in children [46]. The prevalence of celiac disease among children with T1D in our study is consistent with international reports [46].

Another study among 493 children aged 0–18 years diagnosed with T1D during the period 2010–2018 in Poland reported that the incidence of T1D increased from 19.2 cases per 100,000 children in 2010 to 31.7 cases per 100,000 children in 2018, where the highest increase in incidence was seen in 5–9-year-old children (from 19.6 cases per 100,000 children in 2010 to 43.5 cases per 100,000 children in 2018) [50]. Likewise, about 12.4% of children with T1D were diagnosed with at least one other autoimmune disease during the study period, and the prevalence of autoimmune diseases doubled from 10.4% in 2010 to 20.8% in 2018; autoimmune thyroid diseases were found in 7.5% of children with T1D with their incidence increasing from 6.3% in 2010 to 12.5% in 2018; 5.3% of children with T1D were diagnosed with celiac disease and its prevalence increased from 4.2% to 9.8% during the study period; the prevalence of autoimmune thyroid diseases was higher in children with T1D positive for glutamic acid decarboxylase-antibodies, in the age group of 15-18 years and among girls [50]. These findings are similar to the results of our study. The authors concluded that the incidence of T1D among children is increasing by about 4% each year, and autoimmune comorbidities represent a significant additional burden for newly diagnosed T1D patients; also, the number of children diagnosed with autoimmune diseases accompanying T1D is increasing rapidly in all age groups of children in recent years [50].

The frequency of SAT in the diabetic population (including Hashimoto's thyroiditis and Graves' disease) is determined by the presence of an increased titer of antibodies; increased titer of anti-TPO and/or anti-Tg and anti-thyrotropin receptor (TSH-R-Ab) [51], respectively. The presence of antithyroid antibodies in the general population varies from 2.9-4.6% (6) and up to 25% of children and adolescents with T1D [8, 44, 51, 52]. Antithyroid antibodies rarely precede the diagnosis of diabetes. [6,8,9] At the time of diagnosis of T1D for the first time, antibodies are present in 17–25% of patients or within 2.5–3 years after diagnosis of T1D (53,54) and 30% of patients with T1D develop SAT during the course of diabetes [55-57]. The presence of anti-TPO antibodies in patients with T1D increases with age, and the long-term persistence of anti-GAD antibodies (9). The presence of antithyroid antibodies during the first years of T1D [53,54] is a strong predictor for the development of hypothyroidism, with a hazard ratio of approximately 25 [54, 58].

Regardless of the consensus for the screening of SAT in people with T1D, especially in asymptomatic ones, serological screening helps a lot in evaluating the prevalence of autoimmune diseases of the thyroid gland [59]. Due to the high prevalence of SAT and pronounced clinical impact, the American Diabetes Association and the International Society of Pediatric and Adolescent Diabetes (ISPAD) recommend that all children with T1D should be regularly monitored by measured thyroid antibodies and thyroid function (TSH, FT4) close to the time of diagnosis, within a few days of the onset of symptoms of diabetes. If the results are normal, the examination should be repeated every 1-2 years or more often if the clinical data (thyroid enlargement, symptoms of hypo- or hyperthyroidism) suggest the presence of SAT [60,61].

Early diagnosed T1D patients with circulating antibodies may be clinically euthyroid or hypothyroid, with a prevalence of 2 to 5% [8,53,58,62]. In one study, 9.4% of patients sought L-thyroxine therapy and 6.1% of patients with positive antibodies remained euthyroid for a mean duration of diabetes of 3.9 years (0.2-12.4 years) [58].

Hyperthyroidism occurs rarely in children with T1D, with a reported prevalence of about 1%, which is higher than in non-diabetic children [63]. Children with T1D and hyperthyroidism are more likely to have a history of diabetic ketoacidosis, hypoglycemia, and arterial hypertension [63], usually identified at the time of diabetes diagnosis. Thyroid autoimmunity is particularly common in patients with type 1A diabetes (>1/4 of patients) [59].

In patients with T1D, 5% are positive for CD (gluten sensitive enteropathy) in intestinal biopsy [64,65]; 7-10% are positive for anti-endomysial antibodies [66-68] and/or antitissue transglutaminase antibodies [53].

In T1D patients, CD precedes the onset of diabetes in 10% of cases, and approximately 90% of CD cases are diagnosed during screening at the time of T1D diagnosis for the first time as well as during its course [69,70].

Children and adolescents diagnosed with T1D in 62% of cases show CD antibodies within the first 2 years of the onset of diabetes and 79% up to the first 5 years after the diagnosis of T1D [26] and less often after this period [23,26] One study also reported a higher 5-year cumulative incidence of celiac disease in Finland compared

to neighboring Estonia (0.77% vs. 0.27%) [39].

Even though the predisposing risk factors for the development of CD in T1D patients are different from those of T1D [36,43,71] both are immune-mediated diseases and share a number of common genetic (HLA DQ2 & HLADQ8, non-HLA variants), environmental (infections, nutrition, microbiome) and immune dysregulation (acquired and born) predisposing risk factors.

CD in children with T1D is more frequent among females (in a ratio of 2-3:1 to males), in children aged < 5 years old who are diagnosed with T1D [18,25,26,38], in Caucasians [72] and in those with HLA-DR3-DQ2 and DR4-DQ8 haplotypes [73].

The average age of diagnosis in classic CD is usually around 2-3 years, while the average age of T1D diagnosis is 7-8 years. The age of onset of T1D is lower in patients affected by both diseases (CD and T1D) than in those with T1D alone [43]. The risk of CD is inversely and independently associated with age at diagnosis of T1D, with a higher risk in children aged < 5 years than in those aged >9 years [25-27].

The higher prevalence among family members and the high concordance in monozygotic than dizygotic twins (over 80% compared to 11%) indicate that the genetic background plays a major role in the predisposition to CD [74].

Since the prevalence of CD in children with T1D is increasing significantly, due to the significant clinical impact on T1D [75,76] and because CD more often is diagnosed in the silent or possible (potential) phase, before the onset of clinical symptoms of the disease [29,77,78], then all patients with T1D should be screened for CD [75,79].

6. Conclusion

The prevalence of concomitant autoimmune disorders is relatively high among children newly diagnosed with T1D in Albania. There is need to screen and early detect potential accompanying autoimmune disorders among T1D children as an effort to alleviate the burden of these concomitant health conditions on the health and quality of life of T1D children. It is recommended that patients with T1D regardless of the presence or absence of symptoms should be screened for other autoimmune diseases at the time of T1D diagnosis and periodically every 1-2 years or more often according to clinical progress during T1D disease monitoring.

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