

# Type III Polyglandular Autoimmune Syndromes in children with type 1 diabetes mellitus

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## Abstract

**Introduction:** Type III Polyglandular Autoimmune Syndrome (PAS III) is composed of autoimmune thyroid diseases associated with endocrinopathy other than adrenal insufficiency. This syndrome is associated with organ-specific and organ-nonspecific or systemic autoimmune diseases. The frequency of PAS syndromes in diabetic children is unknown.

**Objectives:** The aim of the study was to evaluate the incidence of PAS III in children with diabetes mellitus type 1.

**Patients and methods:** The study consisted of 461 patients with diabetes mellitus type 1 (T1DM), who were 1-19 years of age. TSH, free thyroxin, TPO autoantibodies, and thyroglobulin autoantibodies were determined annually. Autoimmune Hashimoto's thyroiditis was diagnosed in children with positive tests for TPO Ab and Tg Ab and thyroid parenchymal hypogenicity in the ultrasound investigation. Elevated TSI antibodies were used to diagnose Graves' disease. Additionally, Anti-Endomysial Antibodies IgA class were determined every year as screening for celiac disease. During clinical control, other autoimmune diseases were diagnosed. Adrenal function was examined by the diurnal rhythm of cortisol.

**Results:** PAS III was diagnosed in 14.5% children: PAS IIIA (T1DM and autoimmune thyroiditis) was recognized in 11.1 % and PAS IIIC (T1DM and other autoimmune disorders: celiac disease, and JIA, psoriasis and vitiligo) in 3.5% children. PAS IIIA was more prevalent in girls than in boys – 78.4% versus 21.6% ( $p < 0.05$ ). PAS III was observed between 1-5 years of life in 66.6% children; the frequency decreased in consecutive years and successively increased in the adolescence period to 22.7%.

**Conclusions:** PAS III occurs in 14.5% of children with DM type 1 and the incidence is positively correlated with patients' age and female gender. Children with PAS III should be carefully monitored as a group at risk for the development of other autoimmune diseases.

## Key words

type 1 diabetes mellitus, polyglandular autoimmune syndrome-PAS, autoimmune thyroiditis, celiac disease, juvenile idiopathic arthritis

## INTRODUCTION

Polyglandular autoimmune syndromes (PAS) are conditions characterized by the association of two or more organ-specific disorders. Diagnosis should be considered in every patient in the case of coexistence of two or more autoimmune endocrinopathies. On the basis of the clinical picture, they are divided into three different types according to Neufeld and Blizzard's classification [1] with Eisenbarth modification [2].

1) Type I PAS (APECED-autoimmune polyendocrinopathy – candidiasis – ectodermal dystrophy): a monogenic autoimmune syndrome caused by defects in the AIRE gene located on chromosome 21. Its major components include candidiasis of the skin and mucous membranes, hypoparathyroidism, and Addison's disease. Its inheritance exhibits an autosomal recessive pattern. PAS type I usually affects children around the age of 10-12 [1].

2) Type II PAS: defined as a combination of autoimmune adrenal insufficiency with autoimmune thyroid disease and/or type 1 diabetes mellitus. It is characterized by obligatory occurrence of autoimmune Addison's disease

in combination with thyroid autoimmune diseases and/or type 1 diabetes mellitus (also known as insulin-dependent diabetes mellitus, or T1DM). Women are three times more likely to develop it than men [2, 3]. The prevalence of PAS II increases gradually in the first decade of life and reaches the highest values between 25-40 years of age [2].

3) Type III PAS: composed of autoimmune thyroid diseases associated with endocrinopathy other than adrenal insufficiency (e.g. premature gonad failure, type 1 diabetes mellitus). It mainly affects women in their 30s. Thyroiditis usually occurs first.

PAS III can be further classified into the following three subcategories:

A – Autoimmune thyroiditis with immune-mediated diabetes (T1DM) mellitus (also known as polyglandular autoimmune syndrome type 3 variant).

B – Autoimmune thyroiditis with pernicious anemia.

C – Autoimmune thyroiditis with vitiligo and/or alopecia and/or other organ-specific autoimmune disease [1, 2, 4, 5].

The syndrome is associated with organ-specific autoimmune diseases (celiac disease, hypogonadism, and myasthenia gravis), organ-nonspecific or systemic autoimmune diseases (sarcoidosis, Sjögren syndrome, rheumatoid arthritis), and other diseases (gastric carcinoid tumour, malabsorption due to exocrine pancreatic deficiency) [4, 5, 6].

PAS II and III syndromes exhibit polygenic inheritance and are connected with the HLA system. Because of the

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familial pattern seen in PAS II, as well as in PAS III, and the autosomal recessive mode of inheritance in PAS I, physicians are obliged to provide genetic counselling and medical care to the first degree relatives of the patient. Frequent coexistence of diabetes mellitus and thyroid diseases requires monitoring and estimation of thyroid hormones and levels of anti-thyroid antibodies in patients with type 1 diabetes mellitus. The prevalence of type 1 diabetes mellitus is 4-18% in PAS I and 60% PAS II. Clinical manifestations of T1DM in PAS I appear in patients about 20 years of age [7]. It is estimated that about one-fourth of the patients with a single organ-specific autoimmune disease may have or develop other autoimmune diseases during their lifetime [8]. Typical PAS usually occurs around the third and fourth decades of life, but the first manifestations of autoimmune endocrinopathies can be present in childhood.

The frequency of PAS syndromes in diabetic children is unknown and poorly understood. The other autoimmune disorders may have a significant influence on the treatment of diabetes mellitus.

## OBJECTIVES

The aim of the study was to evaluate the incidence of PAS III in children with type 1 diabetes mellitus.

## MATERIALS AND METHODS

The study consisted of 461 patients treated in the Department of Paediatric Endocrinology and Diabetology at the Medical University in Lublin, Poland, during 2001-2011. In each patient, T1DM was diagnosed on the basis of clinical signs and symptoms (polyuria, polydipsia, weight loss), all biochemical criteria (fasting glucose over 125 mg/dl, postprandial glucose over 200 mg/dl, glycosuria, ketonuria, elevated levels of glycosylated haemoglobin over 6.5 %), and immunology investigations (elevated levels of Glutamic Acid Decarboxylase Antibodies –GAD- Elisa IMMUNOTECH). The children were 1-19 years of age. TSH, free thyroxin (Elisa ABBOTT), TPO autoantibodies, and thyroglobulin autoantibodies (Elisa DAKO, Denmark) were determined annually. Hashimoto's thyroiditis (HT) was diagnosed in children with positive tests for TPO Ab and Tg Ab and thyroid parenchymal hypoechogenicity in the ultrasound investigation at normal or decreased free thyroxin. Autoantibodies were analyzed in children with decreased TSH and increased free thyroxin; elevated TPO Ab and TG Ab indicated Hashitoxicosis – a form of Hashimoto's thyroiditis. Elevated TSI antibodies (RIA BRAHMS Germany) were used to diagnose Graves' disease.

Additionally, IgA class Anti-Endomysial Antibodies (IgA EMA ELISA), as screening for celiac disease, were determined in children with T1DM. The children with positive tests were diagnosed in the Department of Children's Gastroenterology, and after positive pathological investigations of duodenal epithelium biopsies, they were qualified for a gluten-free diet as sufferers of coeliac disease. During clinical control, hyperthyroidism or juvenile idiopathic arthritis (JIA) were diagnosed. The adrenal function was examined by the diurnal rhythm of cortisol (Elisa ABBOTT). The complete blood count, transaminases, creatinine, and urea levels and

electrolytes, calcium, potassium, and sodium in serum were determined in all children every year (Tab.1).

The patients were qualified according the Neufeld and Blizzard's classification [1] with modifications by Kahaly [6].

Before commencement of the investigations, all parents signed an informed consent. The investigation was accepted by the local Ethics Committee at the Medical University in Lublin.

Statistical analysis was performed using the Mann-Whitney test. Statistical significance was assumed at  $p < 0.05$ .

**Table 1.** Diagnostic protocol of the patients

	During T1DM diagnosis	Follow-up
Fasting glucose	On the first day	Every day
Postprandial glucose	On the first day	Every day
Glycosuria and ketonuria	On the first day	Every day
Urine status	On the first day	Every 3 months
Hb A1c	On the first day	Every 3 months
Anti GAD Ab	In the first week	-
TSH	In the second week after diagnosis	Every year or every 3 months if elevated
ft4	In the second week after diagnosis	Every year or every 3 months if decreased, every month if elevated
TPO Ab, TG Ab	In the second week after diagnosis	Every year
TSI Ab	-	In children with thyrotoxicosis
Thyroid ultrasound	In the second week after diagnosis if thyroid hormone disorders or goitre developed	Every year
IgA EMA	In children with microsomnia	Every year
Complete blood count	yes	Every 6 months
Transaminases	yes	Every 6 months
Creatinin	yes	Every 6 months
Urea	yes	Every 6 months
Electrolytes	yes	Every 6 months
Cortisol diurnal rhythms (08.00 and 23.00)	In the second week after diagnosis	In children with a tendency for unclear hypoglycaemia

## RESULTS

PAS I and PAS II were not diagnosed in the group of the 461 children with T1DM. PAS III was diagnosed as a result of regular clinical and laboratory investigations in 14.5% of the children: PAS IIIA was recognized in 11.1% and PAS III C in 3.5% of the children (Tab. 2). The patients were diagnosed with T1DM and Hashimoto's thyroiditis (48), or T1DM and Graves' disease (3). All the children from this group exhibited an elevated level of TPO Ab, mean  $3,674 \pm 6,780$  IU/ml (65-10,000 IU/ml – norm range to 35 IU/ml), and TG Ab, mean  $3,545 \pm 2,349$  IU/ml (75-10,000 IU – norm range to 35 IU/ml). In comparison to other children with T1DM (TPO 12-689 IU/ml and TG Ab 5-765 IU/ml), these differences were statistically significant ( $p < 0.05$ ). In thyroid ultrasonography, hypoechogenicity of the thyroid parenchyma was observed

– pictures characteristic for Hashimoto's thyroiditis. 7.6% of patients with T1DM were hypothyroid. The majority of the children (25-5.4%) were diagnosed with subclinical hypothyroidism – thyroxine levels remained within normal ranges and TSH was elevated. 10 children (2.2%) were diagnosed with hypothyroidism with a decreased level of thyroxine and TSH. 9 children (2.0%) were in the euthyroid status (normal TSH and thyroxine levels), but TPO Ab and TG Ab were significantly elevated. In 4 (0.9%) children, an elevated thyroxine level with decreased TSH and elevated TPO Ab and TG Ab, with absence of TSI Ab (antibodies against the TSH receptor) were initially observed. Hashitoxicosis was diagnosed in these patients. Hypothyroidism developed in the course of thyroiditis. In ultrasound investigations, atrophy of the thyroid was observed in 25 children (52%), a normal size of the thyroid in 10 (21%) children, and enlargement of the thyroid gland in 13 patients (27%). Hashimoto's thyroiditis was observed 3-7 years after the T1DM diagnosis. Hashimoto's thyroiditis preceded T1DM only in 2 patients.

Graves' disease was diagnosed in 3 children aged 2-10 after diagnosis of T1DM (6.5%). All the patients presented typical symptoms of thyrotoxicosis: thyroid enlargement, tachycardia, elevated blood pressure amplitude, exophthalmos, insomnia, hand tremor, hyperactivity, hair loss, excessive sweating, heat intolerance, weight loss, and very unbalanced glycaemia, despite intensive insulin treatment.

PAS IIIA was more prevalent in girls than in boys – 78.4% versus 21.6% ( $p < 0.05$ ).

**Table 2.** Frequency of autoimmune disease in patients with T1DM

Diagnosis	No. of patients	%	Girls	%	Boys	%	P-value by comparison girls and boys
T1DM	461	100	240	52.1	221	47.9	0.764
<b>APS III</b>	<b>67</b>	<b>14.5</b>	<b>51</b>	<b>76.1</b>	<b>16</b>	<b>23.9</b>	<b>0.012</b>
<b>APS IIIA</b>	<b>51</b>	<b>11.1</b>	<b>40</b>	<b>78.4</b>	<b>11</b>	<b>21.6</b>	<b>0.014</b>
T1DM and HT	48	10.4	37	77.1	11	22.9	0.009
T1DM and Graves' disease	3	0.7	2	66.7	1	33.3	0.051
<b>APS III C</b>	<b>16</b>	<b>3.5</b>	<b>11</b>	<b>68.7</b>	<b>5</b>	<b>31.3</b>	<b>0.011</b>
T1DM, HAT and JIA	8	1.7	6	75.0	2	25.0	0.046
T1DM, HT and celiac disease	6	1.3	3	50	3	50	0.078
T1DM, HT and psoriasis	1	0.2	1				
T1DM, HT and vitiligo	1	0.2	1				

PAS IIIC was diagnosed in 16 (3.5%) children, i.e. two or more autoimmune diseases that do not follow the typical pattern of the other types of PAS. 8 children were diagnosed with juvenile idiopathic arthritis (JIA), usually 3-5 years before appearance of T1DM (JIA was observed 2 years after the diagnosis of T1DM only in one girl). The signs of JIA were oedema and pain in the knee, ankle, wrist and small joints of the hands and feet, fever, and elevated CRP (C-Reactive Protein) and ESR (erythrocyte sedimentation rate). These children were diagnosed in the Department of Paediatric Rheumatology and treated according to rheumatology standards.

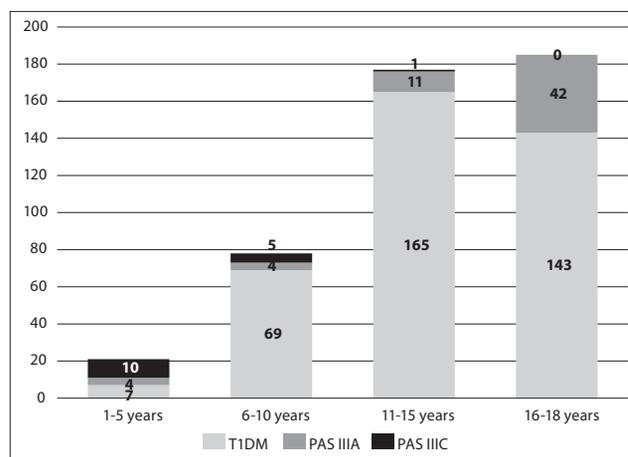
The celiac disease was diagnosed in 6 children with T1DM, usually 2-4 years after T1DM diagnosis. The levels of IgA EMA were estimated and celiac disease was finally recognized in the patients after intestinal biopsy. The first symptoms of the celiac disease were destabilization of glucose levels, despite intensive insulin treatment, and a tendency to unexplained hypoglycaemia and abdominal pain. Diarrhoea did not develop.

One patient presented with vitiligo and one patient with psoriasis, diagnosed 2-4 years before T1DM. PAS III was observed between 1-5 years of life in 66.6% of the children; the frequency decreased in consecutive years, and successively increased in the adolescence period to 22.7% (Tab.3).

Predominance PAS III C was observed in the youngest children, whereas an increased frequency of PAS IIIA was found in teenagers (Fig. 1).

**Table 3.** Occurrence of PAS III in consecutive periods of life in children with T1DM

	1-5 years	6-10 years	11-15 years	16-18 years
T1DM	21	78	177	185
PAS III	14 (66.6%)	9 (11.5%)	12 (6.8%)	42 (22.7%)
PAS IIIA	4 (19.0%)	4 (5.1%)	11 (6.2%)	42 (22.7%)
PAS IIIC	10 (47.6%)	5 (6.3%)	1 (0.6%)	0



**Figure 1.** Frequency of PAS III in consecutive periods of life in children with T1DM

## DISCUSSION

In 1980, Neufeld and Blizzard developed the first classification of polyglandular failure which distinguishes two broad categories: PAS type I and PAS type II (PAS I and PAS II). An additional group, PAS type III (PAS III), was subsequently described. PAS III, in contrast to PAS I and II, does not involve the adrenal cortex. In PAS III, autoimmune thyroiditis occurs with another organ-specific autoimmune disease, but the syndrome cannot be classified as PAS I or II [1, 2]. PAS IIIA – autoimmune thyroiditis with immune-mediated diabetes (T1DM) mellitus (polyglandular autoimmune syndrome type 3 variant), developed in 11.1% of our patients.

The exact worldwide prevalence of PAS III is unknown. Observations in the presented study are similar to the findings of other authors who described the frequency of thyroid autoantibodies in children with T1DM. Their papers did not report autoimmune thyroiditis in the patients (Tab. 4).

**Table 4.** Studies of autoimmune thyroid diseases in patients with T1DM

Author	Country	Patients	Subject
Lorini R et al. <i>Ped Endocrinol Rev</i> 2003 [9]	Italy	212	T1DM and elevated antithyroid antibodies 6.7% Girls 23.7% Boys 10.9%
Karagüzel et al. <i>Diab Res Clin Pract</i> 2008 [10]	Turkey	57	T1DM and elevated antithyroid antibodies 21.4%
Kakleas et al. <i>Ups J Med Sci</i> 2009 [11] Karavanaki K. <i>Horm Res</i> 2009 [12]	Greece	144	T1DM and – elevated TPO Ab 17.4% – elevated TG Ab 11.1% – elevated TPO Ab and TG Ab 10.4%
Kordonouri et al. <i>Diabetes Care</i> 2002 [13]	Germany Austria	7 097	Elevated TG Ab and/or TPO Ab 21.6%
Piątkowska E., Szalecki M. <i>Ped End, Diab and Metab</i> 2011 [14]	Poland	382	T1DM and elevated TPO Ab 14.4% Girls 19.4% Boys 9.7%
Szypowska A et al <i>Przeegl Ped</i> 2010 [15]	Poland	294	T1DM and elevated TPO Ab or TPO Ab 21.4%. hypoechogenic thyroid 11
Authors of the presented study	Poland	461	Diagnosed autoimmune thyroiditis in patients with T1DM- APS IIIA 11.1% Girls 8,2% Boys 2.6%

The prevalence of antithyroid antibodies in the population of children with type 1 diabetes in Poland reaches 14-40%, and 4.5-5% in the remaining 'healthy' part of the population [16]. It depends on the race, age, gender, duration of diabetes, age at disease diagnosis, positive family history, and the type of assayed antibodies [17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27].

An extensive retrospective study carried out by Kordonouri et al. [13] revealed that children with a positive antibody titre were older, developed the disease at an older age, and their disease lasted longer. At the time of the diabetes diagnosis, the proportion of patients with a positive antithyroid antibody titre ranged from 2% to over 30% [17, 23, 24, 25, 26]. Hypothyroidism was diagnosed in 10% of the children with a positive antithyroid antibody titre, whereas ultrasound changes, i.e. thyroid enlargement, disturbances in the echostructure, and/or nodular lesions, were observed in 50% [23, 24]. These observations correspond with findings in the presented study. Clinical hypothyroidism may affect 1-5% of children with T1DM (International Society for Paediatric and Adolescent Diabetes – ISPAD Consensus) [28], and subclinical hypothyroidism – 5-10% (15.8% of patients with positive antithyroid antibody titre – Kordonouri [13]), 5-10% (Glastras [22]), 7.3% (Mantovani [18]), or 15% (Szalecki [24]). In the presented study, clinical or subclinical hypothyroidism was diagnosed in 7.8% of the children, and in 0.9% of patients initially presenting with Hashitoxicosis, which resulted in hypothyroidism within 3-6 months. In the general adolescent population, the proportion of hypothyroid patients amounts to ca. 0.5-1.5% [13, 21]. Kordonouri and Piątkowska [13, 14] reported that the prevalence of antithyroid antibodies increased with children's age.

In the presented study, PAS IIIA was often diagnosed in the group of the youngest children, i.e. those under the age of 5 years. A low incidence was reported in the group of 6-10 year-olds; in older groups, the proportion of APS IIIA

patients gradually increased. The first clinical symptom of hypothyroidism in children may be inhibition of growth [21, 22]. Frequent symptoms include: deterioration of metabolic control in diabetes, mainly hypoglycaemia, resulting from decreased requirement for insulin and inhibited absorption into the circulation which, in turn, leads to increased insulin dosage and unpredictable cumulative insulin secretion.

It is very important to screen the thyroid function upon diagnosis of diabetes mellitus type 1, and every year during the follow-up period, because autoimmune thyroiditis can occur without enlargement of the thyroid and without hypo- or hyperthyroidism. The development of thyroiditis is cryptic and slow. The simultaneous occurrence of immune hypothyroidism and T1DM is often accompanied by hypoglycemia due to a decreased insulin requirement and increased insulin sensitivity. Substitution therapy with levothyroxine leads to increased insulin dosage. There are no uniform standards for tests that should be performed in diabetic patients either at the diagnosis or during disease monitoring. The International Society for Paediatric and Adolescent Diabetes (ISPAD) Consensus 2009 recommends screening according to the following scheme: in the case of autoimmune thyroid diseases, assays of the TSH concentration and antibodies should be performed at the diagnosis of diabetes and followed by biennial tests [28]. In screening examinations, the ISPAD recommends assessment of thyroid function in the case of presence of goitre, a decreased growth rate, thyroid disease symptoms, and elevated antibody titres [28]. In turn, the Australasian Paediatric Endocrine Group (APEG) suggests measurement of antithyroid antibody titres (anti-Tg and -TPO) every 2-3 years, and assessment of the TSH concentration every year, rather than biennially [21, 23]. The American Diabetes Association (ADA) acknowledges that the presence of antithyroid antibodies increases the risk of AITD; however, screening is not recommended, Barker (Barbara Davis Centre). In turn, it is recommended that in children anti-thyroid peroxidase antibodies and TSH and fT4 levels should be assayed at diagnosis and repeated every 1-2 years. In patients with a positive antibody titre, assessment of thyroid function should take place every 6-12 months [21]. According to Kordonouri and Mantovani, antibodies (or rather anti-TPO) should be assayed annually [17, 18, 27].

In the case of a positive antibody titre, the concentrations of TSH and fT4 should be determined and thyroid ultrasound performed. The risk group includes girls, patients affected by diabetes type 1 for more than nine years, patients over 12 years of age, and patients with another autoimmune disease [24, 25, 26]. The Polish Society of Diabetology recommends annual assessment of thyroid function in children [29, 30]. The presented study suggests that assessment of antithyroid antibodies, TSH, and fT4, should be performed annually, particularly in the youngest children and adolescents.

The high prevalence of PAS III, especially PAS IIIC (T1DM, thyroiditis and other autoimmune disease) in children between 1 – 5 years of age, suggest an inherited predisposition to autoimmune disorders. PAS III is associated with HLA class II genes, with apparently distinctive HLA alleles for each. The underlying non-HLA genes of PAS III remain to be further defined genetically. PAS III is often observed in individuals in the same family, suggesting that its inheritance could be an autosomal dominant trait with incomplete penetrance [31, 32, 33]. Family and population studies have shown that PAS IIIA has a strong genetic background. Several

gene variations present in both autoimmune thyroiditis and T1DM have been identified by whole genome and candidate gene approaches. The most important susceptibility genes are the human leucocyte antigen (chromosome 6), cytotoxic T-lymphocyte-associated antigen 4 (chromosome 2), protein tyrosine phosphatase nonreceptor type 22 (chromosome 1), forkhead box P3 (X chromosome), and the interleukin 2 receptor alpha/CD25 gene region (chromosome 10) [34].

Prophylactic treatment with thyroxine in euthyroid patients with a positive antibody reduces the thyroid volume, prevents development of goitre and hypothyroidism by decreasing the TSH concentration and thyroid antigen expression, leading to a decline in the antibody concentration and lower levels of lymphocytic infiltration in the thyroid [27, 35, 36].

The association of T1DM and Graves' disease is described sporadically [37]. In the findings of the presented study, only 3 patients were diagnosed with autoimmune thyroiditis in the form of Graves' disease. In diabetic children with concomitant Graves' disease and at risk of fluctuating thyroid functional status, the treatment of T1DM is much more difficult, which might call for a decision for definitive treatment, especially when remission is not obtained after an antithyroid drug course of reasonable duration. Hyperthyroidism can affect 0.5% of children with diabetes type 1 (in the USA – 0.2-0.4%) [21]. Clinical or subclinical hyperthyroidism is accompanied by deterioration of metabolic control in diabetes; its frequent first manifestation is hyperglycaemia, an effect of increased gluconeogenesis and glycogenolysis and increased glucose absorption. Additionally, reduced insulin sensitivity can be found, i.e., higher receptor affinity accompanied by abnormal post-receptor signal transmission [22]. Treatment of hyperthyroidism with thyrostatic drugs or radioiodine leads to sufficient diabetes control. The association of T1DM with other autoimmune disorders is rare but possible. In such patients, PAS IIIC can be diagnosed.

Celiac disease is one of the most common genetic disorders. Its incidence in the European population ranges from 0.03 – 0.04% and exhibits variation [38, 39, 40]. The highest incidence rates are found in the countries of northern north Europe: Sweden – 2.4/1,000 births, UK – 1.49/1,000, and Finland – 0.86/1,000 [38, 39, 40, 41, 42, 43, 44, 45]. Slightly lower rates are reported from southern Europe [46]. In Poland, the incidence of celiac disease is 0.06% of the population (Warsaw – 0.41/1,000 births [47], Bydgoszcz – 0.92/1,000 [48], the Świętokrzyski Region 0.7/1,000) [49]. Promotion of breast-feeding, as well as delayed introduction of gluten-containing products into the diet, has changed the clinical manifestation of the disease. Classic forms of celiac disease have given way to its atypical forms. In patients with diabetes type 1, celiac disease has been significantly more frequently diagnosed than in the general population, and its incidence, as reported by various authors, ranges from two to several per cent [47, 48, 49]. The frequency of coexistence of both disorders increases with patients' age and duration of diabetes [50]. Crone et al., in their investigations conducted on similar populations in terms of numbers, have reported 5% [51] and Sanchez-Albisua 3.2% [52] of patients with diagnosed celiac disease among diabetes type 1 patients. In the presented study group, the proportions of children affected by celiac disease was relatively insignificant (1.3%). In Poland, Myśliwiec [53] reported celiac disease in 5.7% of children with newly diagnosed diabetes type 1, Górska et al. [54] found it in 4.1% (26, 27), and Szalecki et al. in 4.3% [55].

Since the criteria for celiac disease diagnosis in the presented study included biopsy of villi and an elevated level of IgA EMA antibodies, the number of children diagnosed with celiac disease was smaller. The positive IgA EMA antibodies without positive intestinal biopsy investigations were observed in 16 children (3.5%). In patients affected by diabetes type 1, celiac disease is usually oligosymptomatic or asymptomatic; therefore, it is difficult to identify the risk group requiring regular screening examination among all patients [39, 43, 44, 45]. In Polish screening examinations of children affected by diabetes type 1, Myśliwiec diagnosed celiac disease in 9.4% of patients treated for diabetes for over two years [53]. A reverse phenomenon is also characteristic, i.e. higher prevalence of diabetes type 1 in celiac disease patients and greater frequency of diabetes-specific antibodies in this group of patients [43, 44]. The findings concerning the gluten-free diet used for children with diabetes type 1 that clearly reduces the risk of autoimmunity, are similar [41, 42, 43, 44, 45, 56, 57, 58]. As in other autoimmune diseases, a specific HLA system located on the short arm of chromosome 6 in the 6p23 region was observed. The strongest association with celiac disease is exhibited by centromere-associated HLA class II genes (*DQ2* and *DR3*), which are present in 80-90% of patients. Telomere-associated HLA class I (*B8* and *A1*) genes are responsible for the development of celiac disease to a lesser extent. It has been demonstrated that genes *DQA1\*0501* and *DQB1\*0201* are characteristic for celiac disease [59]. Positive TGA antibodies have been detected in as many as one-third of diabetic patients with *HLA DQ2*, compared with <2% diabetic patients without *HLA DQ2* or *DQ8* [39, 58]. Sumik et al. [40] showed that *HLA DQ2* was present in 80% of patients affected by diabetes type 1 and celiac disease, and in 49% of patients affected by diabetes type 1 without celiac disease. Celiac disease patients who do not express *HLA DQ2* usually have genotype *DQ8*. Therefore, patients with diabetes type 1 with *HLA DQ2* or *DQ8* are susceptible to celiac disease [39, 40, 50, 58]. In the case of celiac disease, the ISPAD Consensus 2009 recommends assessment of the antibody titre at diagnosis of diabetes, followed by annual assessment for five years, and then every two years [28].

Strict use of the gluten-free diet in patients with diabetes type 1 is still a controversial issue. In patients exhibiting even mild clinical symptoms of celiac disease, the gluten-free diet is indispensable in order to prevent worsening of the symptoms [60, 61, 62]. When untreated, celiac disease may lead to changes in insulin requirement and recurrent hypoglycaemia, weight and/or growth disorders, maturation disorders, alimentary anemia, osteopenia, osteoporosis, and neurological disorders. The most severe complications of celiac disease comprise gastrointestinal cancer – lymphomas and tumours. Therefore, despite being inconvenient and restrictive, the gluten-free diet should be introduced in all patients affected by diabetes type 1 and celiac disease and, given the protective effect of the gluten-free diet on pancreatic  $\beta$  cells and improved insulin secretion, in patients with newly diagnosed diabetes [53, 60, 61, 62].

PAS IIIC is sometimes associated with other autoimmune diseases. In the presented study group, JIA was diagnosed most often. In 50% of the cases, autoimmune arthritis preceded the development of T1DM. In a study conducted by Pohjankoski et al. [63], an increase in the occurrence of simultaneous JIA and DM 1 in the last three decades was described. Only a few papers have described the coexistence

of JIA and T1DM in children [64, 65]. Due to the use of steroid therapy, there was always difficulty in diabetes control and treatment. Currently, biological therapy in patients with JIA is disputable, since there are reports on the development of diabetes type 1 after administration of etanercept [66, 67]. For further treatment of the patient, it is vital to know whether IDDM 1 is a consequence of therapy, or whether it may precede development of JIA. It is indicated in the presented study that JIA may develop first, and followed by T1DM, irrespective of the biological treatment.

The arguments presented above justify the need for practical assessment of the risk of development of other autoimmune diseases in children with type 1 diabetes, and particularly with PAS IIIA and PAS IIIC. Early diagnosis of polyendocrinopathic syndromes and their treatment is an essential element in the management of type 1 diabetes.

## CONCLUSIONS

- PASIII occurs in 14.5% of children with T1DM.
- PAS III incidence is positively correlated with patients' age and with the female gender.
- PAS III in childhood frequently occurs with autoimmune thyroiditis (PAS IIIA), and can occur with celiac disease and JIA, and sporadically with psoriasis and vitiligo (PAS IIIC)
- Children with PAS III should be carefully monitored as a risk group of other autoimmune disease development.

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