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Coeliac disease in endocrine diseases of autoimmune origin

Celiakia w chorobach endokrynologicznych pochodzenia autoimmunologicznego

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Abstract

Coeliac disease (CD, sometimes called gluten-sensitive enteropathy or nontropical sprue) is an inflammatory disorder of the small intestine of autoimmune origin. It occurs in genetically predisposed people and is induced by a gluten protein, which is a component of wheat. The prevalence of histologically confirmed CD is estimated in screening studies of adults in the United States and Europe to be between 0.2% and 1.0%. The results of previous studies have indicated that the prevalence of CD is increased in patients with other autoimmune disorders such as: autoimmune thyroid diseases, type 1 diabetes mellitus, and Addison's disease. A coincidence of the above diseases constitutes autoimmune polyglandular syndrome (APS). The high prevalence of CD in APS is probably due to the common genetic predisposition to the coexistent autoimmune diseases. The majority of adult patients have the atypical or silent type of the disease. This is the main reason why CD so often goes undiagnosed or the diagnosis is delayed. CD, if undiagnosed and untreated, is associated with many medical disorders including haematological (anaemia), metabolical (osteopenia/osteoporosis), obstetric-gynaecological (infertility, spontaneous abortions, late puberty, early menopause), neurological (migraine, ataxia, epilepsy) as well as with an increased risk of malignancy, especially: enteropathy-associated T-cell lymphoma, small intestine adenocarcinoma, and oesophageal and oropharyngeal carcinomas. Early introduction of a gluten-free diet and lifelong adherence to this treatment decreases the risk of these complications. **(Pol J Endocrinol 2012; 63 (3): 240–249)**

Key words: *coeliac disease, autoimmune polyglandular syndrome, Graves' disease, autoimmune thyroid disease, type 1 diabetes, autoimmune adrenal insufficiency*

Streszczenie

Celiakia (inaczej: glutenozależna choroba trzewna, enteropatia glutenowrażliwa, *sprue* nietropikalna) jest enteropatią zapalną jelita cienkiego o podłożu autoimmunologicznym, spowodowaną trwałą nietolerancją glutenu zawartego w zbożach, występującą u osób z predyspozycją genetyczną. Częstość potwierdzonej histopatologicznie celiakii w ogólnej populacji dorosłych, według wyników badań przesiewowych przeprowadzonych w Europie oraz Stanach Zjednoczonych, wynosi 0,2–1,0%. Wyniki dotychczasowych badań sugerują, że ryzyko zachorowania na celiakię jest kilkakrotnie większe u pacjentów z innymi chorobami autoimmunologicznymi, jak np.: choroby autoimmunologiczne tarczycy (AITD), cukrzyca typu 1 (T1D) czy choroba Addisona. Powyższe choroby wchodzą w skład autoimmunologicznych zespołów niedoczynności wielogruczołowej (APS). Jedną z przyczyn większej częstości występowania celiakii w APS, w porównaniu z ogólną populacją, jest prawdopodobnie wspólna predyspozycja genetyczna. U osób dorosłych zdecydowaną większość przypadków stanowią postacie atypowe i nieme. Wpływa to na opóźnioną i obniżoną wykrywalność choroby. Nierozpoznana i nieleczona celiakia może prowadzić do wielu zaburzeń, w tym m.in.: hematologicznych (niedokrwistość), metabolicznych (osteopenia/osteoporoza), ginekologiczno-położniczych (niepłodność, wzrost częstości samoistnych poronień, opóźnione dojrzewanie i wcześniejsza menopauza) i neurologicznych (migrena, ataksja, padaczka). Nieleczona celiakia zwiększa również ogólne ryzyko zachorowania na złośliwe nowotwory, w tym przede wszystkim na: chłoniaka jelita cienkiego, gruczolakoraka jelita cienkiego, gardła i przełyku. Skuteczne leczenie (dieta bezglutenowa), wprowadzone wcześnie i kontynuowane przez całe życie, zmniejsza ryzyko wystąpienia wymienionych powikłań. **(Endokrynol Pol 2012; 63 (3): 240–249)**

Słowa kluczowe: *choroba trzewna, autoimmunologiczny zespół niedoczynności wielogruczołowej, choroba Gravesa i Basedowa, autoimmunologiczna choroba tarczycy, cukrzyca typu 1, autoimmunologiczna niedoczynność nadnerczy*

Case report

A 22 year-old female was admitted to the clinic for her regular check-up. She had been diagnosed with Graves' disease (GD) at the age of 15. She was treated with antithyroid drugs from the age of 15 to the age of 20 and twice underwent treatment with radioiodine (at the age of 20). Before admission to hospital, she had been taking 150 μg of levothyroxine. She was suffering from recurrent constipation and moderate abdominal pain. Additionally, she complained of a feeling of enamel oversensitivity and severe migraines, which required treatment with non-steroidal anti-inflammatory drugs. For several years, the patient was diagnosed with an iron deficiency and administered iron orally. She denied having heavy menorrhagia. She pointed out that the presence of autoimmune disorders ran in her family (her father suffered from GD as well). Laboratory

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tests showed a normal TSH serum level (1.07 uIU/mL, N: 0.2–4.0) a low ferritin level (6 ng/mL, N: 13–150), a low iron level (36 ug/ml, N: 37–181), normal serum Hb, folic acid, vitamin B12, calcium, phosphorus, total proteins and albumin levels. Specific serological studies were performed revealing high levels of IgA tissue transglutaminase antibodies (IgA TTG) (178.1 U/mL; N: < 20.0) and IgA endomysial antibodies (IgA EMA) (54.5 U/mL; N: < 20.0). An endoscopy of the upper digestive tract was performed and a biopsy was obtained from the descending part of the duodenum. Duodenal mucosa showed atrophic changes with loss of folds and contained visible fissures. Microscopic examination showed an increase in intraepithelial lymphocytes, crypt hyperplasia and villous atrophy — Type III in Marsh classification (Tab. I, Fig. 1). Coeliac disease (CD) was diagnosed and a gluten-free diet was introduced. The patient was invited for a check-up three months after the introduction of a gluten-free diet, and neither symptoms of digestive system disorders, nor migraines and enamel oversensitivity were present. However, it was observed that serum iron and ferritin concentrations remained low. During following check-ups, the dose of levothyroxine was gradually lowered to 125 μg, with a normal serum TSH level. Iron supplements were stopped and gradually blood iron and ferritin levels stabilised. The patient regularly visits an endocrinologist and a gastroenterologist.

Table I. ***Histologic grading in coeliac disease (Marsh) [34]***

Tabela I. ***Klasyfikacja zmian histopatologicznych w celiakii (Marsh) [34]***

Classification	Description
Marsh 0	No changes in mucosal and villous architecture
Marsh I	Normal mucosal and villous architecture
	Increased numbers of intraepithelial lymphocytes
Marsh II	Similar to Marsh I but with enlarged crypts (hyperplastic)
Marsh IIIa	Partial villous atrophy
Marsh IIIb	Subtotal villous atrophy
Marsh IIIc	Total villous atrophy
Marsh IV	Total villous atrophy and hypoplastic crypts

Introduction

Coeliac disease (CD), also known as gluten-sensitive enteropathy and nontropical sprue,, is a small bowel disorder characterised by mucosal inflammation of autoimmune origin caused by persistent intolerance to gluten, a protein which is a component of cereal (rye, wheat, barley). CD occurs in people with a genetic predisposition [1]. The symptoms of CD were first described by Dr. Samuel Gee in 1888, but the aetiology of the symptoms remained unclear for many years [2]. In the 1940s, a paediatrician from Denmark, Wiliam K. Dicke, recognised the association between diets which contained gluten and the symptoms of CD [3]. In periods of food shortages during the Second World War, there were areas where people were poorly nourished and where bread was replaced by a non-cereal substitute. Dicke observed a recurrence of symptoms when bread was reintroduced after the war. Initially, CD was considered to be a childhood disease, and the frequency of the disease was estimated at about 1:4,000. After introducing new, more sensitive and more specific diagnostic tests, the recognisability of CD markedly increased. CD was more and more frequently diagnosed in adults. Further investigations revealed that the prevalence of CD is more often seen in patients with other autoimmune disorders such as autoimmune thyroid disease (AITD) [4–13], type 1 diabetes (T1DM) [14–16], and Addison's disease [17–20]. The above-mentioned autoimmune

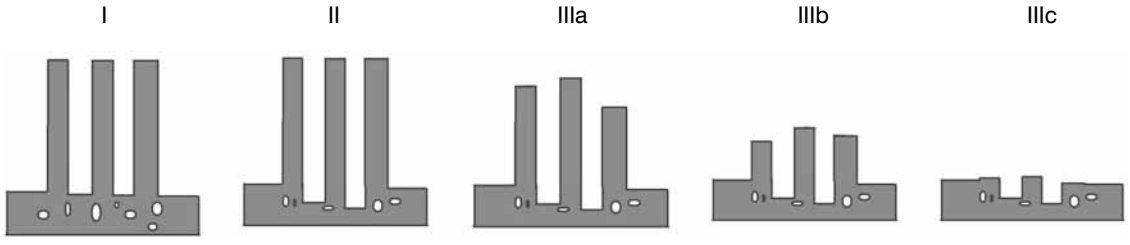

Figure 1. *Extent of small intestinal mucosal changes according to the Marsh histological damage score; the figure shows spectrum of changes in mucosa of small intestine according to the Marsh classification and AGA. Histologically confirmed coeliac disease can be diagnosed in cases IIIa, IIIb, IIIc (villous atrophy at different degree) [34]*

Rycina 1. *Schemat przedstawiający zakres zmian błony śluzowej jelita cienkiego zgodnie z klasyfikacją Marsh; na rycinie przedstawiono zakres zmian w obrębie błony śluzowej jelita cienkiego zgodnie z klasyfikacją Marsh i kryteriami Amerykańskiego Towarzystwa Gastroenterologicznego. Histopatologicznie potwierdzoną celiakię można rozpoznać w przypadku zmian IIIa, IIIb, IIIc (zanik kosmków o różnym stopniu zaawansowania) [34]*

diseases are part of the autoimmune polyglandular syndrome (APS). The coexistence of autoimmune diseases is probably connected to a common genetic predisposition.

Epidemiology

The prevalence of histologically confirmed CD in the general adult population in relation to screening research from Europe (Italy, Holland, Germany, Great Britain, Iceland, Greece) and the United States has been estimated to be between 0.2 and 1.0% [21–27] (Tab. II). The data concerning CD in Poland regards mainly children and is based on classical symptoms of the disease, which is the reason for underdiagnosis (most research was performed in the 1980s and 1990s) [28–33]. There have been no screening studies evaluating the frequency of CD in adults in Poland.

Clinical manifestations and types of coeliac disease

Clinical symptoms of CD are characterised by a wide spectrum within the clinical picture. In younger patients (infants, young children), we often encounter the classical type of CD (chronic diarrhoea with hypoalbuminaemia, electrolyte abnormalities, abdominal pain) (Tab. III). Diarrhoea occurs significantly less often in older children and adults. Complaints in these groups are often non-specific and less intensive (flatulence, temporary abdominal pain) or even absent [34]. These are so called atypical or silent types of the disease, which are difficult to diagnose. Symptoms may actually concern all systems within the human body (Tab. IV). With latent types of CD in patients with genetic predispositions (genotype HLA-DQ2 or DQ8), elevated IgA TTG and/or IgA EMA levels are to be found and minimal changes (increased intraepithelial lymphocytes of the intestine) or lack of any histological changes can be seen in tissue samples taken from the distal part of the duodenum. In order to describe the variability of CD, it is often compared to an iceberg. The tip above the water represents patients with classical symptoms, but the greater part, which is hidden, consists of asymptomatic patients or those with atypical symptoms [35, 36] (Fig. 2). There are no clearly marked borders between the different types of CD because of its numerous clinical symptoms, and its histological and immunological picture.

Table II. *Prevalence of coeliac disease in different populations of healthy individuals*
Tabela II. *Badania przedstawiające częstość występowania choroby trzewnej w różnych populacjach zdrowych dorosłych osób*

Study	Population	Size of the study group (n)	Coeliac disease [%]
Rostami et al., 1999 [25]	Holland	1,000	0.3%
Volta et al., 2001 [27]	Italy	3,483	0.5%
Henker an et al., 2002 [22]	Germany	4,313	0.2%
Fasano et al., 2003 [21]	USA	2,848	1.0%#
Sanders an et al., 2003 [26]	UK	1,200	1.0%
Roka et al., 2007 [24]	Greece	2,230	0.2%
Johannsson et al., 2008 [23]	Island	813	0.7%

Population — group of individuals on whom the study was performed; the study group — number of individuals who underwent serologic tests specific for coeliac disease; coeliac disease (%) — prevalence (%) of histologically confirmed coeliac disease in investigated population; #in Fasano's study only serological tests were estimated (only 20% of individuals underwent endoscopy and histological evaluation)

Table III. *Types of coeliac disease [1, 34]*
Tabela III. *Kliniczne postacie celiakii [1, 34]*

Types of coeliac disease	Clinical symptoms	Serological evaluation: IgA EMA/IgA TTG	Histological evaluation of small bowel biopsy
Classic disease	Symptoms of malabsorption	+	+
Atypical/poor symptomatic	Minor gastrointestinal complaints or other symptoms	+	+
Asymptomatic/silent	No symptoms	+	+
Latent/potential	No symptoms	+	–

Serological evaluation: IgA EMA/IgA TTG (+) — elevated IgA endomysial antibodies and/or IgA tissue transglutaminase antibodies; histological evaluation of the small intestine (+) — at least partial villous atrophy — Marsh III; (–) — no villous atrophy in histological examination

Table IV. *Clinical symptoms of coeliac disease*
Tabela IV. *Objawy kliniczne celiakii*

Organ abnormalities	Symptoms
Digestive system	Diarrhoea, constipation, distension, abdominal pain
Nervous system	Ataxia, polyneuropathy, migraines, epilepsy
Reproductive disorders	Women: delayed menarche, early menopause, higher rates of miscarriage, low birth weight
	Men: hypogonadism, sexual dysfunction, low sperm quality
Haematological disorders	Iron deficiency, vitamin B12 deficiency, folic acid deficiency, anaemia
Metabolic disorders	Osteopenia, osteoporosis
Dermatologic disorders	Dermatitis herpetiformis
Neoplasms	Enteropathy-associated T-cell lymphoma-EATL, adenocarcinoma of small bowel, oropharynx and oesophagus
Others	Elevated transaminase levels, prevalence to liver diseases (like primary sclerosing cholangitis, nonalcoholic fatty liver disease, liver cirrhosis and primary biliary cirrhosis), IgA deficiency, dental-enamel hypoplasia, hyposplenism, psychiatric disorders

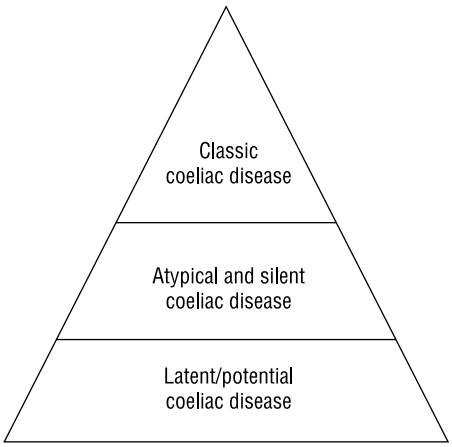

Figure 2. *Iceberg showing wide spectrum of clinical symptoms of coeliac disease (modified according to [35])*

Rycina 2. *Góra lodowa przedstawiająca spektrum objawów klinicznych celiakii (zmodyfikowano na podstawie [35])*

Diagnosis of coeliac disease

Diagnosis of CD is based on serological tests and histological evaluation of a small bowel biopsy. In some doubtful situations, genetic tests can be performed (CD occurs in genetically predisposed individuals with HLA-DQ2 and/or DQ8). An approach to the diagnosis of CD is summarised in Figure 3.

Serological evaluations

All diagnostic tests should be performed during a gluten-rich diet. Nowadays, there are two tests of high sensitivity and specificity: IgA TTG and IgA EMA, which have equivalent diagnostic accuracy (Tab. V). IgA EMA was discovered by a Polish scientist, Professor Tadeusz Chorzelski, in 1983 [37]. Performing both of these tests improves sensitivity by almost 100%. Due to easier ambulatory procedures (ELISA, enzyme-linked immunosorbent assays), some scientists recommend using the IgA TTG test first (the IgA EMA test is frequently performed by a time-consuming indirect immunofluorescence method). It is not advisable to use other serum antibodies' assays (antigliadin, antireticuline). Some scientists recommend an evaluation of serum total anti IgA level, and when the result is negative, tests for IgG EMA and/or IgG TTG are recommended.

Histopathological examination

Patients positive with IgA EMA or IgA TTG should undergo endoscopy of the upper digestive tract with a small bowel biopsy (4–6 biopsies from the distal part of the duodenum). A wide spectrum of histological changes, ranging from increased intraepithelial lymphocytes to flat mucosal atrophy, contribute to histological changes in CD, which can be described using the Marsh classification (Tab. I) [34]. Diagnosis of CD is established in patients who have at least partial villous atrophy (Fig. 1). To avoid false diagnosis, the histological evaluation should be performed in reference clinics.

Genetic evaluations

Antigen HLA-DQ2 is confirmed in 90–95%, and antigen DQ8 in 5–10%, of patients with CD [38]. The presence of HLA-DQ2 and/or DQ8 is necessary for the development of symptoms of CD. However, genetic evaluations are very rarely performed, and they are restricted to situations in which other methods have failed. A negative result of genetic evaluation excludes a diagnosis of CD.

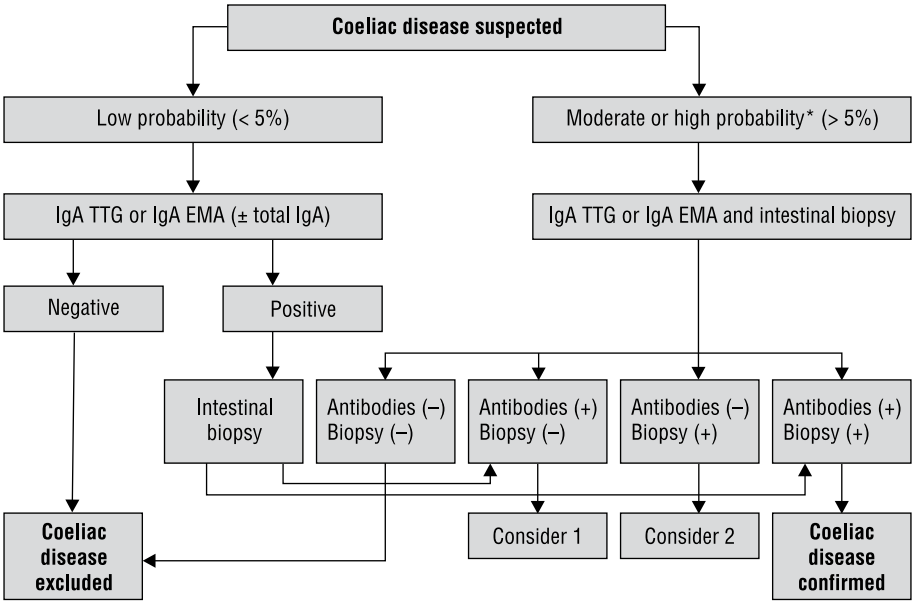

Figure 3. *The diagnostic approach to coeliac disease (adapted from [70], up to date 19.2); *moderate or high probability: family history, iron-deficiency anaemia of unknown origin, diarrhoea, failure to thrive in children, type 1 diabetes; IgA TTG: IgA tissue transglutaminase antibodies; IgA EMA: IgA antiendomysial antibodies; antibodies: IgA EMA and/or IgA TTG; Consider 1: repeat IgA TTG, repeat biopsy in reference clinic, multiply biopsy, histological evaluation by another pathologist, review adherence to gluten free diet; Consider 2: total IgA measurement, perform genetic tests (HLA DQ2, -DQ8), consider other than coeliac disease causes of villous atrophy (cow milk or other proteins intolerance, giardiasis, eosinophilic gastroenteritis, duodenitis, intestinal ischaemia, intestinal lymphoma, Crohn's disease, severe malnutrition)*

Rycina 3. *Schemat diagnostyczny celiakii (opracowano na podstawie [70], uptodate 19.2); *ryzyko średnie i duże: obciążający wywiad rodzinny w kierunku celiakii, niedokrwistość z niedoboru żelaza o niejasnej etiologii, biegunka tłuszczowa, opóźnione wzrastanie u dzieci, cukrzyca typu 1; IgA TTG — przeciwciała przeciwko tkankowej transglutaminazie w klasie IgA; IgA EMA — przeciwciała przeciwendomyzjalne w klasie IgA; przeciwciała: IgA EMA i/lub IgA TTG: Rozważ 1: powtórzenie IgA TTG, powtórzenie biopsji w referencyjnym ośrodku, wykonanie większej liczby wycinków, ocena wycinków przez drugiego histopatologa, sprawdzenie czy pacjent przyjmował regularną dietę; Rozważ 2: pomiar stężenie całkowitego IgA, wykonanie badania genetycznego HLA DQ2, -DQ8, rozważenie innej przyczyny atrofii kosmków (nietolerancja mleka krowiego oraz innych białek, giardioza, eozynofilowe zapalenie błony śluzowej żołądka i jelit, zapalenie błony śluzowej dwunastnicy, niedokrwienie jelit, chłoniak jelita cienkiego, choroba Leśniowskiego-Crohna, ciężkie niedożywienie)*

Table V. ***Sensitivity and specificity of serological tests in diagnostics of coeliac disease (adapted from [34])***

Tabela V. ***Czułość i specyficzność badań serologicznych w diagnostyce celakii (zmodyfikowano na podstawie [34])***

Antibodies	Sensitivity	95% CI	Specificity	95% CI
IgA TTG	95.1%	91.8–98.1	98.3%	97.1–99.6%
IgA EMA	90.2%	86.3–92.5%	99.6%	98.4–99.9%

IgA TTG — IgA tissue transglutaminase antibodies; IgA EMA — IgA endomysial antibodies; CI — confidence interval

Coeliac disease and autoimmune diseases

Previous studies have shown that patients suffering from autoimmune diseases are more predisposed to CD compared to the general population. Examples of autoimmune diseases are: T1DM, AITD, and Addison's disease. The frequency of autoimmune diseases associated with CD is depicted in Table VI. Simultaneously, judging from other studies of patients with CD, it may be stated that the frequency of other autoimmune diseases in patients with CD is also above normal compared to a healthy population. Therefore, in all cases regarding patients with autoimmune disease and suspected of suffering from CD, a proper diagnostic evaluation should be performed. This often leads to the diagnosis of patients with CD of non-typical symptoms. The diagnosis of CD and initiation of the correct therapy (gluten-free diet) can prevent patients from suffering from many disorders. Additionally, effective therapy can influence the course and treatment of other autoimmune diseases

Table VI. *Prevalence of coeliac disease in patients with other autoimmune disorders and healthy volunteers (modified according to [4–27])*

Tabela VI. *Częstość występowania celiakii u pacjentów z innymi chorobami autoimmunologicznymi i u zdrowych ochotników (zmodyfikowano na postawie [4–27])*

Study group	Prevalence of coeliac disease (%)
Hashimoto's thyroiditis	0–9.1
Graves' disease	0–5.5
Addison's disease	5.4–12.2
Type 1 diabetes mellitus in children	3.0–8.0
Type 1 diabetes mellitus in adults	2.0–5.0
Autoimmune hepatitis	2.9–6.4
Healthy volunteers	0.2–1.0

which accompany CD (for example lowering doses of levothyroxine in patients with hypothyroidism, and lowering doses of hydrocortisone in patients with primary adrenal insufficiency).

Pathogenesis of the coincidence of coeliac disease and other autoimmune diseases

CD can appear separately or be a part of APS. According to the definition, APS is a group of diseases of autoimmune origin characterised by hypofunction of a couple of endocrine glands [39, 40]. A common genetic origin is the reason that a patient with one autoimmune disease is more predisposed to other autoimmune diseases. The occurrence of the symptoms of these diseases is usually not synchronised in time. A patient diagnosed with one autoimmune disease often shows a positive result with antibodies characterised for another autoimmune disease, although without yet displaying clinical symptoms or organ failure. This can be called potential or silent APS [41]. An example of this kind of syndrome is the statement of presence of antibodies specific for CD (e.g. IgA TTG), without any specific histological changes in a patient with another autoimmune disorder (e.g. GD). More detailed research, for example by using an electron microscope, can confirm microvillous atrophy in some of these patients [42]. It is confirmed that some patients will develop the full histological features of CD in the future.

We can define different types of APS, which depends on the associated conditions of the diseases. Enthusiasts of narrow classification classify APS into two groups [43], while others classify APS into three [40] or even four groups [44] (Tab. VII).

APS types are distinguished according to different modes of inheritance. APS 1 is rare, usually appears in childhood, is monogenic, and is connected to mutations in an autoimmune-suppressor gene (AIRE, autoimmune regulator). It is defined by the presence of hypoparathyroidism, adrenal insufficiency and chronic mucocutaneous candidiasis. Other APS types are multigenic disorders and occur in adulthood [40]. A strong association with the HLA complex, mainly DR3-DQ2 and DR4-DQ8, could be an explanation for the coexistence of CD and other autoimmune disorders [45–49]. It was stated in a course of self study that the frequency of CD was significantly higher ($p < 0.05$) in the subgroup of patients with Graves' disease carrying HLA DRB1*03 alleles [50].

Table VII. *Classification of autoimmune polyendocrine syndromes (APS)*

Tabela VII. *Podział autoimmunologicznych zespołów niedoczynności wielogruczołowej (APS)*

Authors	APS-1	APS-2	APS-3	APS-4
Neufeld et al., 1980 [44]	AD, candidiasis#, hypoparathyroidism‡ (at least two present)	AD (always present) plus AITD and/or T1DM	AITD plus another AID (except from AD and hypoparathyroidism)	Combination of AID not mentioned in the previous groups
Eisenbarth et al., 2004 [43]	AD, candidiasis#, hypoparathyroidism‡ (at least two present)	AD, AITD, T1DM (at least two present)		
Lewiński 2005, [44]	AD, candidiasis#, hypoparathyroidism‡ (at least two present)	AD (always present) plus: AITD†, AITD and T1DM* T1DM	AITD, ABD, T1DM, vitiligo: (at least two present) APS-3A: AITD and T1DM APS-3B: AITD and ABD APS-3C: AITD plus other organ--specific AID (e.g. coeliac disease)	

The table shows classification of APS and components of each type according to above-mentioned authors; #candidiasis — chronic candidiasis of mucosa and skin; ‡hypoparathyroidism — hypoparathyroiditis of autoimmune origin; †Schmidt syndrome; *Carpenter syndrome; AD — Addison's disease; AITD — autoimmune thyroid disease; T1DM — type 1 diabetes; AID — autoimmune disease; ABD — Addison-Biermer disease

Autoimmune disorders associated with coeliac disease

Type 1 diabetes

The majority of studies released so far concern the presence of CD with another autoimmune disorder: T1DM.

Prevalence

Research was first performed by paediatricians over 30 years ago. At that time, only the classical form of CD was diagnosed. Diagnosis was based on symptoms such as steatorrhoea, malnutrition, and growth and development disorders in children. The frequency of CD in patients with T1DM was established at the level of 1.0–1.5% [51] which was significantly underestimated (as it later turned out after the introduction of serological assays as a diagnostic tool). In recent investigations, where specific diagnostic tests are used, the frequency of histologically confirmed CD in patients with T1DM is estimated at the level of 2–5% in adults and 3–9% in children [14–16]. According to some researchers, the following criteria are connected to a higher prevalence of CD in patients with T1DM: young age [53], female gender [52], younger age at diagnosis of T1DM [53].

Clinical manifestations

Among the clinical symptoms suggesting association of CD with T1DM, apart from typical symptoms, there may be episodes of hypoglycaemia caused by malabsorption. A gluten-free diet for patients with TD1 and CD can reduce these episodes in some cases. Therefore, changing the diet of these patients to one which is gluten-free usually increases insulin requirements, thus doses of insulin must be changed. We have to remember that diarrhoea, a clinical feature of CD, can also occur in association with bowel neuropathy as observed in T1DM.

Recommendations for diagnostic evaluation

The Polish Diabetes Association, in its guidelines from 2011, recommends CD screening in children and young people with T1DM once a year [54]. The American Diabetes Association (ADA), in its guidelines from 2011, recommends CD diagnosis when there is an appearance of clinical symptoms, periodic screening studies of asymptomatic patients with T1DM and diagnostic tests in all children with recently diagnosed T1DM [55]. However, the guidelines of the National Institute of Health (NIH) from 2004 [56] and the American Gastroenterological Association (AGA) [34, 57] from 2006 recommend a diagnostic approach to CD in patients with T1DM when the symptoms of CD are present.

Autoimmune thyroid diseases

Studies of the presence of CD among patients with autoimmune thyroid diseases (AITD) have concerned mainly individuals with Hashimoto's thyroiditis (HT). Because of the different genetic factors of HT and GD, these two diseases cannot be analysed as one group [58].

Prevalence

There were two studies performed concerning the frequency of CD in patients with GD [4, 5]. In other investigations patients with GD have constituted only a small subgroup of patients with AITD (from 18 to 100 individuals). In these studies, elevated antibody levels, typical of CD, were present in approximately 3.7% of patients (ranging from 0 to 7.2%) and CD was finally diagnosed (histological evaluation) in approximately 2.5% (ranging from 0% to 5.5%) [4–10, 13]. In self studies performed on 238 patients with GD, an elevated level of antibodies specific to CD (IgA TTG or IgA EMA) was confirmed in 5.9% of patients and a histological diagnosis of CD was diagnosed in 3.4% of patients [59]. In studies estimating the prevalence of CD in patients with HT, an elevated level of autoantibodies specific to CD was present in approximately 3.9% of patients (ranging from 0% to 9.1%) [6, 7, 9–13]. Diagnosis of CD was established in approximately 3.1% (ranging from 0% to 9.1%) of patients. In all studies carried out so far, no predisposition to CD in AIDT patients concerned with age or gender has been observed. In a study in2010, the frequency of autoimmune diseases in a group of 2,791 patients with GD and 491 patients with HT was 0.9% and 1.0% respectively [60]. The coexistence of CD and AITD was assessed only according to a questionnaire, which was probably the reason for the underestimation.

Clinical manifestations

Many patients with HT and GD suffering from CD have atypical CD. Some symptoms typical of CD such as diarrhoea and weight loss can be incorrectly interpreted as symptoms of hyperthyroidism in GD, which leads to delayed diagnosis. One of the symptoms which indicate the possibility of a coexistence of CD and AITD (HT or GD after radical treatment) is related to situations connected to hypothyroidism. In these cases, often a higher dose of levothyroxine (up to 200 ug per day and more) is required and a gluten-free diet leads, after some time, to a reduction in doses of hormonal substitution.

Recommendations for diagnostic evaluation

Currently, there are no indications from the Polish Endocrine Society concerning establishing a diagnosis of CD in patients with HT and GD. The NIH (2004) [56] and the AGA (2006) [4, 57] recommend a diagnostic approach towards CD in patients with AIDT in case of the appearance of CD symptoms.

Other autoimmune disorders

Research projects concerning the presence of CD among other autoimmune disorders are numerous and are usually performed on small groups of patients. In a couple of published studies regarding patients with primary adrenal insufficiency, in various groups of 17 to 109 patients, a diagnosis of CD was established in 5.4% to 12.2% of patients [17, 20]. Authors focus on the possibility of similar symptoms in both diseases, which leads to a postponement in establishing a diagnosis of CD (losing weight, abdominal pain, diarrhoea). In numerous case reports, there is some data about the coincidence of CD and primary hypoparathyroidism of autoimmune origin [61–63]. It is important to remember this, especially in patients with deep hypocalcaemia accompanied by the symptoms of tetany. As opposed to this situation in which parathormone serum concentration is low, in patients with hypocalcaemia, connected to malabsorption in CD, an elevation of serum PTH concentration may occur.

There is some data regarding CD and its coexistence with lymphocytic hypophysitis [64], alopecia areata [65–67], and pernicious anaemia. It is essential to remember that megaloblastic anaemia of B12 vitamin deficiency can be caused by poor absorption in patients with CD and the presence of autoantibodies in patients with pernicious anaemia as well. As a result, when CD is associated with pernicious anaemia there are indications for a diagnostic evaluation of the presence of autoimmune features (autoantibodies to intrinsic factor).

Studies estimating the prevalence of autoimmune diseases in patients with CD relate to a much larger group of patients. Among these studies, the vast majority concern AIDT and Addison's disease. In a study of 14,021 patients with CD compared to a control group of 68,068, for the first time a significant increase in AITD was diagnosed (HR = 2.9; 95% Cl = 2.0–4.2; $p < 0.001$) [68]. In another study performed by the same authors on the same group of patients with CD, a higher prevalence of Addison's disease was observed compared to a healthy control group (HR = 11.4; 95% Cl = 4.4–29.6; $p < 0.001$) [69].

Recommendations concerning the diagnostic approach to coeliac disease in patients with autoimmune disorders

Recommendations concerning the diagnostic approach to CD in patients with autoimmune disorders are ambiguous and differ according to which autoimmune disease is present, and the Society summarising the data. At present, the most up-to-date and strict guidelines are those formulated by the ADA. There are no guidelines from Polish Societies, apart from the Polish Diabetes Society. This probably stems from a lack of data concerning the prevalence of CD in the Polish population of patients with other than T1DM autoimmune disorders. According to the present guidelines of the NIH (2004) [56] (Tab. VIII) [34, 57], patients with autoimmune disorders should undergo a diagnostic approach to CD in the presence of any symptoms suggesting CD. With relevance to atypical or even silent course of CD types, it may lead to lower detectability.

It would require further clinical studies on larger groups of patients with autoimmune disorders to estimate the prevalence of CD in these patients, and potential modification of the guidelines.

Remember!

CD is one of the most frequent diseases of autoimmune origin, diagnosed, on average, in one out of 100

Table VIII. ***Recommendations concerning the diagnostic approach to coeliac disease in adult patients based on NIH recommendations [56]***

Tabela VIII. ***Zalecenia dotyczące diagnostyki celiakii u dorosłych oparte na zaleceniach NIH [56]***

Diagnostic approach to coeliac disease	Diagnostic approach to coeliac disease in symptomatic patients	Diagnostic approach to coeliac disease not recommended
Malabsorption, isolated iron deficiency	Family history of coeliac disease	General population
Infertility	Autoimmune thyroid disease	Short history of symptoms from digestive system
Osteoporosis	Sjögren's syndrome	Type 1 diabetes**
Ataxia and polyneuropathy	Type 1 diabetes*	
Arthritis of unknown origin	Addison's disease	
Chronic liver disease of unknown origin	Symptoms from digestive system	
Dermatitis herpetiformis		
Irritable bowel syndrome		

*With symptoms of coeliac disease, **without symptoms of coeliac disease

individuals. The results of studies indicate that there is an increased prevalence of CD in patients with other diseases of autoimmune origin. The coexistence of CD with other autoimmune diseases is probably connected to a common genetic predisposition.

The majority of adult patients suffer from atypical or silent types of the disease, something which postpones proper diagnosis. CD, if undiagnosed or untreated, can lead to many medical disorders.

The diagnostic approach to CD is based on serological evaluation (specific antibodies — IgA TTG and IgA EMA of equivalent diagnostic accuracy). In many cases, an evaluation of IgA TTG can be routinely considered as a screening test. A patient with a positive serological evaluation should undergo endoscopy with a biopsy of the descending part of the duodenum.

Introducing a strict gluten-free diet in patients with CD can decrease the risk of many of the medical disorders mentioned above.

In patients with endocrinopathies of autoimmune origin, in the diagnostic process of many symptoms and diseases (for example iron deficiency, non-specific abdominal symptoms, abnormal serum transaminases, infertility), the coexistence of CD should always be considered.

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