

WHEN SHOULD ENDOCRINOLOGISTS THINK OF CELIAC DISEASE IN CHILDREN?

Belei Oana¹, Marginean Otilia¹, Brad Giorgiana¹, Daescu Camelia¹

Abstract

Background: Recent researches proved that classical definition of celiac disease (CD) comprises only 30% of cases with genetic predisposition, the vast majority of patients being pauci-symptomatic. Active-case finding in groups at risk for CD is considered a cost/effective strategy. The association of CD with several autoimmune conditions is well-known. **Objectives:** The aim of this study was to determine the prevalence of CD in a pediatric population from the Western part of Romania with associated autoimmune thyroid disorders (AITD) and insulin-dependent mellitus diabetes (IDDM) as well as in a control lot and to assess the clinical forms of presentation and the HLA polymorphism in all cases. **Methods:** Between Oct 2009 and Dec 2012 there were screened for CD 74 children with AITD (lot 1), 98 children with IDDM (lot 2) and 80 healthy children (control lot). In patients with at least one positive serologic test for CD, intestinal biopsy was performed. All children underwent HLA typing for DQ2/DQ8. **Results:** CD prevalence after screening in lot 1 was 7% (5 patients), in lot 2 it was 6% (6 patients). In the control lot there weren't any CD cases diagnosed by screening. There were not significant differences between the frequency of CD cases among children with AITD and the frequency of CD cases among children with IDDM ($p > 0,05$). Most of the cases presented as silent CD (82%) - 9 cases out of 11. All children diagnosed with CD presented DQ2 or DQ8 haplotype. 20% of the control subjects associated heterozygous DQ2 alleles. From 69 children with AITD and without CD, only 3 patients (4%) presented heterozygous DQ2 haplotype predisposing for CD. The rest of 66 patient (96%) associated nonDQ2/DQ8 alleles. From 92 children with IDDM and negative results for CD screening, 25 patients (27%) associated homo or heterozygous DQ2 and DQ8 alleles. The rest of 67 patients (73%) did not present characteristic genetic background for CD. There were significantly more cases with IDDM without CD but with predisposing haplotype for CD (27%) compared to the number of patients with AITD seronegative for CD and with DQ2/DQ8 alleles (4%) $p < 0,005$. **Conclusions:** Recommending AITD and IDDM as selection parameters for CD screening in asymptomatic children is justified by the high frequency of gluten enteropathy obtained in this study (7% and 6% respectively). HLA assessment can not highlight a significant role of a certain allele in the

pathogenesis of autoimmune comorbidity AITD/CD or IDDM/CD. DQ2 and DQ8 alleles are mandatory but insufficient for CD development. The intervention of environmental factors is very important. Performing as first line approaching HLA typing in asymptomatic at risk children may be a valuable proposal. A negative result for DQ2 or DQ8 alleles will render CD highly improbable and there will be no need for subsequent CD antibodies testing in such cases.

Keywords: celiac disease, children, autoimmune thyroid disorders, insulin-dependent mellitus diabetes

Introduction:

Gluten intolerance is defined by the presence of three major features: malabsorption, atrophic changes in the structure of the intestinal mucosa and clinical and morphological response following the exclusion of gluten from the diet. Nowadays, the current trend is to replace the concept mentioned above with a new one - gluten-sensitive enteropathy, which is defined as an exaggerated immune response of intestinal mucosa to gluten protein. This response occurs only in genetically predisposed subjects. Histologically it can be translated by a great variety of morphological abnormalities: from a discrete intraepithelial hyperlymphocytosis to total villous atrophy. (1)

Recent research demonstrated that the classical definition of the disease is limited to 30% of patients with genetic susceptibility and morphological changes and does not include the vast majority of subjects with gluten sensitivity, which have minor villous injuries. Most cases of celiac disease (CD) present as atypical, silent or latent form of disease, without clinical manifestations. This model was described by Richard Logan in 1992 as the celiac iceberg. (2) Nowadays, celiac disease is defined as an immune-mediated enteropathy caused by intolerance to gluten in genetically susceptible individuals (HLA DQ2 or DQ8). CD has a low incidence estimated at about 1% of the general population. This disease occurs in subjects presenting gastrointestinal and extradiagnostic symptoms. Also it can occur in some asymptomatic subjects affected by autoimmune or genetic diseases (insulin dependent diabetes mellitus - IDDM, autoimmune thyroid disorders-AITD, Turner syndrome, Down syndrome, Williams syndrome), patients with selective IgA deficiency and first-degree relatives of patients with CD.

¹ First Pediatric Clinic, University of Medicine and Pharmacy "Victor Babeş" Timisoara

E-mail: oana22_99@yahoo.com, otiliamarginean@yahoo.com, giorgiana.brad@gmail.com, camidaescu@yahoo.com

Several classifications of CD have been used. Classical CD includes chronic diarrhea, abdominal distension and failure to thrive. Atypical form of CD can associates one or more of the following: constipation, iron-deficiency anaemia, short stature/growth failure, increased level of liver enzymes, ameoreea s.a. Silent CD is defined as the presence of positive CD-specific antibodies, HLA and small-bowel biopsy findings that are compatible with CD but without sufficient symptoms and signs to warrant clinical suspicion of CD. Latent CD is defined by the presence of compatible HLA but without enteropathy in a patient who has had a gluten-dependent enteropathy at some point in his or her life. The patient may or may not have symptoms and may or may not have CD-specific antibodies. Potential CD is defined by the presence of CD-specific antibodies and compatible HLA but without histological abnormalities in duodenal biopsies. The patient may or may not have symptoms and signs and may or may not develop a gluten-dependent enteropathy later.(3)

Serological screening of CD in a population with associated risk factors is now considered the most efficient strategy, taking into account cost-effectiveness. The efficiency of this serological screening is to identify the cases with atypical or oligosymptomatic forms of CD in the study group. The benefits are prevention of clinical expression of silent CD and ability to take specific remedial measures - gluten-free diet.

The prevalence of various comorbidities association with CD can vary from one study to another. Recent data show that the prevalence of autoimmune diseases among patients with CD is proportional to period of time they have been exposed to gluten. (4). IDDM is reported to be present in patients with CD in a proportion of 3.5% to 10% (5), AITD in celiac population appear in a proportion of 4% to 8% (6), the presence of rheumatoid arthritis is cited in 1.5% to 7.5% of CD patients (7), autoimmune hepatitis is found in a proportion of 6% to 8% (8), Sjögren's syndrome appears to have a prevalence ranging between 2% and 15% of the CD patients (9), selective IgA deficiency occurs in 7% - 9% of all patients with gluten enteropathy (10) and dermatitis herpetiformis is reported in 20% - 25% of patients with CD. (11)

Objectives:

The aims of this study were to perform a serological screening in a pediatric population from the Western part of Romania with autoimmune diseases associated (AITD and IDDM) considered risk factors for CD and to asses the prevalence and the clinical forms of gluten enteropathy in this population comparing with a control group. We also analyzed the HLA DQ polymorphism in children with autoimmune thyroiditis, diabetes and autoimmune comorbidity CD- thyroiditis, CD - diabetes and in control group.

Material and methods:

We developed a descriptive, prospective study in 1st Pediatric Clinic of Emergency Children Hospital, "Louis Turcanu" Timisoara. The serological screening for CD was performed in all the patients diagnosed with AITD and IDDM admitted to the Endocrinology Department and in all

subjects from the control grup without gastrointestinal, autoimmune or genetic disorders.

Autoimmune thyroiditis is considered risk factor for CD. All children diagnosed with Basedow Graves disease and Hashimoto's autoimmune thyroiditis were screened for CD. Hashimoto thyroiditis was defined by the presence of thyroid antibodies: anti-tireoglobulin (anti-Tg) and anti-tiroid peroxidase (anti -TPO) and hyper, euthyroidism or hypothyroidism (low, normal or high TSH). The majority of cases with Hashimoto's thyroiditis associated clinical or subclinical hypothyroidism. Overt hypothyroidism was defined by low fT4, high TSH level and subclinical hypothyroidism was defined by normal fT4 and TSH levels. Patients with Basedow Graves and goiter associated high level of tiroid stimulating immunoglobulins antibody (TSI), anti-Tg anti -TPO, low TSH level and high fT3 and fT4 values.

The patients with AITD and IDDM and those from the control group were all tested for CD using IgA/IgG combined assessment for anti tissue-transglutaminase and deaminated gliadin peptide antibodies (IgA/IgG tTG/DGP) and IgA anti-endomysial antibodies (EMA).

For IgA/IgG tTG/DGP combined assessment, we used Quanta Lite h-tTG/DGP Screen kit, based on an enzyme-linked immunosorbent assay (ELISA) for semi-quantitative detection of IgA and IgG antibodies to synthetic DGP and human tTG in serum. This test allows detection of celiac serological markers even in patients with selective IgA deficiency.

Anti-endomysial antibodies (IgA EMA) were assessed using indirect immunoflorescence method on monkeys' esophagus smooth muscle using ImmuGloTM Anti-Endomysial Antibody (EMA) test kits.

Intestinal biopsy was performed to the patiens with at least one positive test. 4 biopsy samples were obtained for each patient during upper gastrointestinal endoscopy from second part of the duodenum. Histological interpretation of the intestinal samples was performed by an experienced pathologist using Marsh classification modified by Oberhuber.

All the patients enrolled in this study were haplotyped for the detection of HLA DQ2/DQ8 alleles. The HLA DQ2/DQ8 detection was performed to the control group also. We used QIAamp DNA Blood Mini kit (Qiagen) for the extraction and isolation of the genomic DNA. An optimal concentration of genomic DNA (50 ng/μl) was required, in order to obtain an efficient PCR amplification. The isolated genomic was analysed using PCR-SSP (polimerase chain reaction sequence specific primers) method for the quantification of HLA DQ2 and DQ8 haplotypes. AllSet Gold HLA DQA1 (32 mix), AllSet Gold HLA DQB1 02/04 și AllSet Gold HLA DQB1 03, Dynal – Invitrogen were used for this purpose. The interpretation of the results was done according to the specific Worksheet - Gel Documentation Form associated to the primers kit used which contained all the possible alleles combinations.

The study was approved by Ethical Committee of the host institution, Emergency Children Hospital "Louis Turcanu", Timisoara.

Statistical analysis was performed using specific informatic applications - R statistic soft program version 2.7.1 Data were analyzed by chisquare test. For all statistical

analyses, a two-tailed p value <0.05 was considered significant.

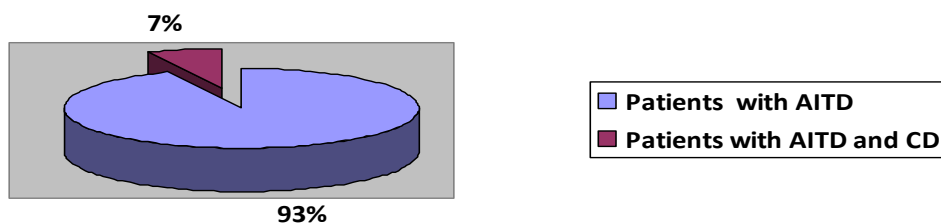


Figure 1: Frequency of CD cases in lot I

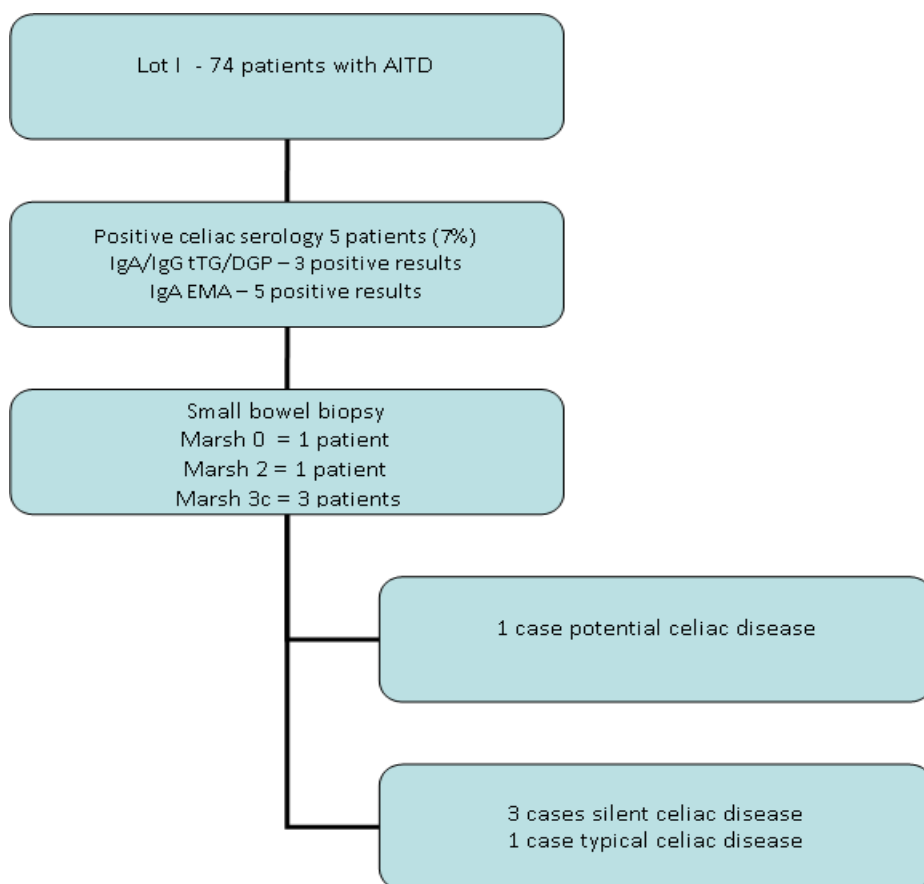


Figure 2: Flow chart of AITD/CD patient recruitment

Results and discussions:

During the study period (October 2009 – December 2012), 74 patients diagnosed with AITD from the first, 98 patients with IDDM from the second lot and 80 healthy patients from the control group were screened for CD.

From the 74 patients with AITD screened, 16 patients had goiter associated with hyperthyroidism as Basedow Graves' disease and 58 had Hashimoto's thyroiditis associating subclinical and overt hypothyroidism.

The term autoimmune thyroid disorders (AITD) encompasses a number of different entities characterized by varying degree of thyroid dysfunction and the presence of serum auto-antibodies against thyroid tissue-specific components, such as thyroglobulin (Tg) and thyroid peroxidase (TPO). Goiter accompanied by hyperthyroidism (due to Basedow disease or Hashimoto's autoimmune thyroiditis) is described in some studies to be associated with celiac disease. Biologically, the hormonal status in these two entities presents with elevated FT3 and FT4 levels and low value of TSH, with anti-TPO antibodies and increased anti-thyroglobulin level. As a marker of differentiation, thyroid stimulatory immunoglobulin (TSI) in high titer is specific for Basedow disease.

5 patients (7%) from the first lot were diagnosed by screening with CD, having at least one positive serologic test. 4 of them associated villous lesions and one child had normal intestinal morphology (Marsh 0). He was classified as having latent celiac disease because he presented positive IgA/IgG tTG/DGP and positive IgA EMA, associated with a genetic background predisposing for CD - HLA DQ2 heterozygous. None patient from those with Basedow's disease had positive serological tests for CD. All 5 patients diagnosed with gluten enteropathy had Hashimoto thyroiditis with overt or subclinical hypothyroidism. Prevalence of CD confirmed histologically after screening in patients with AITD from group I was 7%, taking into account the case with potential CD.

The distribution of clinical forms of CD was: a case of potential CD, 3 cases of silent CD asymptomatic but with positive serology and characteristic histology and a case with classical form of CD, associating chronic diarrhea, malnutrition, serological and histological markers suggestive of gluten enteropathy.

The screening results from the first group of patients with AITD are described in Figure 2.

From 74 cases with AITD screened in this study, CD was confirmed in 5 patients (7%), a higher value compared to similar adults reports. A pediatric study published by Larizza and collaborators described a similar prevalence of CD - 7.7% among children with AITD (12).

Collin et al screened 83 Finnish patients with autoimmune thyroid disease for CD and he found 3 asymptomatic celiac patients which, with one previously diagnosed CD patient, obtaining an overall frequency of 4.8%. In contrast, one (0.4%) out of 249 age and sex matched blood donors was found to have CD.(13) Sategna-Guidetti et al found that 5 of 152 patients with autoimmune thyroid disease (3.3%) also had CD using IgA-EMA and confirmed on duodenal histology. Only one patient

presented with gastrointestinal symptoms.(14) Valentino et al screened 150 newly diagnosed patients with autoimmune thyroid disease using EMA and found 5 celiac patients (3.3%).(15)

6 children (6%) out of 98 patients with IDDM from the second group were diagnosed with CD having at least one positive serologic test and different degrees of villous lesions suggestive for gluten enteropathy. The prevalence of histologically confirmed CD after screening in the second lot was 6%.

All cases with CD diagnosed by screening in the second group presented as silent forms of disease.

The screening results in the second group of patients with IDDM are described in Figure 4.

The association of CD and type I diabetes has been the subject of several studies. Recent studies showed a low prevalence of symptomatic CD (0.7%) at the onset of diabetes, underlining the increased prevalence of CD up to 10% in patients with diabetes in the first 2 years after diagnosis. (16) Most forms of CD associated with type I diabetes may be subclinical, silent or latent forms. This is the reason why screening for gluten enteropathy is recommended at the onset of the disease and during the first 2 years after the diagnosis of diabetes. The prevalence of CD in children with type I diabetes is about 10 times higher compared to the prevalence of this disease in the general population. (17) This prevalence of gluten enteropathy in patients with insulin-dependent diabetes varies between 5 and 10%. (18). The percent of 6% cases with CD in all children diagnosed with diabetes encountered in this study was similar with the results of other pediatric studies.

In the control group none positive serological test was detected, so the detection rate of CD in this group was 0%.

There were not statistically significant differences between the prevalence of CD in the first group with AITD (7%) versus the prevalence of CD in the second group with IDDM (6%), $p > 0.05$.

We compared separately the two subgroups of children with autoimmune comorbidities (AITD and IDDM respectively) and CD. The distribution of the clinical forms of gluten enteropathy is shown below:

The combined analysis of the patients with autoimmune comorbidities (AITD / IDDM) and CD demonstrated the predominance of silent form of disease in children with autoimmune diseases that were tested. From 11 children diagnosed with CD (7 males and 4 females, mean age 6.5 yrs, range 1-18 yrs), 9 patients (82%) had silent form of CD, significantly more than those with the classic form - 1 patient (9%) or potential CD - 1 patient (9%) $p < 0.005\%$.

DQ2 and DQ8 haplotypes were identified as class II HLA genetic determinants of gluten sensibility. HLA-DQ2 heterodimer is encoded by alleles DQA1 0501 and DQB *0201 in cis form by DR3-DQ2 haplotype. HLA-DQ2 heterodimer can be encoded in trans position by the alleles DQA1*0505 and DQB *0202 in the DR5-DQ7/DR7-DQ2 haplotype. HLA DQ8 heterodimer is encoded by alleles DQA1*0301 and DQB1*0302 in cis conformation by DR4-DQ8 haplotype. (19)

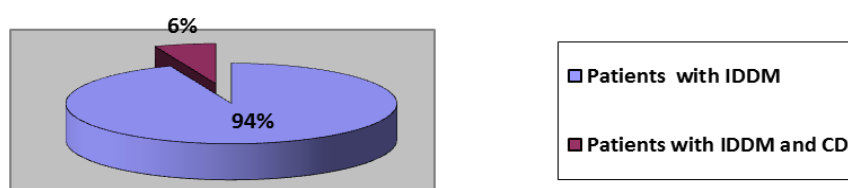


Figure 3: Frequency of CD cases in lot II

The haplotype has become an important first step in screening candidates with risk for CD and monitoring these patients later on. Its important role can be noted in seropositive cases with normal intestinal architecture, when it can be used to exclude this disease. The presence of HLA-DQ2 or DQ8 haplotype is highly suggestive for the potential form of CD, excluding false positive serological results. Some authors have proposed for the diagnosis of CD the histological aspects of the intestinal villous and the detection of HLA DQ2 or DQ8 in these patients. In this cases, the molecular typing of the HLA has no additional diagnostic value if serological tests are positive. (19)

There are multiple evidences that HLA typing for DQ2/DQ8 molecules plays a role in the case-finding strategy in subjects with autoimmune conditions considered risk factors for CD. The coexistence of CD and autoimmune disease is thought to be partly due to a common genetic predisposition. HLA-DQ2 and DQ8 haplotypes are over-represented in many autoimmune diseases. The inheritance of these haplotypes and the associated immunological phenotype may explain the link. (20)

In this study we performed molecular typing for HLA-DQ2/DQ8 in all patients included in the first and the second lot and in the control group.

All 5 children diagnosed with CD from the first group with AITD had HLA-DQ2 heterozygous haplotypes. Out of the remaining 69 children without CD, only 3 (4%) had HLA-DQ2 heterozygous haplotype and the rest (96%) associated other HLA alleles, non DQ/DQ8.

Out of the 6 patients diagnosed with CD after screening from the second group with IDDM, one case presented HLA-DQ8 haplotype, 2 children had HLA-DQ2 homozygous haplotype and 3 cases had heterozygous HLA-DQ2 haplotype.

The rest of 92 patients with IDDM and without CD associated the following haplotypes: 21 (23%) had HLA-DQ2 heterozygous haplotype, 3 (3%) had HLA-DQ2 homozygous haplotype, one patient (1%) had HLA-DQ8 heterozygous haplotypes and the rest (73%) were non DQ2/DQ8.

In the control group (80 subjects enrolled), there weren't any CD cases diagnosed by screening. 16 subjects (20%) had predisposing genetic background for CD (HLA DQ2 heterozygous haplotype) and the rest (80%) associated other non DQ2/DQ8 HLA combinations.

These results are similar with those reported in the medical literature highlighting the fact that the presence of

HLA-DQ2 or DQ8 haplotypes is required, but not enough for the disease to become manifest. The development of CD is multigenic, in which the presence of HLA-DQ2 or DQ8 heterodimers is essential. The HLA-DQ2, DQ8 haplotype are characterized by high sensitivity and low specificity, which gives them a low positive predictive value, with a high negative predictive value for the diagnosis of celiac disease. The absence of these molecules had a negative predictive value of 100% for the diagnosis of celiac disease. (20)

The majority of cases with autoimmune disease and negative serologic markers for CD showed non DQ2/DQ8 haplotype.

Among those 69 patients with AITD and without CD associated, the percentage of those with predisposing haplotype for CD (HLA-DQ2) was significantly lower (3 patients - 4%) compared with those with nonDQ2/DQ8 alleles (66 patients - 96 %) $p < 0.05$.

From 92 patients with IDDM and negative results at CD screening, 67 patients (73%) had non DQ2/DQ8 alleles, significantly more than those with characteristic genetic background (DQ2 or DQ8 HLA) and without CD (25 patients - 27%) $p < 0.05$.

Comparing the percentage of children with IDDM /without CD, DQ2/ DQ8 positives (27%) with the percentage of children with AITD/without CD, DQ2/ DQ8 positives (4%), a statistically significant difference ($p < 0.005$) can be noted. The higher number of patients with diabetes and typical HLA haplotypes characteristic for CD, without developing gluten enteropathy can be explained by a more pronounced genetic similarity between IDDM and CD compared to the relationship between the AITD and celiac disease. Despite this, there weren't any differences between the frequency of CD diagnosed by screening in lot I (7%) and II (6%) respectively, as shown.

In this study, the percentage of children with AITD and without CD who had HLA compatible with CD was low, only 4% - 3 patients from 69.

Comparing this result with other published reports, the results are contradictory.

A study conducted by Valentino showed that 10 (71%) of 14 patients with Hashimoto's thyroiditis had genotypes compatible with CD (3 patients had DQ heterodimer A1*0501, B1*0201, 6 had DRB1*04 and 1 had A1*0101, B1*0501). Six of these 14 patients showed intestinal histologic alterations typical of CD. Among 4 of these 6 patients were described HLA genotypes associated with CD

(3 with DRB1*04, DQB1*03 and 1with DQA1*0501, DQB1*02). (21) In contrast, Larizza screened 90 children and adolescents with autoimmune thyroid disease and showed 7 cases to have CD (7,7%) , indicating a prevalence of 1 in 13 pediatric patients. All 90 patients were typed for HLA antigen class I and II and for HLA-DQA1 and DQB1 heterodimers. Celiac disease and DQA1*0501, DQB1*02 were found only in 7 (7.8%) patients.(12)

The pathogenesis of co-existent autoimmune thyroid disease and CD is not known, these conditions may share similar HLA haplotypes and more important, are associated with the gene encoding cytotoxic T-lymphocyte-associated antigen-4. HLA-DQ2 and DQ8 show a weak association with Hashimoto's thyroiditis, although HLA-DQ2 association is less clear in Graves' disease.(22)

It is important to highlight the fact that in this study in both lot I and II there were patients with autoimmune comorbidities AITD/CD and IDDM/CD respectively, with typical histological finding for CD, but with negative serology for IgA/IgG tTG/DGP combined assay. Only IgA EMA antibodies were positive. All these children had predisposing genetic background for CD, encoding DQ2 or DQ8 alleles. Using the new combined assay IgA/IgG tTG/DGP for CD screening in pediatric patients at risk may provide negative results. Therefore, performing as first line approaching HLA typing in asymptomatic at risk children may be a valuable proposal. A negative result for DQ2 or DQ8 alleles will render CD highly improbable in these children and there will be no need for subsequent CD antibodies testing in such cases, due to the high negative predictive value of HLA typing.

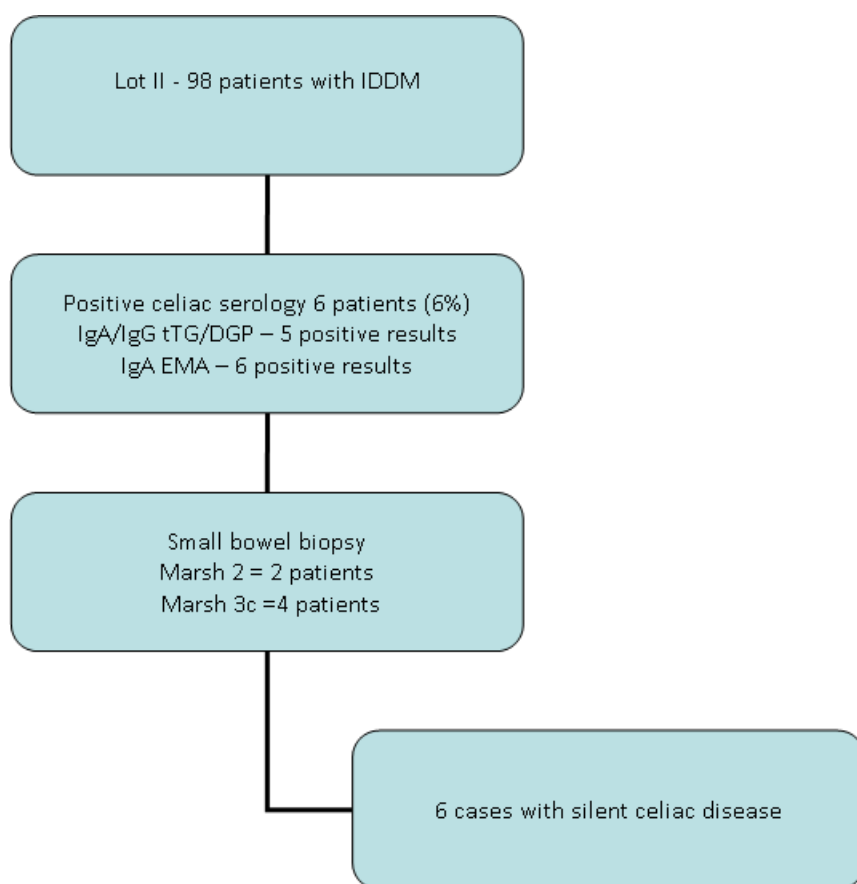


Figure 4: Flow chart of IDDM/CD patient recruitment

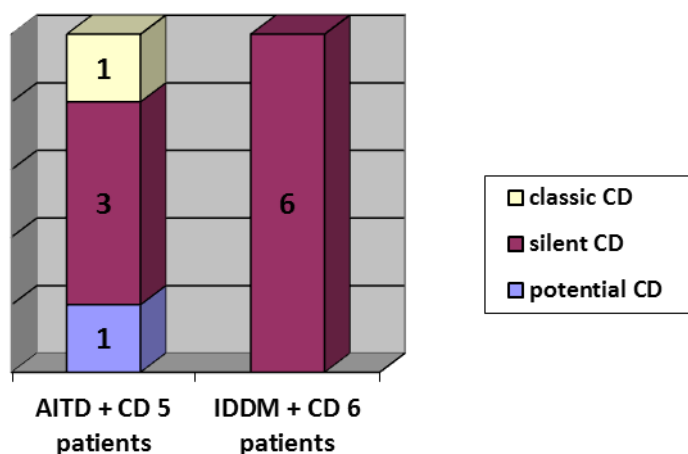


Figure 5: Distribution of CD clinical forms in each group of patients with comorbidity
AITD – CD and IDDM – CD respectively

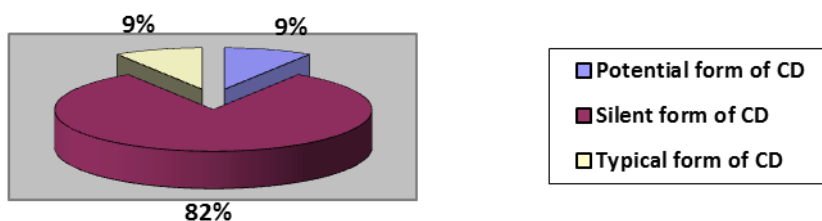


Figure 6: Repartition of clinical forms of celiac disease among children with autoimmune disorders referred to screening.

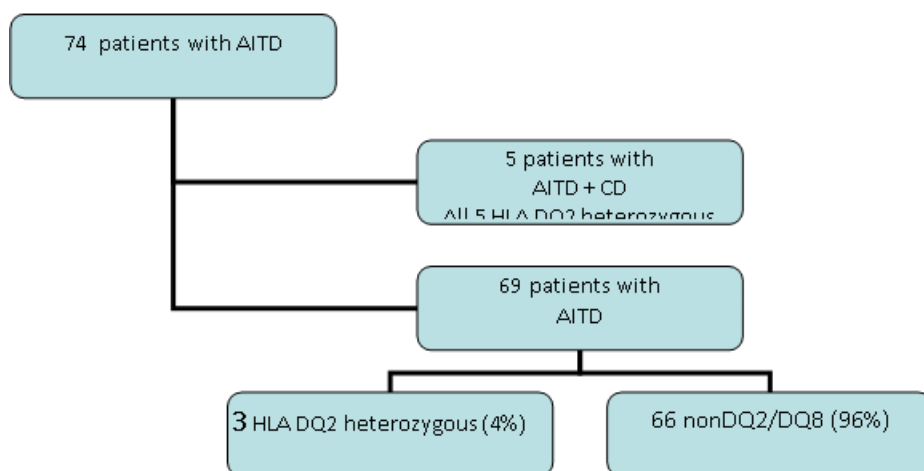


Figure 7: Distribution of HLA DQ alleles in patients from lot I

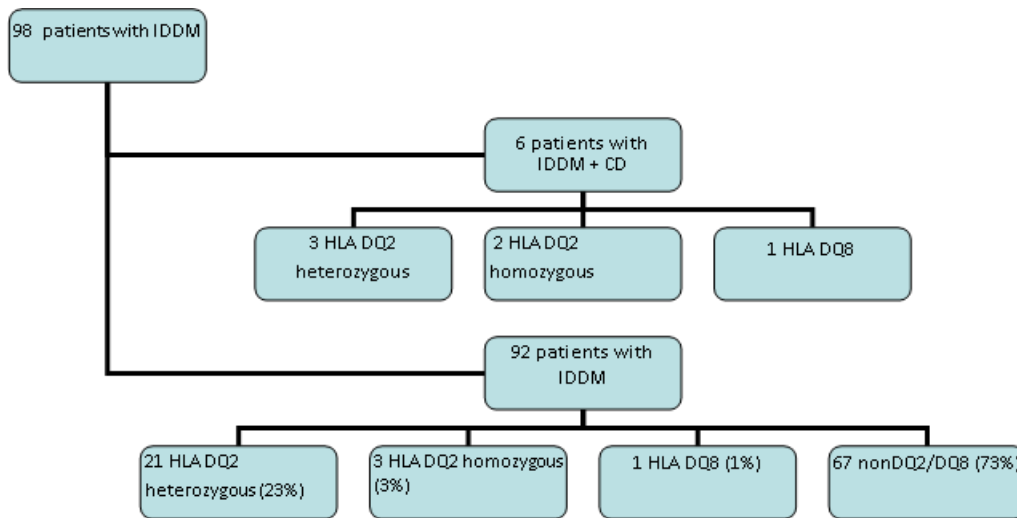


Figure 8: Distribution of HLA DQ alleles in patients from lot II

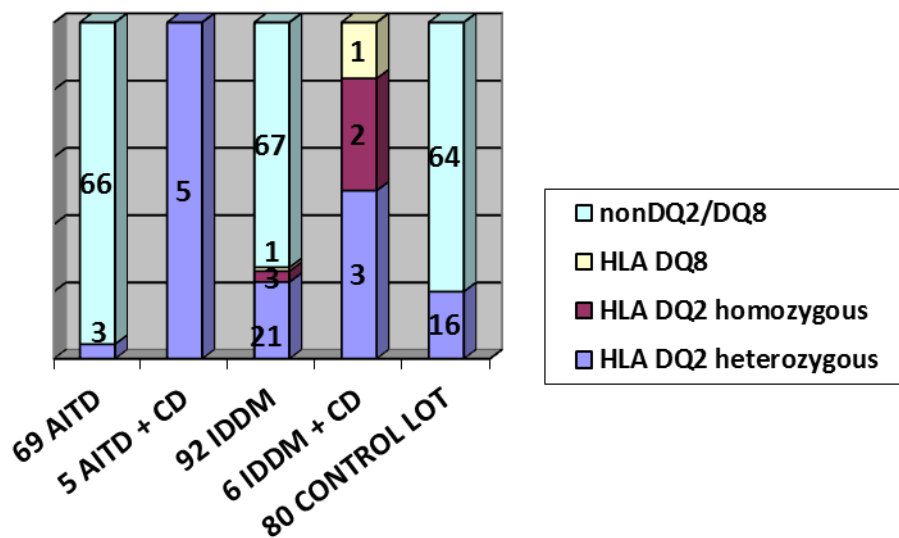


Figure 9: Alleles distribution in each lot of study

Conclusions:

Recommending AITD and IDDM as selection parameters for CD screening in asymptomatic children is justified by the high frequency of gluten enteropathy obtained in this study (7 % and 6% respectively).

The availability of serological tests for CD screening and the possibility to prevent severe complications such as malabsorption, grow impairment and intestinal lymphoma among undiagnosed cases underline the importance of screening patients with autoimmune thyroiditis or diabetes even in the absence of suggestive symptoms.

Haplotypes assessment can not highlight a significant role of a certain allele in the pathogenesis of autoimmune comorbidity AITD/CD or IDDM/CD. DQ2 and DQ8 alleles

are mandatory but insufficient for CD development. Except the haplotype, genetic and environmental factors play a major role in an individual with an autoimmune condition for the initiation and the maintenance of the autoimmune response

Serologic screening performed only once in life is not sufficient to detect/rule out the presence of CD in subjects with high risk of autoimmune disorders. Performing as first line approaching HLA typing in asymptomatic at risk children may be a valuable proposal. A negative result for DQ2 or DQ8 alleles will render CD highly improbable and there will be no need for subsequent CD antibodies testing in such cases.

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Correspondance to:

Belei Oana
 Heinrich Heine Street no 4,
 code 300041, Timisoara,
 e-mail: oana22_99@yahoo.com