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Celiac and Inflammatory Bowel Diseases in Children with Primary Humoral Immunodeficiency

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Additional information is available at the end of the chapter

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1. Introduction

The co-existence of immunodeficiency and autoimmunity called as "old couple" is known from the clinics, but the background and mechanism responsible for this phenomenon is far from explanation. The both; immunodeficiency and autoimmune diseases belong to group of rare diseases. The population of children with immunodeficiency of humoral immunity demonstrating clinical symptoms of deficiency is small and only a part of them develops autoimmune disease which means these patients are really very small group. Because of low number of such patients there is a lack of standards of diagnostic procedures and therapeutic approach.

The clinical observations and analysis of co-existence of these two different pathomechanisms lead to questions –

1. why, in diseases with impaired function of immune system, the antibodies and autoantibodies are produced,
2. why the prolonged inflammation develops leading to tissue and organ damage,
3. why these autoimmune diseases are different in clinical features, course and response to therapy,
4. why we are not able to find the factors helping in selection of patients with high risk of autoimmune disease within immunodeficiency group.

The develop of autoimmune diseases is a result of many factors occurring in sequence or at the same time what seems to be the puzzle with hundreds of pieces. In the immune deficiency some of these pieces are missed at the beginning but despite this the puzzle is fulfilled and the autoimmunity develops. It is why, this phenomenon is still fascinating….

2. The role of antibodies in pathomechanism of celiac and inflammatory bowel diseases

2.1. The production of autoantibodies

The autoantibodies are produced by B-1 subpopulation of B lymphocytes, plasma cells localized in lymph nodes and bone marrow, similarly to production of specific antibodies to pathogens; bacterial, viral or parasitic. They react with autoantigens e.g. determinants, receptors present on cell surface, products of cells (e.g. hormones, cytokines, insulin, enzymes), nuclei, DNA and organelles released after cells death. In healthy people the autoantibodies (e.g. antinuclear, rheumatoid factor) are noted in the serum in low titer what is probably an effect of persist low affinity self-reacting T and B lymphocytes in the thymus and bone marrow. The increase of occurrence and amount of autoantibodies with age in the healthy people is supporting the view that this small population of self-reactive lymphocytes is present during whole life [1].

The induction of autoantibodies production is not fully elucidated and the hypothesis about trigger by chronic inflammation, molecular mimicry with microbial antigens, aberrant expression of HLA-DR on cell surface as facilitating factor, are postulated. In systemic autoimmune diseases like lupus the antigens are intracellular so the above suggestions are not very suitable. The possible explanations of anti-DNA antibodies production includes the process of apoptosis and formation of nucleosomes containing pure DNA. It is highly probable, that dying cells e.g. within inflammatory infiltrations of tissues release many different organelles, proteins and enzymes induce production of antibodies to them. The antibodies against structure of nucleus (e.g. histones, centromers, centriols, nucleoli), Golgi apparatus, mitochondria, peroxidase, specific proteins (e.g. Scl-70, RNP), enzymes are associated with different types of autoimmune diseases. Delayed clearing of dying cells and abundance, stability, resistance to degradation of some nucleoproteins are stimulating the immune response through activation of Toll-like receptors. This hypothesis might apply to some of systemic autoimmune diseases [1].

The presence of autoantibodies in high titer is generally associated with damage of target cells or organs and occurrence of clinical symptoms of disease. The deposits of immune complexes (autoantibodies – antigens – complement) in the vessels or located directly in the tissue expressing the autoantigen are injurious for the surrounding tissue. These complexes bind the complement, activate the cascade, stimulate the production of pro-inflammatory cytokines, chemotactic factors for infiltrating cells leading to support of autoantibodies production and amplification of the inflammation (self-perpetuating inflammatory process). In animal models this damaging effect of autoantibodies and immune complexes was showed for systemic autoimmune diseases. In celiac disease, the anti transglutaminase antibodies are associated with reduction of intestinal epithelial cells endocytosis, differentiation and proliferation. In general, they lead to decrease of intestinal/epithelial barrier function. The studies demonstrated the reduction of the epithelial cells adhesion in experimental model with CaCo cell line and anti-transglutaminase antibodies implicated the role of these antibodies in pathogenesis of celiac disease. In histology of mucous membrane

from patients with untreated celiac disease, the epithelium tends to blister or totally detach from the basement membrane. The antibodies mediated inhibition of epithelial cells adhesion might be an explanation for the detachment [2]. The mechanism of tissue damage and role of autoantibodies in IBD (Leśniowski-Crohn's disease and ulcerative colitis) are not fully described [3-5].

3. Primary deficiency of humoral immunity

3.1. Isolated IgA deficiency (IgAD)

IgAD is the most common immunodeficiency of humoral immunity. The frequency of this deficiency is variable in different regions e.g. 1:400 in Finland, 1:600 in USA and 1:15000 children in Japan. The environmental factors, diet and food type, climate are suggested as explanation for this wide range of IgAD frequency [6-8]. The diagnosis of IgAD is based on low level (often below detection) of IgA, normal or compensatory high level of IgG, normal level of IgM in child older than 4 years of life. In this defect the majority of affected children (70-80%) is asymptomatic [6,7]. The remaining (20-30%) IgAD patients suffer from recurrent infections, allergies and autoimmune diseases. The respiratory and gastrointestinal tract are mainly involved. Recurrent infections of upper respiratory tract caused by different bacterias, often encapsulated are noted in younger children, the prolonged sinusitis is typical for older children and teenagers. Within IgAD patients the incidence of allergies is 20 times higher then in healthy population. The asthma, allergic rhinitis, conjunctivitis, food allergy, atopic dermatitis and urticaria are common. The autoimmunity is represented by hematological symptoms e.g. thrombocytopenia, neutropenia, hemolytic anemia and gastrointestinal disease like celiac disease, IBD. In adults with IgAD the lupus erythematodes, rheumatoid arthritis, thyroid diseases and chronic active hepatitis are noted [6,9-12]. In gastrointestinal tract, besides the autoimmune chronic inflammatory disease, the infestation with *Giardia lamblia*, bacterial infections, nodular hyperplasia are very often observed within IgAD patients [6,12]. The occurrence of clinical symptoms like abdominal pain, discomfort, diarrhea, constipation is 10-20 times higher within IgAD than within healthy children. The most probable explanation is deficient production of secretory IgA [9,13].

The pathogenesis of IgAD is based on defective terminal maturation of B cells into IgA secreting plasma cells leading to reduced level of serum and secretory (mucosal) IgA [13]. The IgA exists in both monomeric and polymeric (mainly dimeric) forms. In humans two subclasses are distinguished – IgA1 and IgA2. The dimeric IgA is formed with joining (J)-chain. The secretory IgA (sIgA) is produced locally within lymphoid tissue under the mucous membrane and released at the luminal surface of jejunum [14]. sIgA composed of IgA2 molecules characterizes high resistance to enzymatic digestion by bacterial proteases. This immunoglobulin plays an important role in protection of mucous membranes lining the gastrointestinal, respiratory and urinary tracts from pathogens present within the lumen. It is the first line of defense against microorganisms based on agglutinating activity and facilitating the clearance of pathogens [12]. The role of sIgA in selection of antigens

entering through the mucous membrane is also postulated. Functions of sIgA include direct neutralization of pathogens, intracellular neutralization of viruses during transepithelial transport and inhibition of receptors mediated activation of immune system [12]. The lack of sIgA is compensated by IgG and IgM [12]. The chronic inflammatory diseases as celiac disease, Leśniowski-Crohn's disease, ulcerative colitis are only a part of gastrointestinal symptoms seen in IgAD patients. The other causes of clinical symptoms (abdominal pain, discomfort, constipation or diarrhea) include bacterial infections e.g. *Helicobacter pylori*, *Campylobacter jejuni* (preferentially in adults) and parasitic *Giardia lamblia* infestation. In jejunum biopsy the type of mucosal damage, villous flattening are suggesting celiac disease. After therapy eliminating *Giardia lamblia* the damage of mucous is repaired, however, in some cases this damage may be irreversible. The deep mucous damage difficult to repair is also an effect of the prolonged infection and diarrhea. sIgA is necessary for clearance of jejunum surface from e.g. parasites, bacterias and yeasts so the lack of this immunoglobulin facilitates attachment and proliferation of the organism on the surface of intestinal epithelium [6,9,11,12,15].

The frequency of Leśniowski-Crohn's disease, ulcerative colitis (mainly in adults) is not well recognized in IgAD [13,16]. Moreover, in adult patients with IgAD and gastrointestinal symptoms the nodular lymphoid hyperplasia (NLH) is observed and diagnosed as a separate clinical entity. In histology, the nodules contain the large amount of IgM-bearing cells. There are found in lamina propria, superficially in submucosa of small intestine, occasionally in large bowel, rectum or stomach. Massive occurrence of these nodules and/or large size are associated with malabsorption, flattening of villi and with obstruction in some cases [16]. The differential diagnosis of Leśniowski-Crohn's disease, nodular lymphoid hypertrophy (NLH) or celiac disease is difficult because the clinical symptoms and histological changes are overlapping.

3.2. Common variable immunodeficiency (CVID)

The common variable immunodeficiency is a heterogeneous disease with the frequency of 1:25000 to 1:66000 diagnosed first in adults. Following this, the description of clinical features and course of disease was based on observations of adult patients. CVID is diagnosed after exclusion all other known causes of hypogammaglobulinemia in adults and in children older than 4 years of life. The criteria of CVID include hypogammaglobulinemia (IgG only or IgG and IgA, IgM), low production of specific antibodies in response to vaccination and, in reasonable amount of patients, disorders of cellular response e.g. low number of T cells, reverse CD4:CD8 ratio, low response of T lymphocytes to stimulation *in vitro* [7,12,17-20]. The hypogammaglobulinemia is a result of deregulation of B-cell differentiation process and disturbances of T-cell regulatory function [18]. Impaired T-cell function (e.g. proliferation) and signaling have also been reported, including abnormalities in expression and function of T cell receptor. Number of B lymphocytes in peripheral blood and in lymph nodes are within normal range usually but the amount of plasma cells is diminished. However, in 12% of CVID patients the number of B lymphocytes in peripheral blood is below detection level [21]. Analysis of B cell subpopulation showed the reduction of

memory B cells (CD19+CD27+IgD-) number in majority of CVID patients. The reduction of memory B cells is associated with more severe clinical course of CVID (e.g. splenomegaly, bronchiectases, autoimmunity). Up to now, it is the one and only parameter with predictive value for the clinical course of CVID [22,23]. However, the reduction of memory B cells did not correlate with genetic mutation described in CVID patients [17]. In subset of CVID patients (5-10%) mutation in TACI (transmembrane activator and calcium-modulator) gene was discovered. TACI is a member of TNF-like receptor family involved in transduction of signals associated with cell survival, apoptosis and isotype switching. The ligands for TACI expressed on peripheral B cells include BAFF (B-cell activating factor) and APRIL (a proliferation-inducing ligand) both in TNF ligand family expressed on monocytes and dendritic cells. BAFF and APRIL can induce isotype switching but in the absence of TACI (their receptor) plasma cell maturation and immunoglobulins production is inhibited [18]. The heterogeneity of clinical features noted within CVID patients might resembled defects like TACI deficiency, BAFF deficiency, APRIL deficiency, loss of inducible co-stimulator and others diagnosed as one disease although named "variable" [18].

The observations of CVID in children showed the difference between these patients and adults in clinical symptoms and course of disease [24]. Within patients diagnosed as adults, the chronic sinusitis, bronchiectases, chronic lung disease are more common than in CVID diagnosed in childhood (Table 1). The level of IgG (before substitution) is not predictive for type, severity and clinical course of infections [21,28]. The bacterial cultures showed *Haemophilus influenzae, Streptococcus pyogenes, Staphylococcus aureus* and *Streptococcus pneumoniae* in european population of CVID patients [16,25-26]. Moreover, the susceptibility of CVID patients to specific type of microorganism is noted so *Ureaplasma uraelyticum, Mycoplasma* (different species), enteroviruses are leading to infections and destructive chances of organs (e.g. fibrotic process in bladder). Despite the cumulating data about deficiencies of humoral immunity, the diagnosis of CVID is delayed 6 to 8 years an average, what lead to sequelae of recurrent infections e.g. lung fibrosis, bronchiectases, chronic sinusitis, underweight, inhibition of growth, anemia [20-21,25-27]. In a large study of 248 CVID patients (children and adults) the severe and recurrent infections, mostly in respiratory system, were noted in 90% of patients [19]. The chronic lung disease was noted in 27% of adult patients. The recurrent infections of lower respiratory tract may be associated with the bronchiectases. However, the bronchiectases often are a consequence of few but severe lung infections. In children, the chronic lung disease and bronchiectases are rare and seen in group of teenagers (the time of disease seemed to be an important factor). Moreover, in children with CVID the lymphoid interstitial pneumonia (LIP); unusual and rare type of lung disease is seen. In our group of 52 children with CVID the histology of lung biopsy showed LIP in 2 patients (boy and girl). In both cases the prolonged therapy with steroids was effective but adverse reactions to steroids limited this therapy. The lung fibrosis was slowed down although still progressing what lead to respiratory insufficiency despite of regular IgG substitution [personal observations]. The chronic sinusitis, LIP or bronchiectases are developing independently to regular substitution of IgG, even in higher dose [28].

Common variable immunodeficiency	Adults	Children
Infections before the diagnosis	Chronic sinusitis, chronic lung disease, bronchiectases	Recurrent acute infections of respiratory tract, ORL and sinuses (90% of patients)
Autoimmunity:hematology	thrombocytopenia, leukopenia (neutropenia), hemolytic anemia	thrombocytopenia, leukopenia (neutropenia), hemolytic anemia
gastrointestinal tract	atrophic gastritis, pernicious anemia, ulcerative colitis, primary biliary cirrhosis, autoimmune hepatitis, Leśniowski-Crohn's disease	celiac disease, Leśniowski-Crohn's disease, atrophic gastritis (teenagers)
systemic	rheumatoid arthritis, sclerodermia, systemic lupus erythematosus, Sjogren syndrome	juvenile rheumatoid arthritis (rare, teenagers)
other	lymphomas, gastric cancer, granulomas formation	LIP (lymphoid interstitial pneumonia), lymphomas

Table 1. The differences between CVID in adults and children

The autoimmunity is associated with CVID in about 20-30% of patients and the hematological symptoms are most common [10,16,17,19,21,29-34]. The dysregulation of immune system in CVID seemed to be paradoxical; while antibody production in response to pathogens and vaccines is impaired, at the same time the production autoantibodies might be excessive [32]. In large study of 311 adult patients with CVID the autoimmunity was diagnosed in 37% (116 patients). The cytopenias were noted in 55 patients including thrombocytopenia (41 patients), hemolytic anemia (17 patients) and neutropenia (10 patients) [30]. The slightly lower percentage of autoimmunity (22%) was noted within other studied group of 248 CVID adult patients but the thrombocytopenia was most frequent [19,32]. In reasonable number of patients the autoimmune symptoms preceded the diagnosis of CVID [17,19,21,34].

The autoimmune/inflammatory diseases of gastrointestinal tract (IBD) including Leśniowski-Crohn's disease, celiac disease, pernicious anemia, autoimmune liver disease, ulcerative colitis and nodular lymphoid hyperplasia (NLH) are the second group of complications (coexisting symptoms/diseases) noted in 20-50% of CVID patients [9,13,16,18-19,21,28-29,34-36]. The clinical symptoms of IBD in CVID are similar to patients without CVID but often more discrete, milder and unspecific. In children unspecific abdominal pain, weight loss and inhibition of growth are prominent. The typical symptoms like diarrhea, constipation and dyspepsia, disturbances of jejunum motility, weakness are present too but they could be often neglected and explained by school stress, problems of diet, life style and maturation. In both groups of CVID patients the results of malabsorption are observed [13,16,19].

The diagnosis of autoimmune diseases is based on presence of antibodies and autoantibodies in serum. In CVID there are two problems: low production of specific antibodies as a marker of immune system dysfunction and lack of antibodies of given immunoglobulin class e.g. IgA in cases of CVID with IgA deficiency. The second problem is associated with histology of tissues involved in autoimmune process. The disturbances of B cell ontogeny seen as abnormal maturation, impaired somatic hypermutation and lack of memory B cell are associated with different histology of jejunum in IBD in CVID [13,36]. In biopsy of jejunum mucous of patients with celiac or Leśniowski-Crohn's disease the low number, even lack of B cells and plasma cells in infiltrations are observed. This atypical pattern of infiltrating cells in CVID became a reason for named the celiac disease as celiac-like, similar – Crohn's-like instead Crohn's disease [13,37].

3.3. Substitution of immunoglobulins in CVID

The main goal of regular substitution of immunoglobulin IgG (intravenous or subcutaneous) in CVID is replacing the specific antibodies. These antibodies produced by healthy blood donors after vaccinations and contact with common pathogens prevent the infections with spectrum of common pathogens. The dose for substitution is wide (0.4 - 0.8 g/kg body weight) with the suggestion for higher dose in first period of IgG substitution to obtained patient's stabilization ("steady-state"). After 6-8 months of regular substitution, the maintaining dose is usually about 0.4 g/kg body weight. The half-life of IgG is 21-24 days indicating intravenous infusion of IgG (IVIG) in every 3-4 weeks [16-17,20,28,38-40]. The modifications of dose are possible in two ways – higher (or lower) dose for singular infusion and shorter (or longer) distance between infusions. The bacterial infections, wounds healing after injuries or surgery are consuming immunoglobulins so higher dose of IgG is recommended. Moreover, the individual variations in half-life of administered IgG, shorter half-time in patients with chronic lung disease or gastrointestinal disease need the modifications of IVIG substitution (patient-tailored), precise monitoring of IgG level and clinical status of patient [20]. The purpose of substitution is to prevent infections, at least, to decrease their frequency and moderate their clinical course. Moreover, the regular substitution of IgG in replacing dose is effective in some autoimmune disease like chronic thrombocytopenia, chronic neutropenia [16]. This effect is probably associated with anti inflammatory activity of IgG, although the precise mechanisms are not described. The different mechanisms responsible for anti-inflammatory activity on IgG preparation are defined for the high dose of immunoglobulins used in autoimmune diseases. It might be that; the regularity, long time of substitution and accumulation of small repeated effects are responsible for anti-inflammatory activity of IVIG in low dose, similar to anti-inflammatory effects of IVIG high dose (1.0-2.0 g/kg b.w.) [20,38]. The adverse reactions of IVIG occurred immediately during the infusion or after up to 4 days. They are mild or sever including anaphylactic shock [16,41]. Most often the fever, chills, pain (headache, abdominal pain) are noted in children during the infusion. The most severe, late reactions are the consequence of tissue distribution of immunoglobulin particularly into central nervous system. Heavy and progressive headache, vomiting, disturbances of vision, speech and balance keeping are

typical. The therapy with intensive hydration and steroids given intravenously are usually effective. In a case of occurrence of severe adverse reactions the subcutaneous (SCIG) form of substitution is recommended. The amount of immunoglobulins given monthly is divided in four portions (0.1 g/kg of body weight per week) administered with special pomp. The effectiveness is similar to intravenous substitution, the adverse reaction are very rare and limited to the place of injection. SCIG is form of home therapy very comfortable for patients, offering the independence from the hospital.

3.4. Antibiotics in prophylaxis of infections

In part of children with CVID the effect of IVIG or SCIG is weak and the infections occurred despite regular substitution. In this group of patients, especially with chronic inflammation (sinusitis, lymphocyte infiltrating pneumonia – LIP), bronchiectases, lung fibrosis and (in some cases) permanent leukopenia; the prophylaxis with antibiotics is suggested. The 3-4 months' periods of antibiotics or trimetoprim introduced in prophylactic dose help in control of infections and improve the patient's comfort. The therapy with antibiotics is still a matter of discussion and approaches to this therapy varies depending of clinical centre, severity of cases. The recommendation for antibiotics prophylaxis is prevention of the endocarditis during invasive procedures [28].

4. Diagnostic procedures in celiac disease and inflammatory bowel diseases

4.1. The standards of IBD and celiac disease diagnosis

Standard of IBD diagnosis includes the clinical symptoms, laboratory tests (e.g. antibodies detection), imaging procedures (gastroscopy, colonoscopy, other radiological methods) and histological examination of jejunum biopsy [4,42-49]. The laboratory markers are helpful in early diagnosis preceding the onset of severe clinical symptoms in many patients. In last years the detection of antibodies associated with autoimmune process in gastrointestinal tract are commonly used as screening in risk group of children including immunodeficiencies (IgAD, CVID).

4.1.1. The immunological markers

The typical clinical symptoms of celiac disease (periods of diarrhea or constipation, abdominal pain, cramps, feeling of discomfort, low weight with difficulty to gain) in small children are noted in about 20% of all patients diagnosed as celiac [51]. The remaining patients demonstrate the results of jejunum functional disorders leading to sideropenic anemia, osteopenia, afts, enamel damage, delay of puberty, concentrations problems and hypoproteinemia or many others without direct association with gastrointestinal tract. The latent, silent or asymptomatic forms of celiac disease are diagnosed in older children, teenagers and adults. The familiar predisposition is associated with expression of HLA-DQ2 and HLA-DQ8 determinants [43,48-50].

For celiac disease the serological assays include antibodies to: endomysium, transglutaminase and gliadin. The antibodies against gliadin (deamidated form – GAF) are tested in IgA and IgG class with indirect immunofluorescence in serum diluted 1:10 [52]. The sensitivity and specificity is declared as 100% in IgG class and 95-99% in IgA class [53]. The endomysial antibodies (EMA) are associated with reticulin-gliadin complex and transglutaminase as enzyme active in formation of this complex. Antibodies are tested with indirect immunofluorescence in serum (dilution 1:10) with tissue slides of monkey's jejunum or smooth muscles (endomysium contains reticulin type 1 (R1) - basic antigen for endomysial antibodies). The serial dilution of serum is helpful in monitoring the results of Gluten Free Diet (GFD). The sensitivity and specificity of these antibodies in IgA class is up to 100% [48,50]. The test performed in IgG class is valid and clinically significant for IgAD patients.

The discovery of role of tissue transglutaminase (tTg) in pathomechanism of celiac disease helped in understanding the induction of immune response to gliadin. This enzyme deamidated and/or transamidated gliadin proteins increasing their immunogenicity. Moreover, tTg is facilitating the formation of gliadin-reticulin complex and location of these complexes deposits on subepithelial basic membrane. The role of tTg in reduction of intestinal epithelial cell adhesion and in detachment of epithelium was described recently [2]. Antibodies against tTg are tested with ELISA commercially available kits for IgA and IgG class of immunoglobulins. The sensitivity of this test is 96%, the specificity – 98% [48,50]. The results of detection tTg antibodies are showed as optical density recalculated to standard curve. Results above 20 units are recognized as positive. High specificity of tTg antibodies and occurrence in level above 200 units seemed to be satisfactory for celiac disease diagnose without further biopsy of jejunum [50]. These antibodies are clinically significant in IgA class preferentially; with exception for IgAD when antibodies in IgG class are considered [52]. The introduction of GFD leads to decrease of antibodies production below detection level in 3-6 months in majority of patients [48,50]. Persistent high level of antibodies to tTg is observed in celiac disease refractory to GFD (RCD type I and RCD type II)[54]. Moreover, antibodies against tTg are observed in about 20% of patients with Leśniowski-Crohn's disease. The clinical significance of these antibodies in Leśniowski-Crohn's disease is unknown. It might be thought; that the inflammation and lymphocytic infiltrates are spreading from region typical for celiac disease to another part of jejunum. However, the localization of Leśniowski-Crohn's disease in other parts of gastrointestinal tract like esophagus or large bowel and presence of anti tTg antibodies is not supporting this idea [50].

The antibodies against *Saccharomyces cerevisiae* (ASCA) antigens are observed in 60-80% of Leśniowski-Crohn's disease patients [5,55]. Occurrence of these antibodies is explained by increased permeability of barrier between jejunum lumen:submucosal tissue and loss of precise selective role of this barrier. The direct contact between yeast and immunocompetent cells is possible and uncontrolled what stimulates production of antibodies. In healthy people this yeast is normally seen in distal region of jejunum (Bauchin' valve) without the induction of antibodies production. ASCA in IgA class are clinically significant in patients

with normal IgA level as for IgAD patients the IgG class antibodies are assayed. For both class IgG and IgA the level above 20 RU/ml is considered as positive. However, comparison of ASCA in IgA and IgG in Leśniowski-Crohn's patients showed ASCA in both immunoglobulin's classes in majority of patients what suggested (according the author) that both IgA and IgG ASCA should be measured [5]. The diagnostic specificity of ASCA is 99% and sensitivity in Leśniowski-Crohn's patients is 80%, positive predictive value - 88% [5]. The new tests (for ELISA) are based on eluated singular proteins of *Saccharomyces cerevisiae* membrane with the similar specificity for Leśniowski-Crohn's disease.

The immunofluorescence indirect test offers detection of antibodies to exocrine pancreas cells cytoplasm (PAB) and their products as useful for diagnosis of Leśniowski-Crohn's disease [55]. Two distinct patterns were noted with the patients' sera tested on human pancreas tissue. The following pancreatic autoantigens were identified; glycoproteins expressed as glycosyl phosphoinositol (GP1) and membrane-anchored protein (GP2) [4]. GP2 is a glycosylated protein accounting for more than half of the zymogen granule membrane proteins in acinar cells. Recent studies showed the expression of GP2 is not limited to pancreatic acinar cells but is noted on epithelial cells follicle-associated or in Peyer's patches too [4]. In the follicle-associated epithelial cells GP2 is restricted to M cells. These cells are located mainly in distal part of ileum being a site of original inflammation in reasonable percentage of patients with Leśniowski-Crohn's disease [4]. The frequency of PAB antibodies in patients with Leśniowski-Crohn's disease is rather low (14%-30%)[4,55-56] however, the specificity of this assay is 93%, positive predictive value is 77% and negative predictive value – 45% [55-56]. The clinical observations indicated the association of PAB with stricturing or penetrating form of the Leśniowski-Crohn's disease [4] but this data were not supported by others. It means, that PAB are independent to disease activity, localization, clinical course and response to therapy with corticosteroids and/or immunosuppression [4,55].

The antinuclear (ANA), antimyeloperoxidase antibodies (pANCA) and against goblet cells (mucins are autoantigen, GAB) antibodies are commonly used for immunological diagnosis of ulcerative colitis (UC). Presence of these antibodies is detected with immunofluorescence and ELISA. The antibodies against neutrophils cytoplasmic antigens (ANCA) are recognized as cytoplasmic (proteins 3 - cANCA) and perinuclear (myeloperoxidase - pANCA) based on microscopic pattern [5,56]. pANCA prevalence in UC is estimated as 71.4%, in comparison to Leśniowski-Crohn's patients – 2.3% and healthy control – 4.8% of positive seras. Comparison of IgA and IgG class of pANCA in group of 28 UC patients showed higher titer for IgA but in majority of patients pANCA were present in both classes of immunoglobulins. The results of ELISA assay for ANCA with different eluated antigens showed lower percentage of patients with positive results than immunofluorescence. Probably the antigens used for ELISA are not covering all possible neutrophil cytoplasmic antigens reacting with patients serum [56]. The antigens identified as responsible for pANCA immune response in UC patients are localized not only in cytoplasm of neutrophils but also inside nucleus (histone 1, nonhistone chromosomal protein, high mobility group of proteins) [56].

The presence of antibodies against goblet cells (GAB) is tested with immunofluorescence (normal jejunum slides) or ELISA. In study of 28 UC patients GAB was detected in 46.4%

[56] in both classes of immunoglobulins with much higher titer for antibodies in IgA class. The sensitivity of GAB is estimated as 46%, specificity – 100% predictive positive value – 100% and predictive negative value – 73% [56]. Studies of reactivity of GAB with different tissue slides from gastrointestinal tract showed the best reactivity in appendix tissue [3]. The reaction with ileum, sigmoid and rectum tissue was from weak to strong with the tendency to resemble clinically affected intestinal segments [3].

The antibodies to enterocytes were described as clinically significant marker for autoimmune enteropathy [43,57]. The detection of these antibodies with indirect immunofluorescence showed a linear pattern most frequently along the apex or brush border of enterocyte on frozen section of human small bowel. These antibodies are predominantly IgG class and have been reported to occur after the mucosal damage onset [57].

4.1.2. The histology of jejunum in celiac disease and Leśniowski-Crohn's disease

The typical changes in celiac disease are classified according Marsh, Oberhuber and Corazza [48]. The classification according Marsh (4 types) is commonly used and number of intraepithelial lymphocytes (IEL), ratio crypts:villi heights, villi structure and height are basic parameters. In advanced stage (Marsh type 3) severe inflammation, flat villi and hyperplastic crypts are noted. In other classification e.g. Oberhuber the mucous of jejunum damage is divide into 8 stages including stage 0 of normal mucous structure, without changes. Classification proposed by Corazza is simplest and described only 3 stages – grade A – normal architecture of mucous, grade B1 and grade B2 – with atrophic villi up to flat mucous. The problem of celiac disease diagnosis arises when patients with clinical symptoms and serology tests results suggesting celiac disease have no visible changes in histology of mucous membrane (Marsh type 0, Oberhuber type 0, Corazza grade A) [48,58]. For these patients, electron microscopy assay is useful for detection of submicroscopical changes of enterocytes which support celiac disease diagnosis or suggest the diagnosis of microscopic enteritis [48,51,57-59]. However, observations of patients with typical clinical symptoms of celiac disease without changes of mucous showed improvement on GFD supporting the clinical diagnosis of latent type of celiac disease [50].

The infiltrations and formation of new lymphoid nodules, increase of IEL number are typical for chronic inflammation of jejunum. Infiltration in celiac disease consists lymphocytes (T and B), plasma cells and some monocytes. Within the lymphocytes present in mucous membrane the cells with TCRγ/δ characteristic are observed. In Leśniowski-Crohn's disease the infiltration contains lymphocytes, monocytes, neutrophils and plasma cells. The similar pattern with increased number of neutrophils is noted in UC. The proportion between the cells within infiltrate is associated with profile of proinflammatory cytokines released locally and induction of antibodies production as effect of contact of antigen presenting cells (APC) with e.g. MPO from neutrophils or the nuclei debris after cell death in situ [45-46].

The nature and function of T regulatory (Treg) subpopulation of T lymphocytes was extensively studied in relation to IBD. Natural Treg (CD4+/CD25+/FoxP3+) from thymus and iTreg (inducible Treg) are involved in monitoring the immune response, maintaining the immune balance, prevention of excessive and potentially harmful immune activation within mucous of gastrointestinal tract [47,61-62]. The study of Treg lymphocytes (CD4/CD25/FoxP3) within the lamina propria patients with Leśniowski-Crohn's disease and UC showed increased number of these cells; whereas the number in peripheral blood was decreased as compare to healthy people. It suggested central role of this population in local regulation of prolonged inflammatory process within jejunum wall [44]. Immunohistochemistry is the basic method for detection of Treg lymphocytes in biopsy specimens, the flow cytometry is used for assay of Treg number in peripheral blood. The immunohistochemistry is commonly used for analysis of proportion and characteristics of different cells within inflammation e.g. macrophages, T and B lymphocytes, plasma cells and others. This approach based on histopathology of jejunum helps to classify the subgroups of IBD patients. It will create specific "biological signature" unique to each patient so this patient can be treated with rational, individual therapy targeting the specific defect or aberrations underlying intestinal inflammatory pathway [47].

5. Problems of gastrointestinal autoimmune diseases in children with PID

5.1. Celiac disease in IgAD and CVID patients

Celiac disease diagnosed as latent, silent or untypical form in children older than infants comprises about 80% of celiac patients. The clinical symptoms are discrete or absent so the diagnosis is often delayed. There have been more than 200 symptoms reported in association with gluten sensitivity [51]. The effects of jejunum dysfunction (malabsorption) presented as low level of iron resistant to oral therapy, vitamins, calcium, zinc and other minerals deficiency are suggesting celiac disease in children and teenagers [63]. The problem of celiac disease diagnosis in CVID and IgAD children lays in paucity and unspecificity of symptoms and overlapping with symptoms typical for IgAD or CVID with lack of IgA (e.g. abdomen pain, episodes of diarrhea, chronic diarrhea, food allergy).

High prevalence of celiac disease in IgAD patients (10-20 times higher risk than in population) suggested the common genetic background for these two diseases. It was demonstrated that ancestral haplotype HLA-A1,Cw7,B8,DR3,DQ2 is important for association between IgA and celiac disease [6,12-13]. However, the observations of frequency of celiac disease within IgAD population did not support this correlation because the observed frequency of celiac disease is still lower than expected based on genetic background [13]. Other hypothesis indicated that abnormal handling of gluten and gliadin in absence of IgA might induce the mucous damage and onset of clinical symptoms of celiac disease. The study of B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL) in patients with IgAD and celiac disease showed increased of both factors in IgAD

as compared to healthy persons but differences between IgAD with celiac disease and without celiac disease were below significance. Increase of APRIL level might be interpreted as part of the mechanism of compensation leading to overproduction of IgG and IgM [64]. The analysis of IEL TCRγ/δ showed highest level in IgAD with celiac disease, increased number in IgAD - higher than control [60].

The production of antibodies to gliadin, endomysium and to transglutaminase are preserved in IgAD patients but in IgG class. However, in some cases of IgAD the presence and high level of anti transglutaminase antibodies in IgA class is seen. In these cases the trace level of IgA (below detection in nephelometry) is enough to show antibodies to tTg with high sensitive technique of ELISA (personal observations). Within our 47 children with IgAD antibodies for celiac disease were noted in 11 patients (23%) – antibodies for gliadin – in 9 patients, for endomysium and for tTg in one patient each. Celiac disease was diagnosed based on anti tTg antibodies (in IgA and IgG class) in one patient without clinical symptoms. The histology of jejunum is typical for the celiac disease including cases diagnosed early with no changes (Marsh type 0) and similar to changes observed in children without IgAD. It is obvious, that in IgAD plasma cells producing IgA are missing, although total number of plasma cells is preserved. In majority of IgAD patients the gluten-free diet (GFD) is effective [16].

In CVID the problem of serological diagnosis of celiac diseases is more complex because of low production of antibodies and IgA deficiency in part of CVID patients. In consequence of these the possibility of serological diagnosis of autoimmune disease in CVID is excluded by many authors [9,13,37]. However, the permanent stimulation with autoantigens is leading to production of antibodies despite of decreased function of immune system. Level of autoantibodies is detectable but lower than in patients without immune deficiency [personal observation, 36]. In our study of 40 children with CVID antibodies for gliadin were noted in 3 patients (7.5%), for endomysium and tTg in 2 patients followed with diagnosis of celiac disease. Algorithm for celiac disease diagnosis is shown in Table 2. In jejunum biopsy the mucous contains excess of IEL (mainly T), lymphoid aggregates, granulomas, crypts distortion. Within this group of patients the celiac disease is often refractory to GFD (RCD) leading to malabsorption syndrome and severe clinical conditions [20]. Poor response to GFD suggests the distinct pathogenesis of celiac disease with 2 forms recently recognized [13]. In type I of RCD the IEL expressed normally CD3 and CD8 determinants as well as polyclonal T-cell receptor (TCR) arrangement. In RCD type II the aberrant lymphocyte population is expanded with loss of surface expression of CD3 and CD8, intracellular presence of CD3 determination and monoclonal TCR arrangement. Type II of RCD is associated with poor prognosis, increased mortality due to progressing malabsorption syndrome and due to T-cell lymphoma in reasonable number of patients [54]. Therapy includes supplementation with proteins, vitamins and microelements, parenteral nutrition, probiotics, steroids (given intravenously in high dose) and antibiotics for bacterial overgrowth in jejunum [16]. The second line of therapy offers immunosuppression (azathioprine) and/or monoclonal antibodies against TNF (infliximab, etanercept, humira) in patients with active, progressive disease [65].
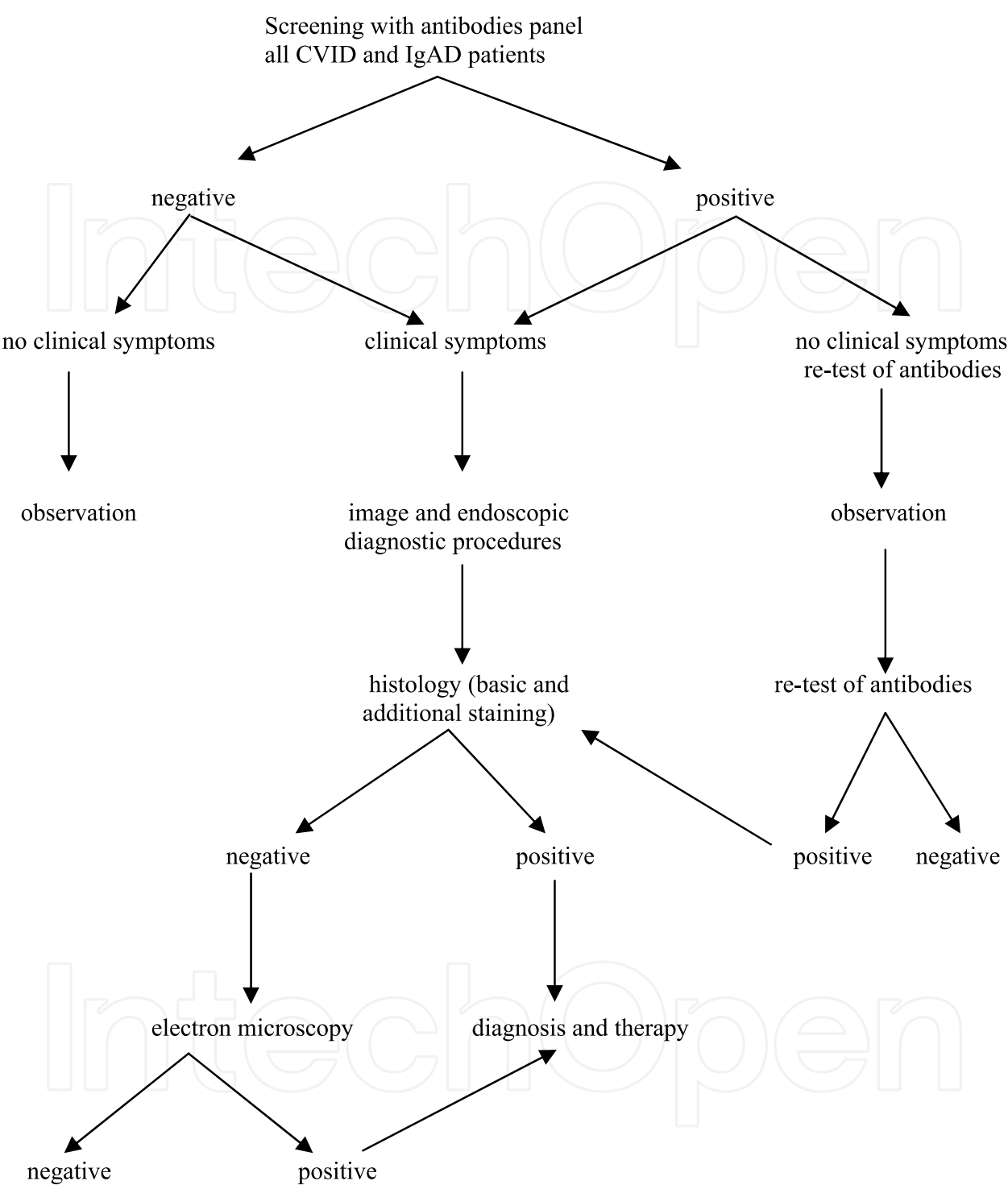
Screening with antibodies panel
all CVID and IgAD patients

negative   positive

no clinical symptoms   clinical symptoms   no clinical symptoms
                                                                   re-test of antibodies

observation   image and endoscopic   observation
                             diagnostic procedures

                             histology (basic and   re-test of antibodies
                             additional staining)

        negative   positive   positive   negative

electron microscopy   diagnosis and therapy

negative   positive

Table 2. Algorithm of the diagnostic procedures for celiac disease and IBD in CVID and IgAD patients

5.2. Leśniowski-Crohn's disease and UC in IgAD and CVID patients

Chronic diarrhea is noted as a typical clinical symptom of gastrointestinal involvement seen in wide range of adult patients (10% - 50%) with CVID [13,16,18,20]. In children with CVID and IgAD the chronic diarrhea is much less frequent but data are based on relatively small

number of patients. IBD are sporadic in IgAD children with clinical course similar to children without IgAD. Within CVID patients IBD remain a significant problem in 19-32% of patients [20]. Moreover, IBD in patients with CVID is recognized as distinct form sharing histological features consistent more with lymphocytic colitis, collagenous colitis than classic IBD [13,37]. In patients, mainly adults, with Leśniowski-Crohn's disease and CVID the formation of granuloma within jejunum wall is observed. Furthermore, the substitution of immunoglobulins does not inhibit and/or reverse symptoms of chronic colitis [13,15]. The different explanations are proposed but hypothesis that IgG from immunoglobulin preparations are not able to reach the lumen of intact jejunum particularly in CVID patients without IgA seemed to be interesting. Other possible explanations include Treg defects, T cell driven inflammation, different patterns of locally produced cytokines as compared to Leśniowski-Crohn's disease in patients without CVID [13]. The special role of T lymphocytes in CVID patients with gastrointestinal symptoms was indicated by different histology of jejunum. Despite the lack of plasma cells in biopsy specimens as typical and characteristic; the villi flattening, increased number of IEL and lymphocytes in lamina propria, increased epithelial apoptosis were observed in CVID patients [13,15,20]. The study of cytokines produced locally in lamina propria showed decreased production of IL-23, IL-17 and TNF in CVID patients with Leśniowski-Crohn's disease as compare to patients without CVID, what suggest alternative pathway of inflammation [13].

Therapy of Leśniowski-Crohn's disease in CVID is generally similar as for patients without immunodeficiency although inflammation in CVID might be more difficult to control. Immunosuppression (e.g.azathioprine, cyclosporine) is used when anti inflammatory drugs and steroids (rapidly metabolized budesonide) are without results and process of inflammation is still active. Induction of remission with anti cytokine monoclonal antibodies (infliximab, etanercept) is effective in CVID patients but the very careful monitoring of infections, particularly fungal, is necessary due to T cell defects [13].

The frequency of UC within CVID and IgAD patients is not known. The large study of 248 patients with CVID including children and adults showed the UC only in 7 patients [19]. In this study ten patients was described as having a significant malabsorption but without specific gastrointestinal diagnosis what showed the problems of establishing the diagnosis in immune deficiency patients [19].

5.3. Differential diagnosis – Collagenous sprue and autoimmune enteropathy

The difficulties in diagnosis of celiac disease, poor response to GFD, IBD with different histology of jejunum seen in patients with CVID, IgAD and gastrointestinal symptoms suggested searching for other diseases overlapping clinical features. The collagenous sprue is severe malabsorptive disorder with histology similar to celiac disease. It is rare disorder characterized by small intestinal villi and crypts atrophy, increased IEL number, subepithelial collagen deposit entrapping cellular components of lamina propria [49]. The clinical and histological similarities (villi atrophy, poor response to GFD during one year) might suggest the refractory or poorly controlled celiac disease. However, in collagenous

sprue the serological test and HLA-DQ2 or HLA-DQ8 are negative what indicate separate entity. The relation between celiac disease, refractory sprue and collagenous sprue is still a matter of discussion but collagenous sprue seemed to be a part of refractory sprue based on poor response to GFD [49]. In histology in collagenous sprue; the subepithelial collagen layer thicker than 12 μm, embedding small capillaries and lamina propria entrapping cells e.g. lymphocytes, fibroblasts are typical. These entrapped cellular elements are a mandatory criterion for this disease. Celiac disease is characterized by increased number of IEL whereas in collagenous sprue these lymphocytes are absent. The precise diagnosis is important because the collagenous sprue is progressing with high ratio of death due to malabsorption and malnutrition. The aggressive therapy includes steroids, immunosuppression and total parenteral nutrition. Up to now, the collagenous sprue was not observed in CVID and IgAD patients but the occurrence of RCD, progressing malabsorption syndrome might suggest existence of this disease within immune deficiency patients.

The term of microscopic enteritis was used for patients with symptoms of malabsorption without prominent inflammation, villous effacement or ulceration seen in conventional light microscopy [59]. This observation may explain the co-existence of symptomatic gluten sensitivity, malabsorption and normally looking mucosa (Marsh 0) [48,58-59]. In patients with RCD the electron microscopy assay seemed to be useful for diagnosis of microscopic enteritis what helps to recognize celiac disease with mild or minimal mucosal abnormalities.

The autoimmune enteropathy is not associated with celiac disease but represents heterogeneous entity consisting protracted diarrhea in young children with circulating antibodies. Affected patients appear to fall into 2 groups: with or without immune deficiency. The syndrome of intractable or protracted diarrhea of infancy was associated with high mortality. Now, the parenteral nutrition, symptomatic therapy of complications, improvement of diagnostic modalities has permitted prolonged survival of these children [57]. Immune deficiency seen in these patients were X-linked syndrome of neonatal diabetes with polyendocrinopathy, IPEX (Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked), T-cell defects, CVID and IgAD. The immunological tests showed a variety of antibodies but most important for diagnosis are antibodies against enterocyte circulating in patients serum. Other antibodies were typical for autoimmune disease of endocrine glands (anti thyroid peroxidase - TPO, Langerhan's islet) and kidney, liver diseases (anti tubular basement membrane, antinuclear, anti-smooth muscles, liver-kidney antigen). Antigens for enterocyte antibodies were characterized as 50 kD and 75 kD proteins present in enterocyte cytoplasm. Diagnosis in neonate and infants with chronic severe diarrhea is based on small jejunum biopsy and immunological tests. The antibodies anti enterocyte are suggesting the autoimmune enteropathy. Symptomatic therapy include diet, parenteral nutrition, "immunological" therapy include steroids (but with no great success), immunosuppression with different drugs e.g. azathioprine, cyclophosphamide and cyclosporine. The second line of therapy offers tacrolimus with a good response. IPEX syndrome patient has been treated with hematopoietic stem cell transplantation [57].

6. General remarks

The diagnosis of IBD and celiac disease is based on clinical symptoms, laboratory tests and endoscopic procedures. Antibodies are the markers of these diseases despite that their role in pathomechanism of chronic inflammation is not fully recognized. The weak production of antibodies in response to vaccine antigens in humoral immunity deficiency seemed to be overestimated since the prolonged stimulation with antigens persistent in contact with immunocompetent cells induce production of antibodies. The antibodies detection used as screening is helpful in early diagnosis due to predictive value of these antibodies. From the other side, in patients with immunodeficiency clinical symptoms might be mild, unspecific and suggesting the association with basic disease (CVID or IgAD) not the concomitant autoimmunity. The high risk of autoimmune diseases in CVID and IgAD is an indication for antibodies screening in these patients but the results should be analyzed with caution. Patients with immunodeficiency are different in all aspects of their immune system function including response to infections, chronic inflammations, autoimmunity prevalence and high risk of tumours. The replacement of specific antibodies with substitution of immunoglobulin for CVID patients is covering only a small part from the complex defect in function of immune system.

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7. References

[1] Elkon K, Casali P (2008) Nature and function of autoantibodies. Nat. Clin. Pract. Rheumatol. 4; 491-498.

[2] Lindfors K, Kaukinen K (2012) Contribution of celiac disease autoantibodies to the disease process. Expert Rev. Clin. Immunol. 8; 151-154.

[3] Ardesjo B, Portela-Gomez GM, Rorsman F, Gerdin E, Loof L, Grimelius L, Kampe O, Ekwall O (2008) Immunoreactivity against goblet cells in patients with inflammatory bowel disease. Inflamm. Bowel Dis. 14; 652-661.

[4] Bogdanos DP, Rigopoulou EI, Smyk DS, Roggenbuck D, Reinhold D, Forbes A, Laass MW, Conrad C (2011) Diagnostic value, clinical utility and pathogenic significance of reactivity to the molecular targets of Crohn's disease specific-pancreatic autoantibodies. Autoimmunity Reviews 11; 143-148.

[5] Papp M, Norman GL, Altorjay I, Lakatos PL (2007) Utility of serological markers in inflammatory bowel diseases: gadget or magic?. World J. Gastroenterol. 14; 2028-2036.

[6] Aghamohammadi A, Cheragi T, Gharagozlou M, Movahedi M, Rezaei N, Yeganeh M, Parvaneh N, Abolhassani H, Pourpak Z, Moin M (2009) IgA deficiency:

correlation between clinical and immunological phenaotypes. J. Clin. Immunol. 29; 130-136.

[7] Fried AJ, Bonilla FA (2009) Pathogenesis, diagnosis, and management of primary antibody deficiencies and infections. Clin. Microbiol. Rev. 22; 396-414.

[8] Vries de E, Driessen G (2011) Primary immunodeficiency in children: a diagnostic challenge. Eur. J. Pediatr. 170; 169-177.

[9] Arkwright PD, Abinun M, Cant AJ (2002) Autoimmunity in human primary immunodeficiency diseases. Blood 99; 2694-2702.

[10] Cunningham-Rundles C (2002) Hematologic complications of primary immune deficiencies. Blood Reviews 16; 61-64.

[11] Diez R, Garcia MJ, Vivas S, Arias L, Rascarachi G, Pozo E, Vaquero LM, Miguel A, Sierra M, Calleja S, De Morales RJM (2010) Gastrointestinal manifestations in patients with primary immunodeficiencies causing antibody deficiency. Gastroenterol. Hepatol. 33; 347-351.

[12] Jacob CMA, Pastorino AC, Fahl K, Carneiro-Sampaio M, Monteiro RC (2008) Autoimmunity in IgA deficiency. J. Clin. Immunol. 28; S56-S61.

[13] Agarwal S, Mayer L (2009) Pathogenesis and treatment of gastrointestinal disease in antibody deficiency syndromes. J. Allergy Clin. Immunol. 124; 658-664.

[14] Vale AM, Schroeder HW (2010) Clinical consequences of defects in B-cell development. J. Allergy Clin. Immunol. 125; 78-787.

[15] Kobrynski LJ, Mayer L (2011) Diagnosis and treatment of primary immunodeficiency disease in patients with gastrointestinal symptoms. Clin. Immunol. 139; 238-248.

[16] Agarwal S, Cunningham-Rundles C (2009) Autoimmunity in common variable immunodeficiency. Current Allergy and Asthma Reports. 9; 347-352.

[17] Blanco-Quiros A, Solis-Sanchez P, Garrote-Adrados JA, Arranz-Sanz E (2006) Common variable immunodeficiency. Old questions are getting clearer. Allergol. Immunopathol. 34; 263-275.

[18] Daniels JA, Lederman HM, Maitra A, Montgomery EA (2007) Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID). Am. J. Surg. Pathol. 31; 1800-1812.

[19] Cunningham-Rundles C, Bodian C (1999) Common variable immunodeficiency. Clin. Immunol. 92; 34-48.

[20] Cunningham-Rundles C (2010) How I treat common variable immune deficiency. Blood 116; 7-15.

[21] Chapel H, Cunningham-Rundles C (2009) Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. Brit. J. Haematol. 145; 709-727.

[22] Alachkar H, Taubenheim N, Haenay MR, Dyrandy A, Arkwright PD (2006) Memory switched B cell percentage and not serum immunoglobulin concentration is associated with clinical xcomplications in children and adults with specific

antibodiy deficiency and common variable immunodeficiency. Clin. Immunol. 120; 310-318.

[23] Huck K, Feyen O, Ghost S, Beltz K, Bellert S, Niehues T (2009) Memory B-cells in healthy and antibody deficient children. Clinical Immunol. 131; 50-59.

[24] Glocker E, Ehl S, Grimbacher B (2007) Common variable immunodeficiency in children. Curr. Opinion Pediatr. 19; 685-692.

[25] Llobet MP, Soler-Palacin P, Detkova D, Hernandez M, Caragol I, Espanol T (2009) Common variable immunodeficiency: 20-years experience at a single centre. Ped. Allergy Immunol. 20; 113-118.

[26] Oksenhendler E, Gerard L, Fieschi C, Malphettes M, Moulliot G, Jaussaud R, Viallard J-F, Gardembas M, Galicier L, Schleinitz N, Suarez F, Soulas-Sprauel P, Hachulla E, Jaccard A, Gardeur A, Theodorou I, Rabian C, Debre P (2008) Infections in 252 patients with common variable immunodeficiency. Clin. Infectious Dis. 46; 1547-1554.

[27] Urschel S, Kaykci L, Wintergerst U, Nothes G, Jansson A, Bolechradfsky BH (2009) Common variable immunodeficiency disorders in children: delayed diagnosis despite typical clinical presentation. J. Pediatr. 154; 888-894.

[28] Bethune CA, Spickett GP (2000) Common variable immunodeficiency. BioDrug 13; 243-253.

[29] Arason GJ, Jorgensen GH, Ludviksson BR (2010) Primary immunodeficiency and autoimmunity. Scand. J. Immunol. 71; 317-328.

[30] Boileau J, Mouillot G, Gerard L, Carmagnat M, Rabian C, Oksenhendler E, Pasquali J-L, Korganow A-S (2011) Autoimmunity in common variable immunodeficiency. J. Autoimmunity 36; 25-32.

[31] Brandt D, Gershwin ME (2006) Common variable immunodeficiency and autoimmunity. Autoimmunity Rev. 5; 465-470.

[32] Bergbreiter A, Salzer U (2009) Common variable immunodeficiency: a multifaceted and puzzling disorder. Expert Review Clin. Immunol. 5; 167-180.

[33] Giannouli S, Anagnostou D, Soliotis F, Voulgarelis M (2004) Autoimmune manifestations in common variable Immunodeficiency. Clin. Rheumatol. 23; 449-452.

[34] Knight AK, Cunningham-Rundles C (2006) Inflammatory and autoimmune complications of common variable immune deficiency. Autoimmunity Rev. 5; 156-159.

[35] Al-Muhsen SZ (2010) Gastrointestinal and hepatic manifestations of primary immune deficiency diseases. Saudi J. Gastroenterol. 16; 66-74.

[36] Malamut G, Verkarre V, Suarez F, Viallard J-F, Lascaux A-S, Cosnes J, Bouhnik Y, Lambotte O, Bechade D, Ziol M, Lavergne A, Hermine O, Cerf-Bensussan N, Cellier C (2010) The enteropathy associated with common variable immunodeficiency. Amer. J. Gastroenterol. 105; 2262-2275.

[37]   Agarval S, Smereka P, Harpaz N, Cunnigham-Rundles Ch, Mayer L (2011) Characterization of immunologic defects in patients with common variable immunodeficiency (CVID) with intestinal disease. Inflamm. Bowel Dis. 17; 251-259.

[38]   Nimmerjahn F, Ravetch JV (2008) Anti-inflammatory actions of intravenous immunoglobulin. Ann. Rev. Immunol. 26; 513-533.

[39]   Nimmerjahn F, Ravetch JV (2010) Antibody-mediated modulation of immune responses. Immunological Rev. 236; 265-275.

[40]   Pituch-Noworolska A, Błaut-Szlósarczyk A (2010) Immunoglobulins: characteristics, indications for use and clinical effectiveness. Int. Review Allergology Clin. Immunol. 16; 94-101.

[41]   Pituch-Noworolska A, Błaut-Szlósarczyk A, Zwonarz K (2010) Stosowanie preparatów immunoglobulin ludzkich – objawy niepożądane. In polish. (The use of human immunoglobulins – adverse reactions). Polski Merkuriusz Lekarski 29; 202-205.

[42]   Akobeng AK (2008) Crohn's disease: current treatment options. Arch. Dis. Child. 93; 787-792.

[43]   Barton SH, Murray JA (2008) Celiac disease and autoimmunity in the gut and elsewhere. Gastroenterol. Clin. North Am. 37; 411-428.

[44]   Kaser A, Zeissig S, Blumberg RS (2010) Inflammatory bowel disease. Ann. Rev. Immunol. 28; 573-621.

[45]   Stange EF, Travis SPL, Vermeiere S, Reinisch W, Geboes K, Barakauskiene A, Feakis R, Flejou JF, Herfarth H, Hommes DW, Kupcinskas L, Lakatos PL, Mantzaris GJ, Schreiber S, Villanacci V, Warren BF (2008) European evidence based consensus on the diagnosis and management of ulcerative colitis. J. Crohn's Colitis 2; 1-23.

[46]   Stange EF, Travis SPL, Vermeiere S, Verlinger C, Kupcinskas L, Geboes K, Barakauskiene A, Villanacci V, von Herbay A, Warren BF, Gasche C, Tilg H, Schreiber SW, Scholmerich J, Reinisch W (2006) European evidence based consensus on the diagnosis and management of Crohn's disease. Gut 55; suppl.1, i1 1- i1 5.

[47]   Schirbel A, Fiocchi C (2010) Inflammatory bowel disease: established and evolving considerations on its etiopathogenesis and therapy. J. Digestive Diseases 11; 266-276.

[48]   Walker MM, Murray JA (2011) An update in the diagnosis of celiac disease. Histopathology 59;166-179.

[49]   Zhao X, Johnson RL (2011) Collagenous sprue. Arch. Pathol. Lab. Med. 135; 803-809.

[50]   Evans KE, Sanders DS (2011) What is the use of biopsy and antibodies in celiac disease. J. Internal. Med. 269; 572-581.

[51]   Nejad AR, Rostami K, Pourhoseingholi MA, Mojarad EN, Habibi M, Dabiri H, Zali Mr (2009) Atypical presentation is dominant and typical for celiac disease. J. Gastrointestin. Liver Dis. 18; 285-291.

[52] Beyazit Y, Sayilir A, Kekilli M, Tas A (2010) IgA and IgG antibody testing for coeliac disease. Eur. J. Int. Medicine 21; 467-468.

[53] Villalta D, Tonutti E, Prause Ch, Koletzko S, Uhling HH, Vermeersch P, Bossuyt X, Stern M, Laass MW, Ellis JH, Ciclitira PJ, Richter T, Daehnrich C, Schlumberger W, Mothes T (2010) IgG antibodies against deamidated gliadin peptides for diagnosis of celiac disease in patients with IgA deficiency. Clin. Chemistry 56; 464-468.

[54] Tennyson Ch, Green PHH (2011) The role of capsule endoscopy in patients with nonresponsive celiac disease. Gastrointestinal Endoscopy 74; 1323-1324.

[55] Demirsoy H, Ozdil K, Ersoy O, Kesici B, Karaca C, Alkim C, Akbayir N, Erdem LK, Onuk MD, Beyzadeoglu T (2010) Anti-pancreatic antibody in Turkish patients with inflammatory bowel disease and first-degree relatives. World. J. Gastroenterology 7; 5732-5738.

[56] Homsak E, Micetic-Turk D, Bozic B (2010) Autoantibodies pANCA, GAB and PAB in inflammatory bowel disease: prevalence, characteristics and diagnostic value. Wien. Klin. Wochenschr. 122; 19-25.

[57] Russo P, Alvarez F (2002) Autoimmune enteropathy; a review. Clin. Applied Immunol. Rev. 2; 203-206.

[58] Sbarbati A, Valletta E, Bertini M, Cipolli M, Morroni M, Pinelli L, Tato L (2003) Gluten sensitivity and "normal" histology. Digestive Liver Disease 35; 768-773.

[59] Rostami K, Villanacci V (2009) Microscopic enteritis: novel prospect in celiac disease clinical and immuno-histogenesis. Digestive Liver Disease 41; 245-252.

[60] Borrelli M, Maglio M, Agnese M, Paparo F, Gentile S, Colicchio B, Tosco A, Auricchio R, Troncone R (2009) High density of intraepithelial γ/δ lymphocytes and deposits of immunoglobulin (Ig)M anti tissue transglutaminase antibodies in the jejunum of celiac patients with IgA deficiency. Clin. Exp. Immunol. 160; 199-206.

[61] Glocker E, Grimbacher B (2012) Inflammatory bowel disease. Cell. Mol. Life Sci. 69; 41-48.

[62] Genre J, Errante PR, Kokron CM, Toledo-Barros M, Camara NOS, Rizzo LV (2009) Reduced frequency of CD4+CD25highFoxP3+ cells and diminished FoxP3 expression in patients with common variable immunodeficiency: a link to autoimmunity? Clin. Immunol. 132; 215-221.

[63] Valletta E, Fornaro M, Pecori S, Zanoni G (2011) Selective immunoglobulin A deficiency and celiac disease. J. Invest. Allergol Clin. Immunol. 21; 242-244.

[64] Fabris M, De Vita S, Visentini D, Fabro C, Picierno A, Lerussi A, Villalta D, Alessio MG, Tampoia MA, Tonutti E (2009) B-lymphocyte stimulator and a proliferation-inducting ligand serum levels in IgA-deficient patients with and without celiac disease. Ann. NY Acad. Sci. 1173; 268-273.

[65] Sandhu BK, Fell JME, Beattie RM, Mitton SG, Wilson DC, Jenkins H (2010) Guidelines for the management of inflammatory bowel disease in children in the United Kingdom. J. Ped. Gastroenterol. Nutrition 50; S1-S13.

[66] Damen GM, van Krieken H, Hoppenreijs E, van Os E, Tolboom JJM, Warris A, Yntema J-B, Nieuwenhuis EES, Escher JC (2010) Overlap, common features and essential differences in pediatric granulomatous inflammatory bowel disease. J. Ped. Gastroenterol. Nutrition 51; 690-697.