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Autoimmunity in Children with Primary Immunodeficiency – Diagnosis, Management and Therapy

Anna Pituch-Noworolska

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1. Introduction

The list of primary immunodeficiencies (PID) includes now more than 200 different diseases and syndromes characterised by dysfunction of immune system with different epidemiology ranging from common, like selected IgA deficiency, to very rare, diagnosed in singular patients. The deficiencies of humoral immunity are frequent including transient hypogammaglobulinemia of infants (THI), common variable immunodeficiency (CVID), selected IgA deficiency (IgAD), hyper IgM syndrome (hyperIgM) or agammaglobulinemia (XLA). The hypogammaglobulinemia of selected immunoglobulins' class (IgG or IgA) or all classes (e.g. CVID) are associated with allergy and autoimmunity in significant percentage of patients. The hypothesis explaining autoimmune diseases in humoral immunodeficiency includes presence of autoreactive T and B lymphocytes, deregulation of immune response associated with number and function of T regulatory cells and other mechanisms. The typical clinical symptoms of autoimmune process in patients with humoral deficiency (CVID, IgAD, hyper IgM) include cytopenias, gastrointestinal tract diseases like celiac or inflammatory bowel diseases, endocrine system autoimmunity, rheumatoid arthritis and systemic autoimmune diseases. The diagnosis of autoimmunity in humoral immunodeficiency is difficult, due to low production of antibodies, overlapping of clinical symptoms of immunodeficiency and autoimmunity. Autoimmunity is noted also in group of well defined immunodeficiency or immunodysregulation syndromes with autoimmune symptoms as criteria of given immunodeficiency, e.g., autoimmune lymphoproliferative syndrome (ALSP) and Wiskott-Aldrich syndrome (WAS). Therapy of autoimmunity in immunodeficient patients includes steroids, immunosuppression, similar to patients without PID. However, if, in some patients with PID, the standard therapy of autoimmune disease is not effective, the immunoglobulins in high dose and/or,

monoclonal antibodies are used. Progress and severity of autoimmune process, resistance to therapy, life-threatening symptoms are now the indications for haematopoietic stem cells transplantation for these patients.

2. Introduction to primary immunodeficiency associated with autoimmunity

The primary immunodeficiencies (PID) consist of more than 200 diseases with one common background – dysfunction of immune system as effect of T, B lymphocytes, NK cells and neutrophils' disturbances in ontogeny and function. The first, most extreme group of PIDs are severe combined immunodeficiencies (SCID) characterised by the lack of immunocompetent cell populations. In these deficiencies, the different patterns of lack of cells are noted- without T lymphocytes and/or NK cells (SCID T-B+NK-, SCID T-B+NK+), and/or B lymphocytes (SCID T-B-NK-, SCID T-B-NK+). The one way to safe life of newborn babies and infants with SCID is haematopoietic stem cells transplantation (HSCT) from matched related or unrelated donor (Table 1). In SCID, the autoimmunity is rare, practically seen only in Omenn's syndrome (Rag1/ Rag2 deficiency). In this type of SCID, besides antibacterial, antifungal, antiviral therapy, substitution of immunoglobulins as standard therapy for SCID, the use of steroids and/or cyclosporine A is indicated to resolve the erythrodermia and eosinophilia. This symptomatic therapy is effective in majority of patients. Thrombocytopenia, neutropenia and leukopenia are often due to hyperactivity of spleen.

Type of deficiency	Laboratory data	Genetic background	Clinical features	Effective therapy
T-B+ Gamma chain deficiency	T, NK decreased, B normal, low IgG	Defect of receptors for: IL-2, -4, -7, -9, -15, -21, X-linked	Severe infections (bacterial, viral, fungal), failure to thrive	Antibiotics, antimycotics, IVIG substitution, HSCT as curative
Other deficiency with known genetic background	like above	JAK3, IL-7R alfa chain, CD45 deficiency Autosomal recessive	Like above	Like above
T-B-(NK-) Omenn's syndrome	T, B, NK decreased, IgG low, IgE high	RAG1/RAG2	Erythrodermia, eosinophilia, autoimmunity, CMV infection, splenomegaly	Steroids and/or cyclosporine A, IVIG, antibacterial, antiviral therapy, HSCT
Reticular dysgenesis	T, B, NK decreased, low IgG	Adenylate kinase (AK2) deficiency	Neutropenia, deafness	Antibiotics, antimycotics, Antiviral therapy, IVIG, HSCT

Type of deficiency	Laboratory data	Genetic background	Clinical features	Effective therapy
Adenosine deaminase deficiency (ADA)	may be progressive decrease of T, B, NK cells number	ADA deficiency	Costochondral junction flaring, neurological features, hearing impairment, lung and liver involvement	Like above
MHC class I	decreased CD8, normal B and NK cells	TAP, TAP2 or TAPBP mutation	Severe infections, vasculitis	Like above
MHC class II	decreased CD4, normal B and NK cells number	Transcription factors mutation (CIITA, RFX5, RFXAP, RFXANK)	Infections, failure to thrive, chronic diarrhoea	Like above

Table 1. Selected types of severe combined immunodeficiencies (SCID) [acc. 1]

In general consensus, the primary immunodeficiencies are divided into groups depending on the basic defect: humoral immunodeficiency — common deficiency with prevalence of disorders in immunoglobulins and antibodies production, cellular immunodeficiency and well-defined syndromes of immunodeficiency with prevalence of cellular mechanisms leading to functional deficiency. The bacterial, viral infections with severe clinical course and poor response to therapy are common and typical symptoms of immune deficiency, due to lack of proper reaction of immune system. In patients with SCID, these infections are life-threatening and together with failure to thrive and weight gaining, they lead to death within first year of life. The autoimmunity process and symptoms are noted as associated disease or complications in different types of immune deficiency. The autoimmunity, in particular types of PID (e.g. hyper IgM syndrome, autoimmune lymphoproliferative syndrome (ALPS), Wiskott-Aldrich syndrome (WAS), is one of criteria of these immunodeficiencies (Table 2). In CVID, one of common immune deficiency of immunoglobulin and specific antibodies synthesis, the autoimmune co-existent process and diseases are noted in more than 30% of patients (up to 60% in different groups). The similar frequency of autoimmunity is observed within IgA deficiency patients.

Type of deficiency	Laboratory data	Genetic background	Clinical features	Effective therapy
WAS Wiskott-Aldrich syndrome	Decreasing T number, B normal, IgA, IgE increased	Mutation in WAS X-linked	Microthrombocytopenia, eczema, autoimmunity, IgA nephropathy, infections, lymphoma	Antibiotics, antiviral therapy, IVIG, HSCT
ALPS (defects of apoptosis) 1.Fas defect (CD95) 2.FasL (CD95L)	Increased DNT (CD3/CD4-/CD8-), normal B and NK cells	Mutation of TNFRSF6 (surface apoptosis receptor)	Lymphadenopathy, splenomegaly, cytopenias, high or normal IgG level	Steroids (often resistance), high-dose IgG, MMF, sirolimus, HSCT

Type of deficiency	Laboratory data	Genetic background	Clinical features	Effective therapy
3.Caspase 10 4. Caspase 8		Mutation TNFSF6 (Fas ligand) Mutation of Casp10 (intracellular apoptosis pathway) Mutation of Casp8	Lymphadenopathy, splenomegaly, cytopenias, recurrent bacterial and viral infections, low IgG	
APECED, Polyendo-crinopathy, candidiasis, enctodermal dystrophy	T, B and NK cells normal, IgG normal	Mutation of AIRE	Autoimmunity of endocrinal glands, chronic candidiasis, hypoplasia of dental enamel	Symptomatic supplementary therapy, steroids
IPEX polyendocrino pathy, enteropathy	Impaired function of T regulatory, B and NK cells normal, high IgA, IgE	Mutation of FOXP3 X-linked	Autoimmune enteropathy, diabetes, thyroiditis, eczema, haemolytic anaemia, thrombocytopenia	Symptomatic therapy
CD25 deficiency	T, B and NK cells normal	Mutation of IL-2 receptor alfa chain	Lymphoproliferation, autoimmunity	Symptomatic therapy

Table 2. Diseases of immunodysregulation with autoimmunity [acc.1]

The primary immunodeficiency described below are selected from a list of known PIDs, based on high frequency or obligatory occurrence of autoimmunity, before or during the course of basic immunodeficiency disease [1-11].

2.1. Humoral immunodeficiency

X-linked agammaglobulinaemia (XLA, former name – Bruton's disease) with *Btk* mutation (Bruton's tyrosinae kinase) is typical example of B lymphocyte ontogeny disturbances. The inhibition of maturation between proB and preB cell stage, results in lack of mature B lymphocytes in the periphery. The first symptoms, typically severe bacterial infections, are noted after 4 months of life, when maternal IgG immunoglobulins have been used, without replacement by immunoglobulins produced by immune system of the affected patient. In serum, the level of IgG, IgA and IgM is often below detection; B cells are below 1% of lymphocyte population; T lymphocytes are normal in all aspects – total number, subpopulations' ratio and function. In part of XLA patients, the activation and function of NK cells are impaired. Sometimes, the number of NK cells is very low, due to particular mutation of *Btk*, essential to normal ontogeny of NK cells. In physical examination, the lack of B cell in periphery is seen as small or absent tonsils and lymph nodes. Autoimmunity is very rare in XLA, but in singular patients, rheumatoid arthritis or myositis symptoms were noted [12-15]. Within our group of 10 boys with XLA, the Shulman disease (eosinophilic fasciitis) was diagnosed in a 14-year-old patient [case report in preparation].

Hyper IgM syndrome (HIGM) is the name for a family of 5 different types of this immuno‐deficiency, with X-linked form as the most severe. This X-linked type of hyper IgM syndrome (HIGM1) is associated with T lymphocytes defect – lack of expression or function of CD40 ligand (*CD40LG*). The other forms of hyper IgM syndrome are results of mutation of genes encoding: CD40 expression on B cells (HIGM3), activation-induced cytidine deaminase (*AICDA*) (HIGM2), uracyl-N-glucosylase (*UNG*) (HIGM5). The signal transduction between T and B lymphocytes are critical for proper response to pathogens, so the disturbances in this function of lymphocytes explain the severe and recurrent bacterial infections in HIGM patients. In laboratory, very low or undetectable levels of IgG, IgA, normal or increased level of IgM, normal number of B and T lymphocytes are found. The other symptoms typical for hyper IgM syndrome include leukopenia, mainly due to severe neutropenia, high sensitivity to infection with *Cryptosporidium parvum* leading to sclerosing cholangitis and liver cirrhosis. In X-linked type of hyper IgM syndrome, HSCT is suggested as curable procedure, especially for patients with neutropenia refractory to G-CSF therapy, patients with cryptosporidiosis and severe bacterial infections, e.g., osteomyelitis [16-19].

Selected IgA deficiency (IgAD) is the most common immunodeficiency of humoral immunity (the mean frequency in Europe is 1/600 people). Diagnosis of IgAD is based on low level (often below detection) of IgA, normal or compensatory high level of IgG, normal level of IgM. IgAD is observed in small children (below 4 years of age), but the stable, definite selected IgA deficiency is diagnosed in children older than 4 years. This time is enough, like in transient hypogammaglobulinemia of infancy (THI), for development of the immune system and correction of immunoglobulin deficiency including IgA. In IgAD, the majority of affected children (70–80%) are asymptomatic. The remaining (20–30%) IgAD patients suffer from recurrent infections, mainly of the respiratory tract. In both sub‐groups of IgAD patients (with and without symptoms of immunodeficiency), allergic and autoimmune diseases are noted. The respiratory and gastrointestinal tract is involved in majority of patients. Recurrent upper respiratory tract infections caused by different bacteria, often encapsulated, are noted in younger children; prolonged sinusitis is typical for older children, teenagers and adults. The incidence of allergy in IgAD patients is 20 times higher than in healthy population with asthma, allergic rhinitis, conjunctivitis, food allergy, atopic dermatitis and urticaria as typical features [5, 11, 20-23].

The pathogenesis of IgAD is based on the defective terminal maturation of B cells into IgA secreting plasma cells, resulting in reduced levels of serum and secretory (mucosal) IgA (sIgA) [5, 22]. The IgA circulating in serum consists of IgA1 and IgA2 subclasses. Depending on the localisation of IgA production', the monomeric and dimeric forms of IgA (with joining (J)-chain in structure) are noted – monomeric circulating in serum, dimeric seen on surface of mucous membranes of small and large intestine, respiratory and urinary tract. The sIgA is produced by cells present within lymphoid tissue under the mucous membranes (MALT) [22, 24]. sIgA composed of IgA2 molecules characterise high resistance to enzymatic digestion by bacterial proteases. This secretory IgA immunoglobulin plays an important role in protection of mucous membranes from pathogens present within the lumen by agglutinating activity and facilitating the clearance of pathogens in the gastrointestinal, respiratory and urinary tracts [25]. Functions of sIgA include direct neutralization of pathogens, intracellular neutralization of viruses during transepithelial transport and inhibition of receptors-mediated activation of immune

system. The role of sIgA in selection of antigens entering through the mucous membrane is also postulated. The lack of sIgA on surface of mucous membranes is compensated by IgG and IgM [22, 25].

Common variable immunodeficiency (CVID) presents variety of symptoms and heterogeneous clinical profiles. CVID has a frequency of 1:25000 to 1:66000 people; however, the delay of diagnosis is serious and estimated as years. Historically, the first description of CVID came from adults with typical clinical symptoms noted in these patients. CVID is diagnosed in adults and children older than 4 years of age (THI) after exclusion of all other known causes of hypogammaglobulinemia. The criteria of CVID include hypogammaglobulinemia in one or more classes of immunoglobulins (IgG only or IgG and IgA, and/or IgM), disturbances of cellular immunity noted in majority of patients. The consequence of disorders in cellular immunity (low number of T lymphocytes, reverse CD4:CD8 ratio, low response to stimulation *in vitro*) and low production of immunoglobulins are poor responses to pathogens and vaccines antigens [6, 8, 21, 25-31]. The hypogammaglobulinemia is a result of deregulation of B-cell differentiation process and disturbances of T-cell regulatory function, including signalling process and function of T-cell receptor. Number of B lymphocytes in peripheral blood and in lymph nodes is usually within normal range, but the disturbances in maturation resulted in decreased number of plasma cells and B memory cells. However, the low number of B cells, even below 1%, is noted in minority of CVID patients (about 10%) [28], suggesting the differential diagnosis of XLA if the patient is a boy with the level of immunoglobulins below detection. The clinical severity of course of CVID (e.g. splenomegaly, bronchiectases, autoimmunity) is associated with the reduction of memory B cells number (CD19+CD27+IgD-) observed in majority of CVID patients. To date, it is the one parameter with predictive value for the clinical course of CVID [32, 33]. The search for genetic background of CVID resulted in description of mutation in TACI gene (transmembrane activator and calcium-modulator) in about 10% of patients. The role of TACI, as member of TNF-like receptor family, is transduction of signals imported for cell survival, apoptosis and isotype switching. The ligands for TACI are BAFF (B-cell activating factor) and APRIL (a proliferation-inducing ligand), both associated with survival of autoreactive B-cell clones and overt autoimmunity. The mechanisms of BAFF and APRIL activity include induction of isotype switching of B cells. The absence of TACI (their receptor) resulted in inhibition of plasma cell maturation and inhibition of immunoglobulin production [34]. Defects like TACI deficiency, BAFF deficiency, APRIL deficiency, loss of inducible co-stimulator and others, led to heterogeneity of clinical features that were observed in CVID patients. This genetic and clinical heterogeneity was the cause of named "variable" this type of humoral deficiency and proposition of CVID subclassifications [5, 11, 35, 36].

The observations of CVID in children showed heterogeneity of clinical symptoms like in adults, but the course of disease is often different. In a large study of 248 CVID patients (children and adults), majority of them (90%) showed severe and recurrent infections, mostly in the respiratory tract [26]. Chronic lung disease developed in a reasonable number (27%) of adult patients. Recurrent infections of lower respiratory tract may lead to the development of bronchiectases. However, the bronchiectases may also be the result of few but severe and prolonged lung infections. In young children, chronic lung disease and bronchiectases are rare. Observations in a group of teenagers suggest that the time of CVID onset and duration are

important for the occurrence of these complications. Moreover, in children with CVID, lymphoid interstitial pneumonia (LIP), an unusual and rare type of lung disease, is observed [37]. In our group of 52 children with CVID, the histology of lung biopsy showed LIP in 3 patients (2 boys and a girl). Chronic sinusitis, LIP or bronchiectases develop and progress independently of regular substitution of IgG, even in higher doses [38, 39].

2.2. Cellular immunodeficiency with autoimmunity

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency and platelets disease caused by mutation of gene WASP (WAS protein) (Table 2). The disease is characterised by microthrombocytopenia (reduced platelets volume); eczema; high susceptibility to bacterial, viral infections; autoimmunity and high frequency of lymphomas (mainly B cell origin) [40-43]. The defects of T lymphocytes include cytoskeletal disorders leading to paucity of surface microvilli, defective polymerisation of actin, defective internalisation of CD3 after cross-linking of T-cell receptor (TCR) resulting in poor response of T cell to stimulation [40, 41]. Typical clinical symptoms of WAS are: thrombocytopenia with poor response to immunoglo-bulins and/or steroids, infections with severe clinical course and eczema from mild to very severe form, progressing with time. The other WASP gene mutations are associated with thrombocytopenia or agranulocytosis resistant to therapy with steroids or G-CSF. For these clinical syndromes, like for typical X-linked Wiskott-Aldrich syndrome, HSCT is suggested as curative therapy [4, 5, 40, 42, 43].

Autoimmune lymphoproliferative syndrome (ALPS) belongs to a group of diseases associ-ated with immunoregulation and apoptosis disturbances (Table 2). The mutation of genes regulating production of proteins responsible for apoptosis process induced by FAS is the basis of this syndrome. Apoptosis disorders lead to polyclonal proliferation of T lymphocytes, accumulation of these cells in lymph nodes and spleen, and severe autoimmune symptoms. Clinical forms ALPS include: type Ia – mutation of FAS gene (CD95), autosomal dominating type of heredity with typical symptoms and high risk of lymphomas; type Ib – mutation of FAS ligand gene (CD95L), autosomal dominating or recessive heredity, often SLE and other autoimmune diseases; type IIa – mutation of Caspase-10 gene, autosomal dominating showing wide spectrum of autoimmune diseases; type IIb – mutation of Caspase-8 gene, autosomal dominating, in clinic – bacterial and viral infections; type III – mutation of NRAS (neuroblas-toma ras viral oncogene homolog) activation gene coding protein binding GTP, autosomal dominating with high risk of leukaemias and lymphomas [4, 5, 44-46]. In the laboratory, increased percentage (and number) of double-negative T lymphocytes (DNT) with phenotype CD3+/CD4-/CD8-, TCR α/β chains and decreased number of T regulatory cells are seen. These DNT T lymphocytes showed high expression of HLA-DR as activation marker, weak response to stimulation, expression of CD45 isoform. It is believed, that the low number of T regulatory cells (Treg) is associated with autoimmune symptoms observed in patients. The B lymphocytes showed low production of specific antibodies to pathogens, but high production of autoanti-bodies against platelets, neutrophils, erythrocytes, and less frequent, antibodies against cell nuclei, phospholipids and rheumatoid factor. Production of autoantibodies is noted despite lower number of B cells in peripheral blood [44-46]. Clinical manifestation of symptoms and severity of disease course depend on type of ALPS and age of onset. The episodes of acute

thrombocytopenia, haemolytic anaemia, splenomegaly (megaspleen) and chronic thrombo-cytopenia are severe, even life-threatening [44, 45, 47]. Steroids are first-line therapy in ALPS, but, in almost half of patients, the results are transient with progress of lymphadenopathy and splenomegaly. The ALPS patients resistant to steroids are treated with second-line therapy, consisting of infusion of immunoglobulins in high doses (1.0–2.0 g/kg b.w.), mofetil myco-phenolate (MMF) and sirolimus. Good response is noted in about 40% of patients; for the remaining, traditional suppression (vincristine, methotrexate, mercaptopurine), rituximab, splenectomy and stem cells transplantation are proposed [44, 45, 48]. Among our 3 infants with ALPS, the resistance to steroid was noted in all; moreover, effect of MMF was partial and short lasting. The best clinical results were obtained with sirolimus, used in children under one year of age. All our patients were transplanted successfully with matched HSC from unrelated donors (in 2 infants) and related donor (father) in one boy. The clinical course and therapy results in these infants with severe symptoms of ALPS are shown in Table 3 [47].

Symptom/patients	D.G. Boy	Z.A. Girl	W.S. Boy
Family history of ALPS Age of diagnosis Lymphadenopathy Splenomegaly	No 20 months Present megaspleen	Father – mild form 12 days of life Present Present	No 12 months Present megaspleen
Autoimmunity: Thrombocytopenia Haemolytic anaemia Allergy:	Severe Mild Bronchial asthma	Severe Severe No	Mild No No
Therapy: Steroids High dose IVIG Other – sirolimus HSCT: Donor Course of transplant	Transient effect Good effect Related Without complications	Resistance No effect Good effect Unrelated Loss of chimerism Second transplant	Transient effect Good effect Unrelated Loss of chimerism Second transplant
Laboratory data:	53 000	67 000	86 000
Platelets (/ul) before and	145 000	159 000	314 000
after sirolimus	2 900	22 100	11 100
Leukocytes (/ul) before	10 500	7 200	5 600
after sirolimus	97	67	73
Hemoglobin (g/l) before	111	96	123
after sirolimus	31	26	22
DNT (CD3+/CD4-/CD8-) (%) before after sirolimus	9	8	2

Table 3. Infants with ALPS – clinical course and therapy results of our patients [acc.47]

3. Pathogenesis of autoimmunity in humoral immunodeficiency

3.1. Role of autoantibodies

Autoantibodies are produced in the same way, like antibodies to pathogens and vaccine antigens, by B-1 subpopulation of B lymphocytes and plasma cells. The main production is localised in lymph nodes and bone marrow. Autoantigens originate from cells and tissues, so the structure of cell surface (e.g. determinants, receptors present on cell), products of cell (enzymes, hormones, pro-hormones, cytokines and other) and particles released after cell death have become recognised antigens. Autoantibodies against DNA result from circulation of nucleosomes containing DNA. The persistence of small population of self-reacting T and B lymphocytes in thymus and bone marrow in physiology is responsible for physiological presence of autoantibodies at low level. The increased occurrence and increasing amount of autoantibodies with age, suggest the presence of this small population of self-reactive lymphocytes during the entire lives of healthy people [49].

The inducing factor of autoantibodies production is not known to date, so different views are postulated, e.g. chronic inflammation, molecular mimicry with microbial antigens, aberrant expression of HLA-DR on cell surface (facilitating factor for immune response) as triggering signal. However, in diseases like lupus with intracellular autoantigen, this hypothesis is not very suitable. Perhaps the release of cytoplasmic organelles by dying cells and formation of nucleosomes containing pure DNA, induce production of antibodies against them. The antibodies' pattern (e.g. against histones, centromers, centriols, nucleoli, Golgi apparatus, mitochondria, peroxidase, specific proteins: Scl-70, RNP) is typical for particular diseases, but the association between autoantibodies' pattern and clinical features is far from explained [49]. The high level of autoantibodies present in serum is, in general view, associated with damage of target cells, tissues or organs, followed by occurrence of clinical symptoms. The reaction of antibodies with antigen forms immune complexes which circulate in serum and/or produce deposits in capillary vessels, in the tissue expressing the autoantigen. With time, injury of tissue is enough for clinical onset of disease. These immune complexes bind the complement and activate its cascade, stimulating the production of pro-inflammatory cytokines, chemotactic factors for infiltrating cells. This stimulation and hyper activation of immunocompetent cells support the permanent synthesis of autoantibodies and amplification of chronic inflammation (self-perpetuating inflammatory process). The antibodies play important role in the pathomechanism of clinical symptoms in autoimmune diseases, though, not in all of them. Although, the precise role of autoantibodies is unknown, their persistent production suggests the participation in pathomechanism of disease. For example, the anti-transglutaminase antibodies present in celiac disease are associated with reduction of intestinal epithelial cells endocytosis, differentiation and proliferation, which results in decreased function of intestinal/epithelial barrier. In histology of mucous membrane in untreated celiac disease, the epithelium tends to blister or totally detach from the basement membrane, possibly the effect of inhibition of epithelial cells adhesion caused by antibodies [50]. On the other hand, the role of autoantibodies in pathomechanisms of tissue damage in inflammatory bowel diseases (IBD – Leśniowski-Crohn's disease and ulcerative colitis) is not fully described [51-53].

3.2. Production of autoantibodies in immunodeficiency

The serological diagnosis of autoimmune diseases is based on autoantibodies circulating in the serum, as a marker of this process and presence of tissue deposits containing autoantibodies and complement. In CVID, the production of specific antibodies including autoantibodies is low, due to immune system dysfunction. Moreover, in CVID the deficiency of IgA is frequent, so there is lack of antibodies in this immunoglobulin class. The histology of affected tissues, in patients without PIDs, is typical and well known. In this group of patients, as an effect of immunoglobulins and cells deficiency, the histology of affected tissue by autoimmune process is different. B-cell deficiency and disturbances in maturation (e.g. memory cell decrease, low number of plasma cells) are probable causes of different histology of intestine in IBD present in CVID patients [8, 54]. In biopsy of jejunum mucous in celiac or Leśniowski-Crohn's disease in CVID patients, the infiltrates contain T lymphocytes, almost exclusively, with low number of B and plasma cells. To differentiate atypical histological pattern of intestine infiltrates in CVID from typical histology of affected intestine in otherwise healthy patients, the celiac disease and Leśniowski-Crohn's disease are termed "celiac-like, " and "Crohn-like" for CVID patients [8, 55-57].

In IgAD patients with celiac disease, the production of antibodies to gliadin, endomysium and tissue transglutaminase are preserved, but in IgG class. However, in some IgAD patients, the presence and high level of anti-transglutaminase antibodies may be shown in IgA, despite lack of IgA in serum (assayed with nephelometry). In these cases, the trace level of IgA in serum is enough to show antibodies to tissue transglutaminase, but with high sensitivity technique (e.g. ELISA). The histology of jejunum in IgAD patients is typical for celiac disease and similar to observed in children without IgAD. In some IgAD patients, serological diagnosis of celiac disease is suggested by other symptoms then directly associated with digestive tract (e.g. underweight, inhibition of growth, afts, low iron level). Moreover, in these patients, the typical changes of structure of jejunum villi may be absent (Marsh type 0). The time of introduction of restricted gluten-free diet (GFD) is a matter of discussion, depending on clinical symptoms from digestive tract, occurrence or progress of other symptoms, e.g. growth inhibition, loss of weight. It is obvious that in IgAD, plasma cells producing IgA are missing, although, total number of plasma cells is normal within infiltrates in jejunum. The GFD is effective in resolving the clinical symptoms of celiac disease in majority of IgAD patients [25, 55].

In CVID, the serological diagnosis of celiac disease is more difficult and doubtful, due to low production of antibodies both in IgG and IgA due to IgA deficiency in CVID [7-8, 55]. However, the permanent stimulation with autoantigens and antigens (e.g. gliadin) is enough to induce and to support the synthesis of antibodies/autoantibodies, overcoming the impaired function of immune system. The level of autoantibodies in serum is often lower than in patients without immune deficiency [54, 56-58]. In our observations, these antibodies present in low level were clinically significant, so, they should be considered in CVID patients as marker of celiac disease.

3.3. Role of T regulatory cells

The T regulatory subpopulation of T lymphocytes (Treg, CD4+/CD25+/FoxP3+) consists of the natural Treg from thymus and inducible Treg (iTreg), both involved in regulation of autoim-

mune reaction of immune system. Extensive studies have shown the role of Treg in monitoring the immune response, especially, in control of hyperactivity leading to imbalance of immune response to pathogens and self-perpetuating inflammation process. Treg cells are important for regulation of the activity of mucous membrane associated lymphoid tissue of gastrointestinal and respiratory tracts [59-61]. The population of Treg lymphocytes in peripheral blood is assayed with flow cytometry; Treg lymphocytes localised in the tissue and in inflammatory infiltrates are detected with immunohistochemistry. The immunohistochemistry is a sensitive method commonly used for analysis of the presence, proportion and characteristics of different – not only Treg – cells, within inflammatory focuses in tissues, e.g. macrophages, T and B lymphocytes, plasma cells. The data from many indicated the central role of this T lymphocytes subpopulation in regulation of prolonged inflammatory process within mucous membrane of gastrointestinal and respiratory tracts, joints and other tissues. The analysis of Treg lymphocytes number in Leśniowski-Crohn's disease and ulcerative colitis (UC) showed increased amount of these cells within lamina propria; whereas, the number of Treg in peripheral blood was decreased as compared to healthy people. This study of Treg cells in biopsy of intestine helped to classify the IBD patients into subgroups, based on relations between Treg number within infiltrates, clinical symptoms and course of disease. It will create specific "biological signature," unique to each patient, leading to individualisation of therapy ("patient tailored") with hope for more rational therapy targeting the specific intestinal inflammatory pathway recognised in this patient [59, 62].

4. Autoimmune haematological syndromes

4.1. Thrombocytopenia acute and chronic

Thrombocytopenia associated with immunodeficiency presents two clinical forms – episodes of acute thrombocytopenia alone or as a part of Evans syndrome, with normal number of platelets in remission, and chronic thrombocytopenia, with number of platelets always below normal level [63-65]. In ALPS and WAS, thrombocytopenia is one of the criteria of a particular immunodeficiency type, so this symptom, in chronic form, is constantly present in all patients. However, the chronic form of thrombocytopenia does not exclude the exacerbations with life-threatening low numbers, or even absence of platelets. Therapy with platelets infusions, high dose of immunoglobulins and other immunosuppressive drugs (e.g. steroids, mycophenolate mofetil, sirolimus, classical drugs, rituximab) is effective; however, in majority of patients, this effect is transient. The severe clinical course of ALPS and progressing symptoms of WAS (with time) are indications for HSCT in these patients [40, 44, 45, 47, 48].

In our group of CVID patients with thrombocytopenia, all these forms (acute, chronic, exacerbations of chronic form) were noted, without relation to time of CVID diagnosis and duration. Moreover, in part of patients, thrombocytopenia was diagnosed prior to CVID onset and established diagnosis. Regular substitution of immunoglobulins in replacing dose (0.4 – 0.6 g/kg b.w. intravenously) is not effective in control of platelets number in exacerbation of chronic thrombocytopenia or prevention of acute thrombocytopenia episodes in CVID. The

standard therapy of thrombocytopenia with steroids and high-dose immunoglobulins (1.0 - 2.0 g/kg b.w.) is required. Moreover, this immunoglobulins therapy is successful in majority of CVID patients, despite regular substitution of immunoglobulins in replacing dose. After infusion of immunoglobulins in high dose, the regular substitution is continued, supporting the remission of thrombocytopenia. However, there are still problems in management of thrombocytopenia in CVID – short effect of therapy for acute episodes, necessity of mainte-nance therapy in remission. Long-lasting remission, with normal number of platelets in CVID patients, is similar to patients without CVID, when good results are obtained with high dose of immunoglobulins and/or steroids therapy. However, in part of CVID patients, acute thrombocytopenia showed tendency to chronicity. In chronic form of thrombocytopenia with number of platelets below 100 000/ul, the regular substitution of immunoglobulins in replacing dose seemed to stabilise platelets number, without need for additional therapy, e.g. steroids or azathioprine. Clinical observations of our CVID patients with chronic thrombocytopenia showed increase of platelets number only for few days after infusion of replacing dose immunoglobulins, followed by low decrease during next 3 weeks, although, the platelets number, in nadir, was still higher than in acute episodes of thrombocytopenia. This stable, safety level of platelets, on regular substitution of immunoglobulins (replacing dose) without additional therapy of thrombocytopenia, allows patients to live normally (Table 4) [66].

Patient number	1 boy	2 boy	3 boy	4 girl	5 boy	6 boy	7 boy
Diagnosis: CVID thromboc.	6 years 14 years	8 years 4 years	3 years 6 mths, 4 years 10 mths	12 years, 8 years	10 years 11 years	8 years, 7 years	5 years, 13 years
Main symptoms of CVID	Infections of respiratory tract, lymphadeno-pathy, splenomegaly	Thromboc. spleno-megaly	Severe thromboc. lymphadeno-pathy splenomegaly	Thromboc. leukopenia	Thromboc.	Thromboc.	Pneumonias lymphadeno pathy, splenomegaly
Laboratory data at diagnosis of CVID	Low level of IgG IgA, low number of T cells, reverse D4:CD8 ratio, weak response to vaccines	Low level of IgG, IgA, IgM, low number of T, B and NK cells	Low number of T cells, lack of response T cells to stimulation, low level of IgG	Low level of IgG, IgA and IgM, low number of T, B and NK cells	Low level of IgG	Low level of IgG, IgA,	Low level of IgG, IgM, lack of IgA, leukopenia, weak response to vaccines
Other symptoms	Mild leukopenia	leukopenia	Severe haemolytic anaemia	Severe leukopenia	no	No	Agenesis of kidney, LIP, lung fibrosis (progression), bronchiectases

Patient number	1 boy	2 boy	3 boy	4 girl	5 boy	6 boy	7 boy
Dose (g/kg b.w. /month) and response to IgG	0.43-0.38 good, no infections	0.36 good	0.35 – 0.42 good	0.35 – 0.45 weak (increase of platelets 2-3 days)	0.38 – 0.3 good	0.4 – 0.35 good	0.45 – 0.3 weak (low level of IgG)
Complications of therapy	Adverse reaction to IVIG						Severe osteoporosis, overweight, delay of puberty
Other therapies	Steroids before IVIG						Steroids, azathioprine (lung fibrosis) progress
Present status	SCIG	IVIG	No substitution, hematology care	IVIG, hematology care	No substitution, no symptoms	No substitution no symptoms	SCIG, lungs and kidney insufficiency, splenomegaly
Therapy of thrombocytopenia	steroids (pulses)	IVIG 1.0g/kg b.w. steroids, azathioprine	steroids, azathioprine, IVIG 1.0 g/kg b.w.	steroids	steroids, IVIG 1.0 g/kg b.w.	steroids	steroids
Complications, other symptom	No	No	Severe haemolytic anaemia (Evans syndrome)	Diabetes, severe overweight	No	No	
Lowest number of platelets (/ul)	28 000	0	0	0	27 000	20 000	37 000
Number of platelets at IVIG beginning	253 000	156 000	133 000	15 000	44 000	87 000	126 000
Mean number of platelets during IVIG (/uL)(range)	149 100 (120 000-196 000)	166 000 (141 000-198 000)	131 000 (97 000-154 000)	51 460 (18 000-68 000)	113 500 (56 000-154 000)	172 400 (99 000-264 000)	112 700 (86 000-133 000)
Number and therapy of thromboc. exacerbations	1 IVIG 1.0 g/kg b.w. steroids		3 (1 severe) Steroids, platelets, erythrocytes and plasma	4 IVIG 1.0 g/kg b.w.	1 (severe) Steroids, splenectomy		

Patient number	1 boy	2 boy	3 boy	4 girl	5 boy	6 boy	7 boy
			transfusions, plasmapheresis IVIG (1.0g/kg b.w.)				
Time of observation	12 years	2 years	7 years	4 years	5 years	4 years	11 years

Table 4. Characteristics and course of CVID in patients with thrombocytopenia (thromboc.) [acc.66]

The regular substitution of immunoglobulins in replacing dose not only supplements specific antibodies, but also stimulates maturation of dendritic cells. This activity of immunoglobulins used in substitution was noted in XLA patients with defective dendritic cells phenotype. Similarly, defective phenotype of dendritic cells was found in CVID patients. The dendritic cells play a critical role in predisposition to pathological conditions, e.g. bacterial infections due to impaired antigen presentation and initiating the immune response, induction of autoimmunity process. Stimulation of dendritic cell maturation might be preventing the development of autoimmunity associated with defective function of these cells in immuno-deficiency patients. It is believed, that regular substitution of immunoglobulins, even in replacing dose, restores the normal phenotypes of dendritic cells and their proper function [67].

In CVID patients demonstrating refractory thrombocytopenia, recurrent episodes of exacer-bations or chronic thrombocytopenia, second-line therapy with immunosuppressive drugs like azathioprine, vincristine, cyclophosphamide and splenectomy is used [63-65]. Moreover, in CVID patients, refractory thrombocytopenia seemed to be more frequent, followed with higher ratio of indications for splenectomy, than in otherwise healthy children. Splenectomy is effective and safe in CVID patients, without higher risk of severe infections due to immu-nodeficiency. Moreover, the long-lasting results are similar to patients without immunodefi-ciency [64]. Another therapeutic option for severe thrombocytopenia in CVID patients with normal number of B cells is monoclonal antibody against CD20 (e.g. rituximab) for elimination of B lymphocytes [68, 69]. For these patients with CVID, the risk for severe infections seemed to be higher and substitution of immunoglobulins in replacing dose should be continued every month, without decreasing the dose and/or pause, e.g. for holidays [11, 63, 64, 69]. Thrombo-cytopenia in CVID patients is considered as unpredictable autoimmune symptom, so a very careful clinical and laboratory monitoring is required.

4.2. Neutropenia/leukopenia, haemolytic anaemia

Neutropenia is very often associated with hyper IgM syndrome (especially in CD40L – X linked and CD40 deficiency type), leading to severe clinical course of infections, e.g. sinusitis, otitis, osteomyelitis [16, 18, 70]. In some patients, recurrent and persistent ulcers of the mucous membrane, e.g. palate, oral cavity, are noted in episodes of deep neutropenia. The symptomatic therapy is based on antibiotics/sulphonamides in prolonged course, granulocyte colony stimulating factor (G-CSF) and immunoglobulin substitution with good effect, but not in all

patients. For hyper IgM patients with severe clinical course, resistance to therapy and episodes of severe bacterial or fungal infections, HSCT is recommended as curative therapy.

In CVID, leukopenia and/or neutropenia, mainly in mild form, is frequently noted. Within our group of CVID children, leukopenia was observed in few patients, but was persistent and refractory to immunoglobulins substitution and without relation to IgG level. However, due to mild clinical form, additional therapy (e.g. G-CSF for neutropenia) is required in singular cases only [71].

It is noted that haemolytic anaemia presents severe clinical symptoms in patients with CVID, hyper IgM, Wiskott-Aldrich syndrome and ALPS. In ALPS, the clinical course of haemolytic anaemia may be life-threatening due to severity and high frequency of episodes. Moreover, these episodes of severe anaemia cause complications, e.g. high level of iron, hepatospleno-megaly (megaspleen), poor general condition of patients. This severe clinical course of ALPS and resistance to steroids, immunoglobulins and immunosuppression therapy are an indica-tion for HSCT as life-saving procedure [47]. Moreover, for patients with milder course of ALPS, symptomatic therapy with good response and careful monitoring of blood parameter are satisfactory.

5. Involvement of the gastrointestinal tract in primary immunodeficiency

5.1. Celiac disease

Celiac disease diagnosed as latent, silent or atypical form, in children older than infants, comprises about 80% of total number of celiac paediatric patients. The clinical symptoms in atypical form of disease are discrete or unspecific, so the diagnosis is often delayed. Moreover, there have been more than 200 symptoms reported in association with gluten sensitivity, which does not facilitate establishing proper, early diagnosis [72]. Low levels of iron, resistant to oral therapy, vitamins (e.g. vit. D), calcium, zinc and other minerals deficiency are symptoms suggesting jejunum dysfunction (malabsorption), typical for celiac disease in children and teenagers [73]. The clinical symptoms of celiac disease may be unspecific (e.g. underweight, inhibition of growth, afts), delicate and overlapping with symptoms characteristic of immu-nodeficiency (IgAD, CVID without IgA), like abdomen pain, episodes of diarrhoea, chronic diarrhoea, food allergy [72, 73]. The co-existence of IgAD and celiac disease (frequency of celiac disease within IgAD patients is 10–20 times higher than in healthy children) supported the idea of the common genetic background for these two diseases. The study indicated the ancestral haplotype HLA-A1, Cw7, B8, DR3, DQ2 as important for this association of two diseases. However, the frequency of celiac disease within IgAD population is still lower, than expected, based on common genetic background, so this hypothesis remains without confir-mation [73]. The other explanation is based on persistent stimulation of immune system associated with mucous membrane, by gluten and gliadin in absence of IgA, which leads to the damage of jejunum and onset of clinical symptoms. Stimulation of immune system, including B lymphocytes, was represented by increased expression of B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL) in patients with IgAD and celiac disease,

although, the difference between IgAD patient with and without celiac disease was non-significant. Stimulation of B lymphocytes (increased APRIL level) might be important for compensatory local production of IgG and IgM [74]. The number of T lymphocytes TCR γ/δ infiltrating epithelial cells (IEL) was higher in IgAD patients than in healthy people, but lower than number of IEL TCR γ/δ noted in IgAD with co-existent celiac disease [75].

5.2. Leśniowski-Crohn's disease and ulcerative colitis

Chronic diarrhoea as typical clinical symptom of gastrointestinal involvement is seen in a wide range of adult patients (10–50%) with CVID [8, 27, 55, 76]. In children with CVID and IgAD, chronic diarrhoea is much less frequent, but clinical data are based on relatively small number of patients. In IgAD children, the IBD was noted sporadically, with clinical course similar to children without IgAD. In CVID patients, the IBD remains a significant problem for 19–32% of patients [27]. In adults with Leśniowski-Crohn's disease and CVID, besides typical changes of intestine wall and surface, the formation of granulomas is noted. Furthermore, the substitution of immunoglobulins does not inhibit and/or reverse the symptoms of chronic colitis [77, 78]. A variety of explanations are proposed, but the hypothesis that IgG from immunoglobulin preparations are not able to reach the epithelium of intestine, even intact, seems to be interesting. It might explain higher incidence of small bowel inflammation, with severe and progressing course, especially in patients with CVID without IgA, treated with regular immunoglobulins substitution in replacing dose. The other possible mechanisms explaining the differences in Leśniowski-Crohn's course between CVID patients and healthy people are associated with Treg defects, inflammation supported by activated T lymphocytes, and different list of cytokines produced locally within intestine wall [77]. The role of T lymphocytes is postulated based on different histology of infiltrates within wall of small intestine in CVID. The main difference in proportion between T and B lymphocytes within infiltrates is lack of plasmocytes. The remaining phenomena, e.g. the villi flattening, increased number of IEL and lymphocytes in lamina propria, and increased epithelial apoptosis, were observed in CVID patients similar to patients without CVID [27, 77, 78]. The distinct pathway of inflammation in CVID depends also on cytokine profile, when the production of IL-23, IL-17 and TNF is lower in CVID than in Leśniowski-Crohn's patients without CVID [77].

5.3. Autoimmune hepatitis

The exact aetiology of autoimmune hepatitis, similar to other autoimmune diseases, is unknown, but viral infections, especially hepatotropic, and drugs may be the trigger. In etiopathology, the immunological mechanisms involved the function of Treg cells, IgA defence against gastrointestinal pathogens, including viruses [79, 80]. In adult patients with CVID, autoimmune chronic hepatitis is noted in about 10% [78]. The study of autoimmune paediatric liver disease showed association between IgAD and autoimmune hepatitis type 2 with slower progression to cirrhosis than in hepatitis type 1 [81]. This association might facilitate autoimmune hepatitis in patients with IgAD and CVID with low IgA. In patients with hyper IgM syndrome (mainly X-linked), typical liver involvement is associated with *Cryptosporidium parvum* infection. After gastroenteritis, this pathogen infected the epithelium of bile vessels

system. In this immune deficiency, T lymphocytes are enable to destroy the infected cells, which results in persistence of pathogen, chronic inflammation, development of sclerosing cholangitis and chronic hepatitis followed by liver failure [7, 11, 78]. One of our patients with X-linked hyper IgM syndrome showed clinical symptoms of sclerosing cholangitis and progressing liver insufficiency. After successful HSCT from MHC-matched healthy sister, the symptoms of cholangitis and cryptosporidiasis resolved. Now, he is free from immunodeficiency and liver symptoms and living normally [personal communication].

5.4. Other autoimmune diseases in patients with immunodeficiency

In adult patients diagnosed with CVID, the autoimmunity presented a different pattern as compared to children. Rheumatoid arthritis, systemic lupus erythematodes are more frequent than gastrointestinal tract disease; however, the haematologic symptoms are equally frequent in children and adult CVID patients [27, 82]. Rheumatoid arthritis is noted in hyper IgM patients and, what seemed unusual, in X-linked agammaglobulinemia [83, 84]. The explanation of this phenomenon is based on detection of small population of immature B cells in peripheral blood. These B cells are often autoreactive, which suggests that the central and peripheral mechanisms of tolerance have failed [11]. One of our boys with XLA developed eosinophilic fasciitis of right crus, with poor response to immunoglobulins in high dose and non-steroidal anti-inflammatory drugs. Now, the improvement was obtained with steroids in high dose (intravenous pulses), followed with steroids in maintenance dose and MTX in prolonged therapy. However, immunosuppression with MTX was complicated with pneumonia (twice) due to XLA, so MTX was changed to mycophenolate mofetil with good response and hope for fewer side effects and better tolerance by immune system. The partial remission (mild symptoms without pain) obtained with MTX continues and, now, the boy is attending school normally, extra effort being the only limitation.

6. Diagnosis and management of primary immunodeficiency with autoimmunity

6.1. Substitution of immunoglobulins

The main goal of regular substitution of immunoglobulin IgG (intravenous or subcutaneous) in X-linked agammaglobulinemia, hyper IgM syndrome and CVID is supply of the specific antibodies. The immunoglobulins, mainly IgG with trace of IgA witout IgM, are separated and purified from serum of healthy blood donors. The antibodies, important for immunodeficient patients, are active against common pathogens and vaccines antigens, so they are able to prevent infections, but with spectrum of common pathogens. The regular substitution of immunoglobulins should be provided according to standard indications for patients with low but basic levels of IgG in serum. The substitution for XLA, hyper IgM patients, in first moment after diagnosis is individualised depending on clinical state and present infections. For patient without infections, but with IgG level below detection, intravenous substitution (IVIG) should be introduced in higher dose (e.g. 0.75 g/kg b.w.) in 2 weeks period, up to the safety level of

IgG in patient's serum (5.0–5.5 g/l). The standard schedule of IVIG is based on half-life of IgG (21–24 days), so the dose 0.4– 0.6 g/kg b.w. is regularly infused every month. The clinical observations of effects of immunoglobulins substitution showed the 6–8 months period as time required for patient's stabilisation ("steady state"). However, in some CVID patients, obtained IgG level within normal value for age is not enough to prevent recurrent infections. For these patients, the "through level" is used as indication for individualised dose of immunoglobulins substitution [27, 39, 77, 85-87]. The modifications of IVIG includes shorter time between the infusion or higher level in singular infusion, due to bacterial infections, wound healing or other causes leading to overconsumption of immunoglobulins. In XLA without infections, the lower dose (0.2–0.3 g/kg b.w.) in longer period (e.g. 6 weeks) may be used. Moreover, adults with complications like chronic lung disease, chronic sinusitis or gastrointestinal disease may require the individual schedule of substitution ("patient-tailored therapy"). These modifica-tions are based not only on clinical patient status, but on careful, precise monitoring of IgG level [27]. The immunoglobulins offered as substitution should prevent the occurrence of infections, at least, to decrease their frequency, soften the clinical course and improve the response to therapy. Moreover, the regular substitution of IgG in replacing dose, seemed to be effective (stabilising) in chronic thrombocytopenia and chronic neutropenia in some patients with this type of autoimmunity [77]. This effect is probably associated with anti-inflammatory activity of IgG, even in replacing dose, although, the precise mechanisms are not described. One interesting observation showed the activation of monocytes subpopulation in patients with CVID after immunoglobulins infusion in replacing dose [88]. It might be that the regular, long-term continued substitution may lead to accumulation of small, repeated effects of IgG, resembling the anti-inflammatory activity of this immunoglulin in low replacing dose. The mechanisms responsible for anti-inflammatory activity of IgG prepara-tions used in high dose of immunoglobulins (1.0–2.0 g/kg b.w.) for autoimmune diseases therapy (e.g. acute thrombocytopenia, Kawasaki disease, Guillain-Barre syndrome, myasthe-nia crisis) are well defined and mainly based on regulatory activity [27, 86, 89].

The adverse reactions of IVIG may occur immediately, during the infusion or after, up to 4 days. The symptoms of adverse reactions are mild or severe, including anaphylactic shock as most severe reaction, occurring often very quickly, after few drops of immunglobulins' solution. Fever, chills, pain (headache, abdominal pain) and cough are noted in children as mild symptoms resolved with appropriate symptomatic therapy. The late, severe reactions are the consequence of immunoglobulins distribution into tissues, especially into central nervous system. Severe and progressive headache, vomiting, disturbances of vision, speech and balance are neurological symptoms typical for this reaction. Intensive hydration (decrease of IgG level, filling the vessels) and steroids (anti-oedematic activity) given intravenously are effective as therapy [77, 90, 91]. In case of severe adverse reactions, the subcutaneous way of immunoglobulins substitution (SCIG) is recommended. The amount of immunoglobulins given monthly is divided in four portions (0.1– 0.2 g/kg b.w. per week), administered with special pump in children or with syringe only ("rapid push") in adults. The effectiveness of SCIG is similar to IVIG, but the adverse reactions are very rare and limited to the place of injection. SCIG is a form of home therapy, very comfortable for patients, offering independence from hospital. In XLA, CVID diagnosed in adults, hyper IgM syndrome, the regular substitu-

tion of immunoglobulins is for life, so the SCIG form of immunoglobulins substitution is preferred for these patients avoiding the pain associated with poor vein access after years of IVIG. The exception from indication for "substitution for life" is patients with X-linked hyper IgM syndrome treated with HSCT [92-94]. In children with CVID, the developing immune system gives the opportunity to hang off the substitution after reaching the stable, normal level of IgG, low frequency of infections with good response to therapy, resembling the immune system maturation.

6.2. Symptomatic therapy and prophylaxis of infections

In part of children with CVID, the effect of regular immunoglobulins substitution (IVIG or SCIG) is weak and infections, mainly in respiratory tract, are still present. With time, in some of these patients, the lymphocytic interstitial pneumonia (LIP, or GLILD – granulomatous lymphocytic insterstitial lung disease), chronic sinusitis and bronchiectases develop, progressing lung fibrosis and persistent leukopenia (neutropenia) are noted, so prophylaxis with antibiotics is recommended. The 3–4 months' period of antibiotics or time-to-prime in prophylactic dose is commonly used as effective schedule of supportive therapy, improving clinical status of patients. However, the therapy with antibiotics is still a matter of discussion and different approaches to this therapy are suggested depending on clinical centre and severity of patients' symptoms. The specific and unique recommendation for antibiotics prophylaxis is aimed at prevention of endocarditis following invasive procedures in immunodeficient patients [39]. In our clinical management of more than 200 immunodeficient patients, such complication was not observed, but because of the severity of this symptom, prophylaxis should be considered.

6.3. Monitoring and therapy of co-existent autoimmunity

Therapy of common autoimmune diseases, e.g. thrombocytopenia, neutropenia, haemolytic anaemia, in patients with immunodeficiency is based on standard therapy of such symptoms; the use of immunoglobulins in high dose, steroids, immunosuppression with methrotrexate, vincristine, azatioprine, but special therapy is required for some of immunodeficient patients. In ALPS, the use of sirolimus is suggested, as possibility to induce apoptosis, helping in elimination of double-negative T lymphocytes. Sirolimus is preferentially used in these patients for resolving symptoms (e.g. lymphadenopathy, splenomegaly) and diminish the severity of clinical course. The expected effect of sirolimus is to diminish the spleen volume (megaspleen), one of most danger symptom in children with ALPS [44-47].

The therapeutic approach to immunodeficient patients with Leśniowski-Crohn's disease is generally similar to therapy of patients without immunodeficiency; although, inflammation process in CVID might be resistant to therapy. In these patients, the process of intestine inflammation is active despite immunosuppression (e.g. azathioprine, cyclosporine) used as second line of therapy, after systemic steroids, budesonite and anti- inflammatory non-steroidal drugs without remission. Therapy with the monoclonal antibodies against TNF (infliximab, etanercept) is effective in inductions the remission in patients with immunodeficiency, similar to patients without immunodeficiency. However, CVID patients are more

prone to infections during such therapy, so very careful monitoring of this group of patients is recommended, not only for bacterial, but fungal and viral infections, due to defects of T lymphocyte function [8].

The frequency of UC in CVID and IgAD patients is not known, but it seems that in children it is even less frequent than in adult CVID and IgAD patients. In a large group of CVID patients (248 children and adults), UC was noted in 7 patients; however, the unspecific significant malabsorption symptoms were observed in other10 patients [26]. It shows the problem of overlapping symptoms, difficulties in establishing the precise diagnosis and requirement for wide differential diagnostic procedures performed in these patients [26].

7. Progress in therapy of autoimmunity

7.1. Indications for monoclonal antibodies

Monoclonal antibodies are used for elimination of target cell population, cytokine or blocking of determinants on cell surface. Humoral immune deficiency is based on B-cell intrinsic deficiency and disturbances of B-cell ontogeny. Autoimmunity in patients with very low number of B lymphocytes is associated with relatively high number of autoreactive B cells within this small B-cell population. Following this hypothesis of autoimmunity in humoral immunodeficiency, the therapy with monoclonal antibodies against B lymphocytes seems to be logical and reasonable. Use of rituximab (monoclonal antibody against CD20 determinant restricted to mature B lymphocytes) in autoimmune cytopenias in CVID, ALPS and hyper IgM syndrome (as alternative to HSCT) was successful [19, 44, 45, 95].

The therapy of autoimmune diseases characterised by chronic inflammatory process (SLE, rheumatoid arthritis, IBD) with important role of cytokines and T lymphocytes includes monoclonal antibodies against cytokines (TNF), IL-2 receptor on T lymphocytes (CD25 as activation marker) and others. Within CVID patients, celiac disease is often refractory to GFD (RCD), leading to malabsorption syndrome and severe clinical conditions [11, 27, 96, 97], which suggests different mechanism present in these patients. Careful observation and studies showed different forms: type I with T lymphocytes with normal phenotype (expression of CD3 and CD8 determinants, normal polyclonal T-cell receptor (TCR) arrangement) and type II with aberrant T lymphocyte phenotype, intracellular presence of CD3, monoclonal TCR rearrange-ment [8, 96, 98]. Type II of progressing celiac disease in spite of GFD and some cases of Crohn-like disease are associated with poor prognosis with increased mortality, due to progressing malabsorption syndrome and T-cell lymphoma in reasonable number of such patients [77, 96]. After standard therapy without effect, the second-line therapy with immunosuppression (azathioprine) and/or monoclonal antibodies against TNF (infliximab, etanercept, humira) is required for patients with active, progressive disease [99].

7.2. Suppressive therapy

The first line of immunosuppressive therapy in patients with or without immune deficiency includes steroids, in individual doses, for all autoimmune symptoms and diseases. For

cytopenias, especially thrombocytopenia, the schedule with high doses of steroids given intravenously every month ("pulses") is often used to increase the number of platelets. Chronic thrombocytopenia is controlled with maintenance dose of steroids, but the side effects of steroids are the main limitation for this therapy. The second-line therapy includes typical immunosuppressants, e.g. azathioprine, metotrexate, vincristine, cyclophophamide, cyclosporine A. In ALPS, sirolimus and mycophenolate mofetil are suggested, with good clinical response in majority of patients. Moreover, this therapy is well tolerated, without severe side effects, even in infants and babies with ALPS. Regular substitution of immunoglobulins (recommended in intravenous form) is important to diminish the risk of infections associated with prolonged immunosuppression [7, 77, 78, 95].

7.3. Indications for haematopoietic stem cells transplantation (HSCT)

Historically, the first group of patients who underwent HSCT as a life-saving and curative therapy were newborn babies diagnosed with SCID. The following group of patients transplanted with HSCT were children with X-linked immunodeficiency, e.g. hyper IgM syndrome, WAS, chronic granulomatous diseases (CGD) [100-104]. The increasing number of children cured from SCID, improvement of transplantation procedure (low risk factor) and post-transplant care, is encouraging transplantologists and immunologists to offer this therapy for patients with other types of primary immunodeficiency. Now, patients with ALPS, X-linked lymphoproliferative diseases, haemophagocytic lymphohistiocytosis are transplanted in increasing numbers [102]. Successful HSCT in SCID patients, after matched donor transplant, in Europe is 90% survival; non-SCID immunodeficiency patients – about 80%, which means real, great progress in treatment of patients with severe clinical forms of immunodeficiency [101].

The hyper IgM syndrome, ALPS, Wiskott-Aldrich syndrome may represent mild clinical course with satisfactory symptomatic therapy, so HSCT is not a first-line therapy. The indications for HSCT in these patients are based on severe clinical course, progress of symptoms associated with immunodeficiency leading to poor prognosis for life [47, 100-104]. The symptomatic therapy in these syndromes include steroids for severe autoimmunity symptoms, regular substitution of immunoglobulins, antibiotics and antimycotic drugs as prophylaxis, and treatment for existent bacterial, fungal and viral infections. This therapy is necessary up to the time of HSCT, as good clinical state of patient decreases the risk of complications after HSCT. The CVID with typical clinical course is not an indication for HSCT, due to satisfactory effects of symptomatic therapy, much more save, than HSCT. However, in individual cases with progressing, severe complications, like RCD, IBD, leading to malnutrition, this procedure is recommended [97]. Within our CVID children, HSCT was performed with success in girl with severe malnutrition due to malabsorption in celiac disease resistant to GFD. She was treated for few years with restricted GFD, antibiotics, steroids, anti-TNF monoclonal antibodies, immunosuppression (cyclosporin A) without effect, so HSCT was the life-saving procedure. HSCT was performed in our 3 patients (children below age of 3 years) with severe course of ALPS, when therapy with steroids, immunoglobulins, mycophenolate mofetil and sirolimus was without long-lasting remission and progression of the autoimmune symptoms [47].

8. Other problems

8.1. Granulomatous and lymphocytic interstitial lung disease (GLILD) – autoimmunity or not

GLILD (former name – lymphoid interstitial pneumonia) is a rare clinical entity with unknown aetiology and pathophysiology. The diffuse infiltration of lymphoid cells localised mainly in the interstitial tissue is a typical histopathological feature. LIP is typically associated with autoimmunity, e.g. Sjogren syndrome, autoimmune thyroid disease, SLE, but also with immunodeficiency, mainly CVID and AIDS [105, 106]. LIP is noted in about 10% of CVID patients, which could indicate the association between these clinical features. This type of interstitial pneumonia is an independent factor of poor prognosis with negative impact on the survival of patients due to lung fibrosis, followed by recurrent episodes of pneumonia with infiltrations. Clinical symptoms of GLILD overlap with chronic bronchitis or bronchiectases, signalled by prolonged cough. Moreover, the regular substitution of immunoglobulins, in replacing dose, is not effective in prevention and resolving of these lung symptoms. Therapy included prolonged steroids and/or immunosuppression (azathioprine, cyclophosphamide) in individual combination, depending on patient immune system and clinical symptoms. Prolonged therapy with steroid or immunosuppression is difficult in CVID patients, due to increased risk of infections, potentiating of leukopenia/neutropenia and thrombocytopenia. Among our patients with CVID, treated with regular substitution of immunoglobulins, LIP was noted in 3 children. The clinical course of CVID was severe due to RCD in girl (later on transplanted with HSCT), leukopenia (neutropenia) and thrombocytopenia in both boys. Moreover, one of these boys diagnosed with LIP, demonstrated hepatomegaly, splenomegaly and lymphadenopahty localised in lungs hilus and in mesenterium. Therapy of LIP included, in first line, only steroids, followed by azathioprine (because of severe adverse reaction after steroids and lack of effect), with good results in second boy. The resolving of LIP symptoms was slow, taking 2–3 years of immunosuppressive therapy and regular substitution of immunoglobulins in 0.5g/kg b.w. The frequency of infections during this therapy was not higher, but the course of the few infections that occurred was prolonged, requiring antibiotic therapy.

9. Conclusions and general remarks

Autoimmune diseases are a large group of heterogeneous diseases characterised by an unpredictable course with variable response to immunosuppressive therapy, from very good (long-lasting remission), to poor with progression of severe and life-threatening symptoms. Autoimmune diseases in immunodeficiency syndromes can develop prior or after the onset of immunodeficiency, during the regular substitution of immunoglobulins.

The management of patients with autoimmunity associated with immunodeficiency is more difficult than patients without immunodeficiency due to various reasons: the production of autoantibodies, the generally used marker of autoimmunity, is weaker in immunodeficiency;

the clinical symptoms may overlap with basic symptoms of immunodeficiency; the response to therapy is often poorer than in patients without immunodeficiency. The level of autoantibodies, below limit of positive results, due to immunodeficiency, should be considered as significant for diagnosis of autoimmune disease in PID. The interpretation of laboratory results in these patients need very careful and different attitude than usual. The resistance to therapy, severe, and progressing symptoms of autoimmunity, as complication of immunodeficiency (e.g. CVID, ALPS) are the indications for HSCT as life-saving procedure.

Acknowledgements

Author details

Anna Pituch-Noworolska

Address all correspondence to: mipituch@cyf-kr.edu.pl

Department of Clinical Immunology, Polish-American Institute of Pediatrics, Jagiellonian University, Medical College, Kraków, Poland

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