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Pregled
Review

AUTOIMMUNITY AND IMMUNODEFICIENCY

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The primary immunodeficiency disorders (PID) are a heterogeneous group of diseases resulting from inherited defects in the development and maturation of immune system which results in increased susceptibility to infection. Autoimmune manifestations are frequent and often multiple in patients with PID. In the last years, novel forms of PID have been discovered and additional pathophysiological mechanisms that account for PID and associated autoimmune symptoms have been unraveled. Recent studies have shown that there are at least three different mechanisms connecting PID with autoimmune symptoms: chronic inflammation, impaired negative regulation of immune responses and linkage between the PID gene and a gene affecting autoimmunity. In the absence of clinical trials investigating specific treatments for autoimmune complications in PID patients, most therapies are empirical. With recent advances uncovering molecular basis of PID and specific pathways responsible for the development of autoimmune complications, it is hoped that more rational treatment will evolve for these challenging patients. Careful analysis and prompt recognition of these disorders is essential for effective treatment and thus to improve survival and quality of life in patients affected with PID.

Descriptors: PRIMARY IMMUNODEFICIENCY DISORDERS, AUTOIMMUNITY, IMMUNODEFICIENCY

INTRODUCTION

The primary immunodeficiency disorders (PID) are a heterogeneous group of more than 150 diseases resulting from inherited defects in the development and maturation of immune system (1, 2). Patients with PID are characterized by an increased susceptibility to infection. They are also associated with troublesome and sometimes life-threatening autoimmune complications (3). In the last years novel forms of PID have been discovered and additional pathophysiological mechanisms that account for PID and associated autoimmune phenomena have been disclosed. Careful analysis and prompt recognition of these disorders is vital for effective treatment and thus to improve survival and quality of life in patients affected with PID (1, 2).

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The 10 warning signs of PID developed by the Jeffrey Model Foundation are being used as a screening tool to help diagnose PID. However, a recent study showed that except for the three signs including family history, need for intravenous antibiotics and failure to thrive, the 10 warning signs are not an optimal screening for PID, particularly in daily pediatric practice (4). The 10 warning signs do not involve autoimmune or malignant manifestations of PID, which may be the presenting clinical feature (5). The early onset of multiple autoimmune disorders should be considered as highly suspicious of PID. The European Society for Immunodeficiency's (ESID) proposed a set of warning criteria that should include inflammatory, autoimmune and lymphoproliferative features, as well as other well-established criteria to allow a better identification of PID by non-immunologists (6).

This review highlights autoimmune complications of PID and discusses recent findings that have uncovered cellular and molecular mechanisms linking PID to autoimmune disease.

EPIDEMIOLOGY

Autoimmune diseases occur in up to 3-5% of the general population (7, 8). Analysis of PID registry data from two neighboring pediatric centers in North-East Italy and in Slovenia conducted on a total of 175 patients showed that autoimmune symptoms were present in 14.8% of patients with PID (unpublished data). Autoimmune manifestation have been reported in 22% of patient with common variable immunodeficiency, increasing up to 50% in the subgroup of patients with chronic granulomatous disease and 70% of patients with Wiskott-Aldrich syndrome. Association with autoimmune disease in PID patient can be considered to be 100% in the group of diseases of immune dysregulation and in Omenn syndrome. Primary immunodeficiency diseases that are most frequently associated with autoimmune manifestations are presented in Table 1.

THE BASIS OF AUTOIMMUNITY IN PRIMARY IMMUNODEFICIENCY DISEASES

There is not a single mechanism that links autoimmune manifestations and PID. Recent studies have shown that there are at least three different mechanisms connecting PID with autoimmune symptoms: chronic inflammation, impaired negative regulation of immune responses and linkage between the PID gene and a gene affecting autoimmunity.

Table 1
Primary immunodeficiency diseases most frequently associated with autoimmune manifestations

Tablica 1.
Primarne imunodeficijencije najčešće povezane sa autoimunim manifestacijama

PRIMARY IMMUNODEFICIENCY DISEASE PRIMARNE IMUNODEFICIJENCIJE	AUTOIMMUNE MANIFESTATIONS AUTOIMUNE MANIFESTACIJE
Combined T&B cell immunodeficiencies Kombinirana T i B stanična imunodeficijencija	
Severe combined immunodeficiency Teška kombinirana imunodeficijencija	immune thrombocytopenia (ITP), alopecia imuna trombocitopenija (ITP), alopecija
Omenn syndrome Omenov sindrom	exudative skin rash, lymphadenopathy, hepatosplenomegaly eksudativni kožni osip, limfadenopatija, hepatosplenomegalija
"Atypical" severe combined immunodeficiency "Atipična" teška kombinirana imunodeficijencija	autoimmune cytopenias autoimuna citopenija
CD40 ligand deficiency Deficijencija CD40 liganda	sclerosing cholangitis, autoimmune cytopenias, inflammatory bowel disease sklerozirajući holangitis, autoimuna citopenija, upala žučnog mjehura
Predominantly antibody deficiencies Predominantno deficijencija antitijela	
Common variable immunodeficiency Uobičajene varijabilne imunodeficijencije	inflammatory bowel disease, autoimmune cytopenias, rheumatoid arthritis upala žučnog mjehura, autoimuna citopenija, reumatoidni artritis
Other well-defined immunodeficiency syndromes Drugi dobro definirani imunodeficijentni sindromi	
Wiskott-Aldrich syndrome Wiskott-Aldrichov sindrom	autoimmune hemolytic anemia (AIHA), vasculitis, arthritis, glomerulonephritis autoimuna hemolitična anemija, vaskulitis, artiritis, glomerulonefritis
DiGeorge syndrome DiGeorge sindrom	autoimmune cytopenias, ITP autoimuna citopenija, ITP
Diseases of immune dysregulation Bolesti s poremećajima imunoregulacije	
Autoimmune lymphoproliferative syndrome Autoimuni limfoproliferativni sindrom	autoimmune cytopenias, glomerulonephritis, optic neuritis, arthritis autoimuna citopenija, glomerulonefritis, optički neuritis, artritis
Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy Autoimuna poliendokrinopatija s kandidijazom i ektodermalnom distrofijom	chronic mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency, hypothyroidism, type 1 diabetes mellitus kronična mukokutana kandidijaza, hipoparatiroidizam, adrenalna insuficiencija, hipotiroidizam, šećerna bolest tip 1
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked Imuna disregulacija, poliendokrinopatija, enteropatija, X-vezana	autoimmune thyroid disease, type 1 diabetes mellitus, enteropathy, eczema autoimuna bolest štitnjače, šećerna bolest tip 1, enteropatija, ekzem
Congenital defects of phagocyte number, function, or both Kongenitalni poremećaj broja fagocita, funkcije, ili oboje	
Chronic granulomatous disease Kronična granulomatoza	chronic inflammation with granuloma formation, inflammatory bowel disease kronične upalne promjene sa stvaranjem granuloma, upalna bolest žučnjaka
Leukocyte adhesion molecule deficiency Deficijencija adhezijskih molekula na leukocitima	leukocytoclastic vasculitis, inflammatory bowel disease leukocitoplastički vaskulitis, upalna bolest žučnjaka
Complement deficiencies Deficijencija komplementa	systemic lupus erythematosus sistemski eritematozni lupus

The basis of many autoimmune manifestations is the inability of the host to eradicate microbial pathogens through the usual immune pathways. The result is chronic inflammatory response by less effective alternative immune pathways. Autoimmunity in many affected patients is not a breakdown of tolerance to self-antigens, but results from tissue damage incurred as the host attempts to rid itself of foreign immunogens (3). Autoimmune complications of PID are sometimes

independent of any known infection, because the underlying immunodeficiency directly predispose to autoimmune disease by disrupting mechanisms that normally negatively regulate immune responses (9). PID may result in a defect in the mechanisms of control of self-reactive B and T cells and favor the occurrence of autoimmune manifestations (10). Although a strong case can be made for a cause-effect relationship between certain PID and autoimmune disease, this association is much less clear in other cases, and the possibility remains that some of the associations are caused by special connection between the PID gene and a gene affecting autoimmunity (11).

SPECIFIC PRIMARY IMMUNODEFICIENCY DISEASES ASSOCIATED WITH AUTOIMMUNITY

Combined T and B cell immunodeficiency's

Severe combined immunodeficiency

Severe combined immunodeficiency (SCID) is the most severe form of primary immunodeficiency, caused by mutation in genes involved in lymphocyte development and function. In their first year of life, children with SCID present with high susceptibility to bacterial, viral and fungal infections, which are often associated with protracted diarrhea and failure to thrive. Engraftment of maternal T cells can lead to symptoms of graft versus host disease, such as severe erythematous skin rash or chronic liver disease. Without bone marrow transplantation (BMT), the disease is usually lethal within the first year of life. Over 20 different molecular defects can result in the clinical syndrome of SCID (12). Severe autoimmune complications can develop in patients with SCID.

Omenn syndrome is a SCID subtype associated with a number of specific autoimmune complications. This syndrome is characterized by severely decreased circulating T and B cells (9). The disorder is caused by mutations in recombination-activating genes (RAG) 1 and 2, which is involved in immunoglobulin and T-cell-receptor gene recombination and thus the generation of immune diversity (3). Association with autoimmune disease can be considered to be primarily as a result of the involvement of autoreactive T cells. The autoimmune diseases are consistently organ specific and usually involve both the skin and the intestine (11). Autoimmune complications include lymphadenopathy, splenomegaly, erythroderma, autoimmune hepatic dysfunction or failure and encephalopathy (3). These complications are associated with eosinophilia and elevated IgE, suggesting involvement of the Th2 subset of T cells that produces IL-4, IL-6 and other cytokines that drive plasma cell differentiation and IgE production by B cells. Patients with these complications have been treated with high-dose steroids, antithymocyte globulin, and cyclosporine A, however BMT remains the only definitive treatment (9).

The clinical presentation and the immunological phenotypes of SCID and Omenn syndrome are well defined and there are clear concepts for these disorders. Diagnosis and treatment is much less clear for patients with mutations in SCID-causing genes, but milder forms of combined immunodeficiency, often termed as "atypical" SCID. Due to their poorly defined clinical and immunological phenotype, these patients are sometimes diagnosed as late as in adulthood. Recently, there have been an increasing number of reports on patients with atypical SCID. Systematic review of the clinical and immunological presentations was recently performed in 73 patients with "atypical" SCID. In this study "atypical" SCID was defined as an immunodeficiency disease due to mutations in SCID-causing genes in patients with a presentation different from typical SCID and Omenn syndrome and T cells above 100/µl. This study revealed that the clinical presentation of "atypical" SCID is not limited to infection susceptibility, but also includes disorders of immune regulation. In particular, immune dysregulation can be a leading clinical manifestation of "atypical" SCID. In at least 10 out of 73 patients autoimmune cytopenias, granulomata or colitis were the first and in 3 patients the only disease manifestation before the molecular diagnosis was established. The most features of immune dysregulation affected predominantly patients with a mutation affecting antigen receptor recombination and patients with adenosine deaminase deficiency. Antibody mediated autoimmunity was almost exclusively observed in patients with SCID variants affecting B cell development (12).

CD40 ligand deficiency (hyper-IgM syndrome)

CD40 ligand deficiency or hyper-IgM syndrome is a primary immunodeficiency from a genetic defect in the CD40 ligand pathway or in other proteins required for immunoglobulin class switch recombination (9). Consequently, patients with hyper-IgM syndrome have normal or high levels of serum IgM and low IgG, IgA and IgE levels associated with sinopulmonary infections. A principal cause of death in these patients is liver failure due to sclerosing cholangitis. The mechanism for this organ-specific autoimmune phenomenon has been described. Cryptosporidium gastroenteritis is common in these patients, and Cryptosporidium parasites may also ascend the biliary tree and infect bile duct epithelium. The inability of T lymphocytes to induce destruction of infected cells results in persistence of the pathogen, chronic inflammation, and consequently, sclerosing cholangitis (3). Other autoimmune complications include autoimmune cytopenias, inflammatory bowel disease, seronegative arthritis, nephritis and autoimmune hepatitis (9). Autoimmune manifestations are also frequent in patients with hyper-IgM syndrome due to mutations in activation induced cytidine deaminase (AID) and NF-κB essential modulator (NEMO) genes. About 25% of AID deficient patients develop autoimmunity (10). The long-term prognosis for patients with hyper-IgM syndrome is poor. Definitive treatment with BMT in early childhood before liver damage is recommended (3).

Predominantly antibody deficiencies

Common variable immunodeficiency

Common variable immunodeficiency (CVID) is the most common symptomatic primary antibody deficiency syndrome, characterized by defective antibody production and underlying T cell defects. CVID is not a single disease but an idiopathic group of diseases characterized by various degrees of defective antibody production, ranging from isolated defects in the production of antibody to carbohydrate antigens to almost complete absence of all immunoglobulin subclasses. Clinical manifestations include recurrent sinopulmonary and gastrointestinal infections, with chronic bronchiectasis. Many patients require immunoglobulin-replacement therapy, prophylactic antibiotic treatment, or both (3). Autoimmune diseases, particularly chronic inflammatory bowel disease, autoimmune cytopenias such as immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA), and rheumatoid arthritis are common in patients with CVID (9, 11).

Inflammatory bowel disease associated with chronic diarrhea and sometimes malabsorption, failure to thrive, or protein-losing enteropathy occurs in about 30% of patients and most often affects the large bowel, although it can affect the stomach or small bowel. If the stomach is involved, associated atrophic gastritis and pernicious anemia may occur. The inflammatory bowel disease may have histological features of celiac disease or Crohn's disease. About 10% of patients with CVID have multisystem, noncaseating granulomatous disease. CVID-associated granulomatous disease can affect solid organs, skin, gut, lymph nodes, and spleen, and it may be confused with idiopathic sarcoidosis, Crohn's disease or chronic granulomatous disease. Patients with granulomatous disease often have clinical evidence of lymphoproliferation with splenomegaly and lymphadenopathy, and laboratory testing frequently shows an expansion of CD8+ T lymphocytes that may underlie the inflammatory reaction. Autoimmune disease in patients with CVID may be associated with particular HLA and mannose-binding protein genotypes. Steroids and other immunosuppressive agents frequently used to treat autoimmune diseases should be used with caution in patients with CVID because such drugs will further increase the patients' risk of infection (3).

Other well-defined immunodeficiency syndromes

Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome (WAS) is a rare X-linked immunodeficiency disorder caused by a maturational defect affecting both lymphocytes and platelets. The mutated gene in WAS encodes a multidomain protein called Wiskott-Aldrich syndrome protein (WASp). WASp is expressed exclusively in cells of the hematopoietic lineage and is critical for cytoskeletal remodeling via actin polymerization. WASp deficiency can affect NK and T cell cytolytic function and T cell help for B cells. WAS patient have reduced antibody responses to polysaccharide vaccines and increased susceptibility to a wide variety of bacterial, viral and fungal infections. WAS is associated with a remarkably high prevalence of autoimmunity, as high as 70% in retrospective cohorts with some patients developing multiple autoimmune manifestations. WASp deficient T cells are defective in their production of IL-2, a cytokine known to be required for survival of regulatory T cells, which are essential in the control of T-cell mediated autoimmunity. The most common autoimmune problems are AIHA and vasculitis, followed by renal disease and arthritis (3, 9). WASp deficient mice were found to develop immune-mediated colitis and other autoimmune manifestations. Recent findings illustrate that even in a single-gene PID, multiple mechanisms may contribute to autoimmune complications, like defective function of regulatory T cells, defective production of Fas ligand or defective clearance of apoptotic cells (9).

DiGeorge syndrome

DiGeorge syndrome is a congenital immunodeficiency characterized by abnormal facies, congenital heart defects, hypoparathyroidism with hypocalcemia and hypoplastic thymus. DiGeorge syndrome is caused by a microdeletion in chromosome band 22q11. The majority of patients with DiGeorge syndrome have only mild T cell deficits and are not clinically immunodeficient. Complete absence of thymus and severe combined immune deficiency is present only in approximately 1 percent of patients with DiGeorge syndrome. A few reports have described autoimmune phenomena in patients with 22q11 deletions including autoimmune cytopenias, arthritis and autoimmune thyroid disease (3).

Diseases of immune dysregulation

In the following group of diseases there is primary deficiency on the level of immune regulation mechanisms causing diseases of immune dysregulation and occurrence of autoimmune manifestations. Moreover, this group of PID is defined by the occurrence of autoimmune manifestations.

Autoimmune lymphoproliferative syndrome

Autoimmune lymphoproliferative syndrome (ALPS) is characterized by the occurrence of lymphadenopathy, splenomegaly and lymphocytosis with circulating $CD4^-/CD8^-$ double negative T cells bearing αβ T-cell receptor (10). Patients with ALPS type I have a defect in Fas, a member of the tumor necrosis factor (TNF) superfamily. Patients with ALPS type II have a mutation in caspase 10, another cellular component of the same apoptotic pathway. The principal clinical features are chronic benign lymphoproliferation and autoimmune disease (3). Autoimmune manifestations occur in 50 to 70% of the cases, mainly in the form of autoimmune cytopenias (AIHA, ITP and autoimmune neutropenia). These cytopenias are usually severe and become more severe with age. Other autoimmune manifestations of proven or suspected autoimmune mechanisms have been reported less commonly: glomerulonephritis, optic neuritis, Guillain-Barre syndrome, arthritis, cutaneous vasculitis, primary biliary cirrhosis and autoimmune hepatitis (10).

Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy

Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED) is a recessive autosomal disease defined by at least two of

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the following symptoms: chronic cutaneo-mucous candidiasis, hypoparathyroidism and Addison's disease. Candidiasis is usually the first clinical manifestation of the disease, occurring around the age of 5, followed in most cases by hypoparathyroidism before the age of 10 and adrenocortical failure before the age of 15.

Other organ-specific autoimmune manifestations encountered in this condition include hypothyroidism, hypogonadism, type 1 diabetes mellitus, autoimmune hepatitis, pernicious anemia, vitiligo, alopecia, primary biliary cirrhosis and ectodermal dysplasia (10). APECED results from a defect in the autoimmune regulator (AIRE) gene which is involved in the negative selection or anergy induction of self-reactive lymphocytes in the thymus (3). Developing thymocytes with a T-cell receptor that recognize tissue-specific genes in thymic epithelial cells undergo apoptosis during development, creating central immune tolerance to these antigens (9). Mice deficient in AIRE also showed evidence of spontaneous organ-specific autoimmunity (3).

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) is a rare disease due to genetic deficiency in the FoxP3 transcription factor that is essential for the development of CD4+ CD25+ regulatory T cells, which are necessary for immunological self-tolerance. As a consequence, T cell activation and cytokine production are increased. Clinical features include early onset type 1 diabetes mellitus, severe enteropathy, autoimmune hepatitis, eczema, AIHA, ITP, hypothyroidism and membranous nephropathy (10).

Almost all patients present concomitant allergic manifestations with eosinophilia and increased serum IgE (11). Immunosuppressive therapy including tacrolimus, cyclosporine, methotrexate, infliximab, and rituximab have been used to treat this syndrome, but BMT remains the only curative therapy (9, 10).

Congenital defects of phagocyte number, function, or both

Chronic granulomatous disease

Chronic granulomatous disease (CGD) affects 1 in 200.000 children and consists of a group of X-linked and autosomal recessive disorders of neutrophil production of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Affected neutrophils are incapable of completely eradicating phagocytosed bacteria and fungi (3). Patients with CGD present with chronic recurrent infections, but inflammatory complications are prominent, including the development of granulomas and severe inflammatory bowel disease occurring in 50% of patients (9).

Inflammation can occur anywhere from mouth to anus. Widespread granuloma formation and fibrosis may result in stomatitis and oral ulcers; esophagitis associated with dysphagia, dysmotility, and obstruction; gastric outlet obstruction and eosinophilic gastritis; intestinal villous atrophy or granulomatous colitis; and liver fibrosis and cirrhosis. Gastrointestinal symptoms of abdominal pain, diarrhea, and malabsorption respond variably to immunomodulatory agents (prednisolone, cyclosporine A, and interferon-γ), but there is an increased risk of reactivating latent infection. Besides, the above-mentioned symptoms are similar for the Crohn's disease which further aggravates the therapeutic dilemma. Chronic inflammation in other systems, such as the lung, may produce fibrosis and cor pulmonale. These patients have poor long-term prognosis and early BMT is recommended (3).

Leukocyte adhesion molecule deficiency

Leukocyte adhesion molecule deficiency (LAD) is due to defects in integrin family adhesion molecules (CD18) that are essential for binding of neutrophils to the endothelial surface and extravasation from blood vessels. Consequently, patients with LAD have high circulating neutrophil counts which may produce a persistent leukocytoclastic vasculitis. Despite the block in what would seem to be a critical pathway for generating an inflammatory response, LAD patients have been reported to develop inflammatory bowel disease (3, 9).

Complement deficiencies

Deficiencies in components of complement are rare, with the most common being a deficiency in C2 that occurs in 1 in 20000 people. Only deficiencies in the earlier components of the classical pathway (C1q, C1r, C1s, C2 and C4) have been linked to autoimmune diseases. Among these patients, systemic lupus erythematosus (SLE) tends to be more severe with earlier age of onset and preponderance for male patients. A deficiency of mannose-binding protein, which cleaves C4 and C2 when bound to antibody in the same way as activated C1s, has been linked to an increase in autoimmune disorders (arthritis, ITP, enteropathy, pernicious anemia, and vitiligo) when associated with CVID. The exact mechanism by which complement deficiencies cause autoimmunity is unknown. The fact that it is C1q that binds to Fc component of IgG or IgM and apoptotic cells suggests that the lack of interaction of complement with immunoglobulin and apoptotic cells may prevent the clearance of cells, thereby leading to production and buildup of circulating autoantibodies (3, 11).

THERAPY OF AUTOIMMUNE COMPLICATIONS IN PATIENTS WITH PID

PID patients are by definition immunocompromised and a thorough exclusion of infections coincident with or possibly causative of autoimmune complications should be undertaken before initiating specific treatments for autoimmune complications. In the absence of clinical trials investigating specific treatments for autoimmune complications in PID patients, most therapies are empirical. A recommended approach is to consider the clinical severity of particular autoimmune complication and need for treatment, similarly as in a patient without underlying immunodeficiency. Specific therapy can then be adjusted to avoid those known to predispose to infections to which a patient may already be susceptible given the specific immunodeficiency involved. If applicable, non-immunosuppressive therapeutics such as intravenous immunoglobulin would be preferable. Targeted therapies that affect specific immune cell subsets may be preferable over the broad immunosuppressive activity of glucocorticoids. With the recent advances uncovering molecular basis of PID and specific pathways responsible for the development of autoimmune complications, it is hoped that more targeted treatments will evolve (9).

CONCLUSION

PID is a diverse and complex group of diseases that includes not only unusual or recurrent infections but also common infections as well as autoimmune manifestations (5). Autoimmune manifestations are frequent and often multiple in patients with PID and can also importantly contribute when considering the diagnosis of PID. The diagnosis of PID should be made as early in disease evolution as possible since it may considerably influence the therapeutic strategy (10). Early diagnosis ensures a 95% chance of cure and/or long-term survival for many patients with PID (5). The ongoing studies should contribute to development and establishment of a set of comprehensive criteria for early diagnosing of PID applicable in pediatric practice. Due to rare occurrence of these diseases, most therapies for autoimmune manifestations in PID patients are empirical (9). Recent studies that uncover molecular basis of PID and specific pathways responsible for the development of autoimmune complications, could contribute to more targeted treatment for this challenging group of patients.

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Sažetak

AUTOIMUNOST I IMUNODEFICIJENCIJA

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Primarne imunodeficijencije su heterogena skupina bolesti nastalih kao posljedica prirođenog poremećaja razvoja i sazrijevanja imunološkog sustava što dovodi do pojačane osjetljivosti na infekcije. U pacijenata s primarnom imunodeficijencijom često su pridruženi i autoimuni poremećaji. U zadnjih nekoliko godina otkrivene su nove forme primarnih imunodeficijencija i razjašnjeni su patofiziološki mehanizmi koji se povezuju s autoimunim simptomima. Najnovija istraživanja dokazuju da su barem tri različita mehanizma odgovorna za razvoj autoimunih simptoma: kronična upala, poremećena negativna regulacija imunog odgovora i povezanost između gena koji su odgovorni za pojavu primarnih imunodeficijencija i gena koji utječu na autoimunost. S obzirom na nedovoljno kliničkih istraživanja na području specifične terapije za autoimmune komplikacije, većina terapijskih pokušaja su empirijski. Međutim, sve veći broj istraživanja molekularne podloge razvoja imunodeficijencije kao i patofizioloških mehanizama autoimunih komplikacija, doprinijeti će racionalnoj terapiji. Pravovremeno prepoznavanje i dijagnosticiranje imunodeficijencije je neophodno za što raniju primjenu odgovarajuće terapije što poboljšava preživljavanja i kvalitetu života pacijenata s primarnom imunodeficijencijom.

Deskriptori: PRIMARNE IMUNODEFICIENCIJE, AUTOIMUNOST, IMUNODEFICIENCIJA

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