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SYSTEMIC MANIFESTATIONS OF SJÖGREN'S SYNDROME

SISTEMSKE MANIFESTACIJE SJÖGRENOVOG SINDROMA

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Abstract

Sjögren's syndrome (SS) is a heterogeneous disease which, in the majority of cases, includes a mild clinical course. However, in some patients it takes on a severe form with numerous systemic manifestations and results in an adverse outcome. Systemic manifestations occur in approximately 25% of patients with primary Sjögren's syndrome (pSS). The clinical presentation of systemic manifestations of SS is very diverse and can involve any organ system. Systemic manifestations can occur due to lymphocytic infiltration of organs or proliferation of B lymphocytes and deposition of immune complexes.

Fatigue is the most common systemic manifestation. The most significant cutaneous manifestations of the disease are palpable purpura, ulcerations, urticarial vasculitis and leukocytoclastic vasculitis. Musculoskeletal manifestations can range from arthralgias to erosive arthritis. Pulmonary involvement may include symptoms such as nonspecific interstitial pneumonia with fibrosis and tracheobronchial disease. Renal changes are observed in 10% to 30% of patients with SS. Tubulointerstitial nephritis, type 1 renal tubular acidosis and nephrogenic diabetes insipidus can develop as a consequence of lymphocytic infiltration. Less often, the inflammatory process affects the glomeruli which leads to glomerulonephritis. Liver diseases are found in approximately 20% of patients with SS and their symptoms usually include inflammation of intrahepatic bile ducts resembling primary biliary cirrhosis. The manifestations of peripheral nervous system involvement include sensorimotor axonal polyneuropathy, mononeuritis multiplex, neuropathies and radiculopathies. Optic neuropathy, hemiparesis, movement disorders, cerebellar syndromes, transient ischemic attacks, transverse myelitis (less commonly), and progressive myelopathy have been described as central nervous system changes. Symptoms of vasculitis can range from mononeuritis multiplex to intestinal ischemia and dysfunction of the affected organs. The development of non-Hodgkin's B-cell lymphoma is a major complication of the disease which occurs in 5%–7% of patients with SS.

Keywords: Sjögren's syndrome, systemic manifestations

Sažetak

Sjögrenov sindrom (SS) je heterogena bolest koja se najčešće prezentira blagim kliničkim tijekom. Međutim, u manjeg dijela bolesnika poprima teški oblik bolesti s brojnim sistemskim manifestacijama i mogućim lošim ishodom. Sistemske manifestacije se pojavljuju u približno 25% bolesnika s primarnim Sjögrenovim sindromom (pSS). Klinička prezentacija sistemskih očitovanja SS-a vrlo je raznolika i može zahvatiti bilo koji organski sustav. Mogu nastati uslijed limfocitne infiltracije organa ili proliferacije limfocita B i odlaganja imunih kompleksa.

Umor je najčešća sistemska manifestacija. Najznačajnije dermatološke manifestacije bolesti su palpabilna purpura, ulceracije, urtikarijalni i leukocitoklastični vaskulitis. Koštano-mišićne manifestacije u bolesnika s pSS-om pojavljuju se u širokom rasponu od artralgija do erozivnog artritisa. Zahvaćenost pluća može se očitovati kao nespeci-

fična intersticijska pneumonija s fibrozom i traheobronhalna bolest s povećanom reaktivnošću bronha, bronhiektazijama, bronhiolitisom ili ponavljajućim respiratornim infekcijama. Bubrežne promjene se uočavaju u 10–30% bolesnika sa SS-om. Kao posljedica limfocitne infiltracije razvija se tubularni intersticijski nefritis, renalna tubularna acidoza tipa I, nefrogeni dijabetes insipidus i ostali poremećaji tubularne funkcije. Znatno rjeđe upalni proces zahvaća glomerule dovodeći do glomerulonefritisa. Jetreni poremećaji se nalaze u oko 20% bolesnika sa SS-om, a najčešće se očituju upalnim promjenama intrahepatalnih žučnih vodova nalikujući primarnoj bilijarnoj cirozi. Zahvaćenost perifernoga živčanog sustava manifestira se senzomotornom aksonalnom polineuropatijom, senzornom ataksičnom i autonomnom neuropatijom, mononeuritisom multipleks, kranijalnim neuropatijama i radikulopatijama. Od promjena središnjega živčanog sustava opisuju se optička neuropatija, hemipareza, poremećaji pokreta, cerebelarni sindromi, tranzitorne ishemijske atake, rjeđe transverzalni mijelitis i progresivna mijelopatija. Simptomi vaskulitisa mogu varirati od mononeuritisa multipleksa do ishemije crijeva i disfunkcije zahvaćenih organa. Razvoj non-Hodgkinovog limfoma B-stanica predstavlja glavnu komplikaciju bolesti i pojavljuje se u 5–7% bolesnika sa Sjögrenovim sindromom.

Ključne riječi: Sjögrenov sindrom, sistemske manifestacije

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disease of the exocrine glands characterised by lymphocytic infiltration of the affected glands. The disease can occur independently, and, in that case, it is known as primary Sjögren's syndrome (pSS). It is a heterogeneous autoimmune disease which includes a broad range of clinical features, from the dryness syndrome, as the main feature of the disease, to numerous systemic or extraglandular manifestations (1). When it occurs as part of other autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or progressive systemic sclerosis (SSc), it is called secondary Sjögren's syndrome.

The clinical presentation of systemic manifestations of pSS is very diverse, as any organ system can be involved (2). Systemic manifestations occur in approximately 25% of patients with pSS (3), and may arise as a result of lymphocytic infiltration of organs or proliferation of B lymphocytes and deposition of immune complexes (4). While the dryness syndrome primarily affects quality of life and localised complications, systemic involvement determines disease prognosis (5).

Musculoskeletal system

Articular involvement occurs in approximately 30%–60% of patients with pSS. Arthritis is mostly polyarticular, peripheral and symmetrical. It is usually not deforming or erosive, and it affects the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints and wrists, while changes such as Jaccoud arthropathy (Figure 1) or sacroiliitis are much less common. Synovitis is generally mild; however, articular involvement is a predictor of other systemic involvement (6, 7). Myalgia and weakness are common symptoms in patients with pSS, but clinically significant myositis is rare. In the study conducted by Lindvall et al., (8) myalgia was described in approximately 30% of patients with pSS and it was determined that 27% of patients fulfil the diagnostic criteria for fibromyalgia,

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Sjögrenov sindrom (SS) je kronična autoimuna bolest žlijezda s vanjskim izlučivanjem obilježena limfocitnim nakupinama u zahvaćenim žlijezdama. Bolest se može javiti samostalno i tada se naziva primarni Sjögrenov sindrom (pSS). Radi se o heterogenoj autoimunoj bolesti sa širokim rasponom kliničkih obilježja, od sindroma suhoće kao glavne odlike bolesti do brojnih sistemskih odnosno izvanžljezdanih manifestacija (1). Kada se javlja u sklopu drugih autoimunih bolesti poput reumatoidnog artritisa (RA), sistemskoga eritemskog lupusa (SLE) ili progresivne sistemske skleroze (SSc) naziva se sekundarnim Sjögrenovim sindromom.

Klinička prezentacija sistemskih očitovanja pSS-a vrlo je raznolika jer može biti zahvaćen bilo koji organski sustav (2). Sistemske manifestacije se pojavljuju u približno 25% bolesnika s pSS-om (3), a mogu nastati uslijed limfocitne infiltracije organa ili proliferacije limfocita B i odlaganja imunih kompleksa (4). Dok sindrom suhoće primarno utječe na kvalitetu života i lokalizirane komplikacije, sustavna zahvaćenost određuje prognozu bolesti (5).

Koštano-mišićni sustav

Zglobovi su zahvaćeni u 30–60% bolesnika s pSS-om. Artritis je uglavnom poliartikularan, periferan i simetričan. Obično nije deformirajući niti erozivan, a zahvaća metakarpofalangealne (MCP), proksimalne interfalangealne (PIP) zglobove i zapešća, dok su promjene poput Jaccoudove artropatije (slika 1) ili sakroileitisa znatno rjeđe. Sinovitis je općenito blag, međutim, zahvaćenost zglobova je prediktor za druga sustavna zahvaćanja (6, 7). Mijalgija i slabost česti su simptomi u bolesnika s pSS-om, ali klinički značajan miozitis je rijedak. U istraživanju Lindvall i sur. (8) mijalgija je opisana u oko 30% bolesnika s pSS-om i utvrđeno je da 27% bolesnika ispunjava dijagnostičke kriterije za fibromijalgiju, dok su Moerman i sur. dokazali polimiozitis u tek oko 4% bolesnika (9). Dokazana je i

while Moerman et al. have proved the occurrence of polymyositis in only about 4% of patients (9). An increased frequency of SS among patients with fibromyalgia has also been proven (10).

Cutaneous manifestations

Cutaneous manifestations of SS include the dryness syndrome, immune-mediated inflammatory diseases such as vasculitis, and other associated disorders. The symptom of dry skin was observed in 50% of patients with SS and it is unclear whether it occurs due to lymphocytic infiltration of the glands or sweating dysfunction (11). Annular erythema is one of the most specific cutaneous manifestations of SS. It occurs in approximately 9% of patients and is clinically identical to erythema in patients with subacute cutaneous lupus erythematosus (SCLE) (12). It has sharply demarcated borders with central clearing, it is photosensitive and usually located on the head and upper body. It heals without scarring and atrophy, but hypopigmented lesions may remain. Perivascular lymphocytic infiltrates, less frequent epidermal changes and positive indirect immunofluorescence are detected through histopathology (13). Raynaud's phenomenon is another manifestation of SS, with a prevalence of approximately 30%, and it can occur years before the diagnosis (14). The manifestations of cutaneous vasculitis include palpable purpura (Figure 2), leukocytoclastic or urticarial vasculitis, and the lesions are predominantly located on the lower limbs (15). Leukocytoclastic vasculitis, hypocomplementemia and hepatitis C are associated with the presence of cryoglobulins in the serum of patients with pSS (16). Vasculitis occurs in approximately 10% of patients with SS (17), and in the study conducted by Kyle et al. it was found that approximately half of all patients from a large group of patients with hyperglobulinemic purpura were diagnosed with SS (18). Cutaneous purpura in patients with SS is associated with the involvement of the central nervous system (CNS), as well as pulmonary involvement, development of lymphoma and increased mortality.(19, 20).

Pulmonary involvement

Pulmonary involvement is defined by the presence of respiratory symptoms, mainly chronic cough or dyspnoea, which are associated with altered pulmonary diagnostic tests (pulmonary function tests and radiographic testing). The frequency of respiratory symptoms in patients with SS varies from 9% to 75%, while clinically significant manifestations occur in 9% to 12% of patients. Respiratory symptoms may occur as a result of glandular damage or diffuse lymphocytic infiltration of the respiratory tract. The reduction or disappearance of secretions in the respiratory tract causes

FIGURE 1. Jaccoud arthropathy in a patient with Sjögren's syndrome
SLIKA 1. Jaccoudova artropatija u bolesnice sa Sjögrenovim sindromom

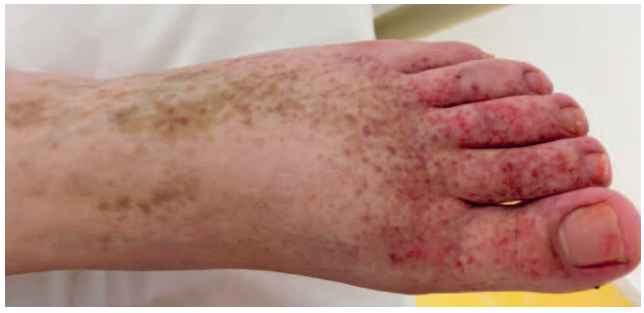

FIGURE 2. Purpura in a patient with Sjögren's syndrome
SLIKA 2. Purpura u bolesnica sa Sjögrenovim sindromom.

povećana učestalost SS-a među oboljelima od fibromijalgije (10).

Koža

Kožne manifestacije SS-a uključuju sindrom suhoće, imunološki posredovana upalna stanja poput vaskulitisa te druge pridružene poremećaje. Suha koža je zabilježena u 50% bolesnika sa SS-om i nejasno je nastaje li uslijed limfocitne infiltracije žlijezda ili disfunkcionalnog znojenja (11). Prstenasti (anularni) eritem jedno je od najspecifičnijih kožnih obilježja SS-a, pojavljuje se u oko 9% oboljelih i klinički je identičan eritemu u bolesnika sa subakutnim kožnim sistemskim lupusom (scLE) (12). Oštro je ograničen sa središnjom blijedom zonom, fotosenzitivan i obično smješten na glavi i gornjem dijelu tijela. Zacjeljuje bez stvaranja ožiljka i atrofije, ali mogu zaostati hipopigmentacije. Histopatološki se otkrivaju perivaskularni limfocitni infiltrati, rjeđe epidermalne promjene i pozitivna indirektna imunofluorescencija (13). Raynaudov fenomen je još jedno obilježje SS-a, s prevalencijom od oko 30%, a može se pojaviti godinama prije postavljanja dijagnoze bolesti (14). Kožni vaskulitis se može manifestirati palpabilnom purpurom (slika 2), leukocitoklastičnim ili urtikarijalnim vaskulitisom, a lezije su pretežno smještene na donjim udovima (15). Leukocitoklastični vaskulitis, hipokomplementemija i hepatitis C povezani su s pri-

damage to the mucociliary apparatus and difficult expectoration, which can lead to infections. Consequently, bronchiectasis, bronchiolitis, recurrent respiratory infections or bronchial hyperresponsiveness may occur. Interstitial lung disease (ILD) occurs in 8%–38% of patients with SS (21). The most common manifestation of ILD is nonspecific interstitial pneumonia with fibrosis (NSIP). Changes such as bronchiolitis obliterans organizing pneumonia (BOOP), usual interstitial pneumonia (UIP) and lymphocytic interstitial pneumonia (LIP) are less common. Through high-resolution computed tomography (HRCT) of the lungs, bronchiectasis, bronchiolar deformations, and interstitial changes such as ground-glass opacity are most often detected, while nodules, interlobular septal thickening, and reticular pattern are less frequently observed. The presence of signs of lung involvement detected through HRCT or abnormalities found through pulmonary function tests present a risk factor for mortality in patients with SS. (22).

Renal involvement

Studies of renal involvement in SS show significant differences in prevalence and indicate that the level of renal involvement ranges from 4.2% to 67%, which can be explained by differences in diagnostic criteria and research protocols. Tubulointerstitial nephritis (TIN), which is histopathologically characterised by peritubular lymphocyte infiltration and fibrosis, is the most common renal manifestation in patients with SS which rarely leads to renal failure. Renal tubular acidosis (RTA) is the main clinical presentation of TIN and is caused by damage to the renal tubules resulting in acid retention or bicarbonate loss. Its main manifestations include weakness or paralysis due to potassium loss, renal colic due to nephrocalcinosis and polyuria/polydipsia due to nephrogenic diabetes insipidus (NDI) (23). Glomerular disease is most often the result of immune complex deposition in the kidneys and is more often associated with the development of lymphoma than it is with the occurrence of tubulointerstitial disease. (24). Clinical presentations of glomerulonephritis include proteinuria, nephrotic syndrome, haematuria, arterial hypertension, and renal failure. Histopathological findings of kidney biopsies mainly reveal membranoproliferative, proliferative or membranous glomerulonephritis. The presence of glomerulonephritis in patients with SS significantly contributes to the increase in morbidity and mortality rates and affects disease prognosis(25).

GI system involvement

Gastrointestinal manifestations in patients with SS include dysphagia, dyspepsia, nausea, and epigastric

sutnošću krioglobulina u serumu oboljelih od pSS-a (16). Vaskulitis se pojavljuje u oko 10% bolesnika sa SS-om (17), a Kylea i sur. su utvrdili da među velikom skupinom bolesnika s hiperglobulinemijskom purpurom oko polovica boluje od SS-a (18). Kožna purpura se u bolesnika sa SS-om povezuje sa zahvaćanjem središnjega živčanog sustava (CNS), pluća, razvojem limfoma i povećanom smrtnošću (19, 20).

Pluća

Zahvaćenost pluća se definira prisutnošću respiratornih simptoma, uglavnom kroničnog kašlja ili zaduhe, koji su povezani s promijenjenim plućnim dijagnostičkim testovima (funkcionalnim i radiografskim). Učestalost respiratornih simptoma u bolesnika sa SS-om varira od 9 do 75%, dok se klinički značajne manifestacije pojavljuju u 9 do 12% bolesnika. Do pojave respiratornih simptoma može doći uslijed žljezdanog oštećenja ili difuzne limfocitne infiltracije dišnih puteva. Smanjenje ili nestanak sekreta u dišnim putovima uzrokuje oštećenje mukocilijarnog aparata i otežano iskašljavanje, što pogoduje infekcijama. Posljedično se mogu javiti bronhiektazije, bronhiolitis, ponavljane respiratorne infekcije ili bronhalne hiperreaktivnosti. Intersticijska bolest pluća (ILD) javlja se u 8–38% bolesnika sa SS-om (21). Najčešća manifestacija ILD-a je nespecifična intersticijska pneumonija s fibroznim promjenama (NSIP). Promjene poput organizirane upale pluća (BOOP), uobičajene intersticijske upale pluća (UIP) i limfocitnoga intersticijskog pneumonitisa (LIP) su rjeđe. Na kompjutoriziranoj tomografiji pluća visoke rezolucije (HRCT) najčešće se opisuju bronhiektazije, bronhiolarne deformacije i promjene intersticija poput „mliječnog stakla", dok se čvorići, interlobularna septalna zadebljanja i retikularni crtež rjeđe opisuju. Prisutnost znakova zahvaćenosti pluća na HRCT-u ili poremećaj plućnih funkcionalnih testova predstavlja čimbenik rizika smrtnog ishoda u bolesnika sa SS-om (22).

Bubrezi

Istraživanja zahvaćenosti bubrega u SS-u pokazuju velike razlike u prevalenciji te pokazuju da su bubrezi zahvaćeni od 4,2 do 67%, što se objašnjava razlikama u dijagnostičkim kriterijima i protokolima istraživanja. Tubularni intersticijski nefritis (TIN), koji je histopatološki obilježen peritubularnom infiltracijom limfocita i fibrozom, najčešća je bubrežna manifestacija u bolesnika sa SS-om i rijetko dovodi do zatajivanja bubrežne funkcije. Renalna tubularna acidoza (RTA) jest glavna klinička prezentacija TIN-a, a nastaje zbog oštećenja bubrežnih tubula koje za posljedicu ima zadržavanje kiselina ili gubitak bikarbonata. Uglavnom se očituje slabošću ili paralizom zbog gubitka kalija, bubrežnim kolikama zbog nefrokalcinoze te poliuri-

pain, which may be associated with hyposalivation, decreased oesophageal motility, gastritis, and decreased stomach acid production. Patients with SS are more susceptible to gastroesophageal reflux disease (GERD) due to the lack of saliva, which has a neutralising effect on stomach acid (26). In patients with SS and patients who experience symptoms of gastritis, Helicobacter pylori infection should be ruled out, especially due to the connection with MALT lymphoma (extranodal marginal zone lymphoma) (27). Abnormal values of liver enzymes, after excluding the hepatotoxic effect of drugs and fatty liver, are most often associated with disorders such as hepatitis C virus (HCV) infection, autoimmune hepatitis, primary biliary cirrhosis, or nonspecific hepatitis (28). Distinguishing between viral and autoimmune aetiology of liver disease in these patients is extremely important since they require different therapeutic approaches and have different prognoses. Chronic HCV infection is the main cause of hepatic involvement in patients from the Mediterranean region, while chronic hepatitis B virus (HBV) infection is a more common cause of hepatic involvement in patients from Asian countries (29, 30). After the exclusion of viral hepatitis, the second most common cause of liver disease in pSS is primary biliary cirrhosis (PBC) (31). It is believed that immune-mediated injury to the epithelium of the bile ducts occurs, which is histologically characterised by inflammation composed of clusters of lymphoid cells and/or granulomas. The prevalence of primary biliary cirrhosis (PBC) in patients with pSS is high and ranges from 4% to 9%. This may lead to the conclusion that both diseases share common etiopathogenetic mechanisms, which is why they are described as autoimmune epithelitis (32). The presence of antimitochondrial antibodies (AMA) in the serum of patients with SS is a risk factor for the development of PBC during a five-year period (31).

Nervous system involvement

Neurological complications are observed in approximately 20% of patients with pSS, they are manifested by involvement of the peripheral and central nervous system and may be associated with vasculitis (33). The prevalence of peripheral neuropathy varies from 20% to 60% and may precede the diagnosis of the syndrome. Its most common form is peripheral sensory neuropathy (PSN) and it is considered a characteristic neurological feature of SS. Patients report symmetric and distal paresthesias, neuropathic pain and a burning sensation in the feet, while reduced or absent deep tendon reflexes can be detected through clinical examination (34). Cranial nerves can also be damaged. The cochlear nerve is often affected, resulting in hearing loss

jom/polidipsijom zbog nefrogenog dijabetesa insipidusa (23). Glomerularna bolest je najčešće rezultat odlaganja imunokompleksa u bubrezima i češće je povezana s razvojem limfoma od tubulointersticijske bolesti (24). Kliničke prezentacije glomerulonefritisa uključuju proteinuriju, nefrotski sindrom, hematuriju, arterijsku hipertenziju i zatajivanje funkcije bubrega. Patohistološki nalazi bioptata bubrega uglavnom otkrivaju membranoproliferativni, proliferativni ili membranski glomerulonefritis. Prisutnost glomerulonefritisa u bolesnika sa SS-om značajno pridonosi povećanju stope morbiditeta i mortaliteta te utječe na prognozu bolesti (25).

Probavni sustav

Gastrointestinalne manifestacije u bolesnika sa SS-om uključuju disfagiju, dispepsiju, mučninu i bol u epigastriju, što može biti povezano s hiposalivacijom, smanjenim motilitetom jednjaka, gastritisom i smanjenom proizvodnjom želučane kiseline. Bolesnici sa SS-om podložniji su nastanku gastroezofagealnog refluksa zbog nedostatka sline koja ima neutralizirajući učinak na želučanu kiselinu (26). U bolesnika sa SS-om i simptomima gastritisa potrebno je isključiti infekciju *Helicobacterom pylori*, osobito zbog povezanosti s MALT limfomom (ekstranodalni limfom marginalne zone) (27). Poremećene vrijednosti jetrenih enzima, nakon isključenja hepatotoksičnog učinka lijekova i masne jetre, najčešće su povezane s poremećajima poput infekcije virusom hepatitisa C (HCV), autoimunog hepatitisa, primarne bilijarne ciroze ili nespecifičnog hepatitisa (28). Razlučivanje virusne i autoimune etiologije bolesti jetre u ovih bolesnika izuzetno je važno, budući da zahtijevaju različite terapijske pristupe i imaju različite prognoze. Kronična HCV infekcija glavni je uzrok zahvaćenosti jetre u bolesnika s područja Mediterana, dok je kronična infekcija virusom hepatitisa B (HBV) češći uzrok zahvaćenosti jetre u bolesnika iz azijskih zemalja (29, 30). Nakon isključenja virusnog hepatitisa, primarna bilijarna ciroza (PBC) jest sljedeći najčešći uzrok bolesti jetre u pSS-u (31). Smatra se da dolazi do imunološki posredovanog oštećenja epitela žučnih kanala, što je histološki obilježeno upalom koja se sastoji od nakupina limfoidnih stanica i/ili granuloma. Prevalencija PBC-a u bolesnika s pSS-om je visoka i kreće se od 4% do 9%. To može upućivati na zaključak da obje bolesti dijele zajedničke etiopatogenetske mehanizme, zbog čega se opisuju kao autoimuni epitelitis (32). Prisutnost antimitohondrijskih protutijela (AMA) u serumu bolesnika sa SS-om predstavlja rizični čimbenik razvoja PBC-a tijekom petogodišnjeg razdoblja (31).

Živčani sustav

Neurološke komplikacije opažene su u oko 20% bolesnika s pSS-om, a očituju se zahvaćanjem perifernog

and vestibular symptoms, and disorders of the trigeminal and facial nerves are common. Other neurological manifestations in SS include painful sensory neuropathy, multiple mononeuropathy, polyradiculopathy, and autonomic neuropathy. Central nervous system manifestations include diffuse and focal brain and spinal cord lesions, subacute aseptic meningitis, chorea, and optic neuritis. Estimates of the prevalence of these manifestations range widely from 8% to 40%. Patients with pSS often show cognitive changes with poor concentration and memory as well as visual-spatial disorders and long-term or short-term memory loss with often present depressive disorders (33).

Haematological system involvement

Haematologic diseases are observed in approximately 5%–15% of patients with pSS and they most often include leukopenia and thrombocytopenia, and haemolytic anaemia with a positive direct antiglobulin (Coombs) test can also be observed (35). Lymphomas occur in approximately 5% of patients, and it is considered that patients with SS have a 20 to 40 times higher risk of lymphoma than those that do not have SS. Non-Hodgkin's lymphoma is considered the most severe SS complication (36), and in a study conducted by Ioannidis et al. it was found that 20% of mortality cases in patients with pSS can be attributed to lymphoma (20). According to some studies, various infectious agents, such as Helicobacter pylori, human herpesvirus and Epstein-Barr virus, are associated with the development of lymphoma in patients with pSS (1). Lymphoproliferative neoplasms are almost exclusively of B cell lineage. Most lymphomas are extranodal, such as lymphoma connected with mucosa-associated lymphoid tissue (MALT – extranodal marginal zone B-cell lymphoma), and salivary glands are the most common target. Permanent enlargement of the parotid gland, peripheral lymphadenopathy, palpable purpura, cryoglobulinemia and low complement C4 levels are predictors of the development of lymphoma, and their simultaneous presence further increases the risk of its occurrence (37). With regard to the risk of developing lymphoma, it was proposed that patients with SS be divided into two groups. The first group includes low-risk patients without simultaneous presence of palpable purpura and low complement C4 levels. The second group that includes patients with simultaneous presence of the mentioned features has a high risk of developing lymphoma and an adverse prognosis (20).

CONCLUSION

Sjögren's syndrome is a relatively prevalent autoimmune disease with a broad range of clinical manifesta-

i središnjeg živčanog sustava te mogu biti povezane s vaskulitisom (33). Prevalencija periferne neuropatije varira od 20 do 60% i može prethoditi dijagnozi sindroma. Najčešći oblik je periferna senzorna neuropatija (PSN) i smatra se karakterističnim neurološkim obilježjem SS-a. Bolesnici prijavljuju simetrične i distalne parestezije, neuropatsku bol i osjećaj pečenja stopala, dok se kliničkim pregledom mogu dokazati smanjeni ili odsutni duboki tetivni refleksi (34). Kranijalni živci također mogu biti oštećeni. Kohlearni živac je često zahvaćen, što rezultira gubitkom sluha i vestibularnim simptomima, a često se javljuju poremećaji trigeminalnog i ličnog živca. Ostale neurološke manifestacije u SS-u uključuju bolnu senzornu neuropatiju, multiplu mononeuropatiju, poliradikulopatiju i autonomnu neuropatiju. Manifestacije središnjega živčanog sustava uključuju difuzne i fokalne lezije mozga i leđne moždine, subakutni aseptični meningitis, koreju i optički neuritis. Procjene prevalencije ovih manifestacija kreću se u širokom rasponu od 8% do 40%. Bolesnici s pSS-om često pokazuju kognitivne promjene s lošom koncentracijom i pamćenjem te vizualno-prostornim poremećajima i deficite dugotrajnog ili kratkoročnog pamćenja uz često prisutne depresivne poremećaje (33).

Hematološki sustav

Hematološki poremećaji uočeni su u približno 5–15% bolesnika s pSS-om i najčešće uključuju leukopeniju i trombocitopeniju, a može se uočiti i hemolitička anemija s pozitivnim izravnim antiglobulinskim (Coombsovim) testom (35). Limfomi se pojavljuju u oko 5% bolesnika te se smatra da bolesnici sa SS-om imaju 20 do 40 puta veći rizik od limfoma od onih bez SS-a. Non-Hodgkinov limfom smatra se najtežom komplikacijom SS-a (36), a Ioannidis i sur. su otkrili da se 20% smrtnosti u bolesnika s pSS-om može pripisati limfomu (20). Prema nekim istraživanjima, različiti se infektivni uzročnici, poput *Helicobactera pylori*, humanog herpesvirusa i Epstein-Barrova virusa povezuju s nastankom limfoma u bolesnika s pSS-om (1). Limfoproliferativne neoplazme su gotovo isključivo B-stanične linije. Većina limfoma je ekstranodalna, poput limfoma povezanog s limfnim tkivom sluznice (MALT – ekstranodalni B-stanični limfom marginalne zone, engl. *mucosa-associated lymphoid tissue*), a najčešće sijelo su žlijezde slinovnice. Trajno uvećanje parotida, periferna limfadenopatija, palpabilna purpura, krioglobulinemija i niske vrijednosti C4 komponente komplementa predskazatelji su razvoja limfoma, a njihova istodobna prisutnost dodatno povećava rizik njegova nastanka (37). S obzirom na rizik razvoja limfoma predložena je podjela oboljelih od SS-a u dvije skupine. Prva skupina uključuje bolesnike s niskim rizikom, u kojih nije istodobno prisutna palpabilna purpura i niske vrijednosti C4 komponente komplementa. Dru-

tions and significant morbidity, which, in the majority of cases, includes a mild clinical course. Disease prognosis depends on the presence of extraglandular forms of the disease, the occurrence of lymphoproliferative neoplasia or the clinical manifestation and activity of the associated autoimmune disease in secondary Sjögren's syndrome. To improve the care of these patients, it is necessary to conduct a comprehensive assessment of the condition and the involvement of the target organs, and it is extremely important to take a multidisciplinary approach and raise awareness of the complexity of this disease.

Conflict of interest statement: The authors declare no conflict of interest.

ga skupina s istodobnom prisutnošću navedenih obilježja ima visoki rizik za razvoj limfoma i lošiju prognozu (20).

ZAKLJUČAK

Sjögrenov sindrom je relativno česta autoimuna bolest sa širokim rasponom kliničkih manifestacija i značajnim morbiditetom koja se ipak najčešće prezentira blagim kliničkim tijekom. Prognoza bolesti ovisi o prisutnosti izvanžljezdanih oblika bolesti, pojavi limfoproliferativne neoplazije ili kliničkom očitovanju i aktivnosti pridružene autoimune bolesti u sekundarnom Sjögrenovom sindromu. Za poboljšanje skrbi ovih bolesnika potrebna je sveobuhvatna procjena stanja i zahvaćenosti ciljnih organa, a svakako je neophodan multidisciplinaran pristup i podizanje svjesnosti o složenosti ove bolesti.

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