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DIAGNOSIS AND CLASSIFICATION CRITERIA OF SJÖGREN'S SYNDROME

DIJAGNOZA I KLASIFIKACIJSKI KRITERIJI SJÖGRENOVOG SINDROMA

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Abstract

Sjögren's syndrome (SS) is a chronic, systemic autoimmune disease of unknown aetiology that manifests with various clinical manifestations. It is characterized by dense lymphocytic infiltration of exocrine glands which leads to functional impairment. Involvement of the salivary and lacrimal glands, and the consequent dryness of the eyes and mouth, are among the most common clinical manifestations of the disease. SS may occur as a primary disease or secondary to another organ-specific autoimmune disease or overlap with other rheumatic conditions. The disease is named after the Swedish ophthalmologist Henrik Sjögren. The diagnosis of SS is made based on clinical and laboratory indicators and objective findings of involvement of the salivary glands and lacrimal glands. In clinical practice, classification criteria often help in making a diagnosis, although they were initially developed and validated to standardize a cohort of patients for inclusion in the clinical trials and studies. Over the years, more than ten different classification criteria for SS have been proposed. In 1993, the first multicentric preliminary European classification criteria for SS were proposed. These criteria were subsequently revised by the American-European Consensus Group (AECG) in 2002. In 2012, the new modified classification criteria of the American College of Rheumatology (ACR) for SS were published, which did not provide any significant diagnostic changes. The 2016 criteria of the ACR and the European Alliance of Associations for Rheumatology (EULAR) are currently used for the classification of the disease. A significant shift with the new criteria is that symptoms of dry eyes or mouth are not necessary for classification, and it is sufficient to have only one of the systemic manifestations of the disease.

Key words: Sjögren's syndrome, diagnosis, classification criteria

Sažetak

Sjögrenov sindrom (SS) je kronična, sustavna autoimunosna bolest nepoznate etiologije koja se manifestira širokim rasponom kliničkih očitovanja. Histološki je karakterizirana gustom limfocitnom infiltracijom egzokrinih žlijezda, što pridonosi oštećenju njihove funkcije. Zahvaćanje žlijezda slinovnica i suznih žlijezda te posljedična suhoća očiju i usta spadaju u najčešće kliničke manifestacije bolesti. SS se može pojaviti kao primarna bolest ili sekundarno uz drugu organ-specifičnu autoimunu bolest te u preklapanju s drugim reumatološkim stanjima. Bolest je ime dobila po švedskom oftalmologu Henriku Sjögrenu. Dijagnoza SS-a postavlja se na temelju kliničkih i laboratorijskih pokazatelja te objektivnih nalaza zahvaćenosti žlijezda slinovnica i suznih žlijezda. Najčešće u kliničkoj praksi za postavljanje dijagnoze pomažu klasifikacijski kriteriji, iako su oni prvotno razvijeni i validirani u svrhu standardiziranja kohorti bole-

snika za uključivanje u klinička ispitivanja i studije. Tijekom godina je predloženo više od deset različitih klasifikacijskih kriterija za SS. Godine 1993. predloženi su prvi multicentrični preliminarni europski klasifikacijski kriteriji za SS. Te kriterije naknadno je revidirala 2002. godine Američko-europska grupa stručnjaka (AECG – prema engl. *American-European Consensus Group*). Godine 2012. objavljeni su novi, dosta izmijenjeni klasifikacijski kriteriji Američkoga reumatološkog društva za SS koji nisu donijeli velikih dijagnostičkih pomaka. Za klasifikaciju bolesti trenutno se koriste kriteriji iz 2016. godine Američkog reumatološkog društva (ACR – prema engl. American College of Rheumatology) i Europskog saveza udruga za reumatologiju (EULAR – prema engl. *European Alliance of Associations for Rheumatology*). Značajna je izmjena u novim kriterijima da za klasifikaciju nije nužna prisutnost simptoma suhoće očiju ili usta, već je dovoljno imati neku od sustavnih manifestacija bolesti.

Ključne riječi: Sjögrenov sindrom, dijagnoza, klasifikacijski kriteriji

INTRODUCTION

Sjögren's syndrome (SS) is a chronic systemic autoimmune inflammatory disease characterised by dense lymphocytic infiltration of the exocrine glands, as well as other tissues and organs (1). Depending on whether it is a case of an isolated entity or an entity within another systemic inflammatory disease, it is divided into primary (pSS) and secondary Sjögren's syndrome (sSS) (1). Sjögren's syndrome is a disease with extremely heterogeneous clinical features and a variable course and prognosis. There is no single clinical, pathological or radiological marker that would serve as a "gold standard" for the diagnosis or classification of the disease. Involvement of the salivary and lacrimal glands, and the consequent dryness of the eyes and lack of saliva are among the most common clinical manifestations of the disease. The course and long-term prognosis of the disease as well as the clinical features depend on the distribution of inflammatory activity. Symptoms of dryness, pain and fatigue are benign manifestations of the disease that are present in the majority of patients and significantly affect the quality of life, while severe systemic manifestations occur in 20 to 40% of patients, and some patients will also present with lymphoma (2,3). SS is a relatively common autoimmune disease, the second most common after rheumatoid arthritis (1,4). In over 95% of cases, patients with primary SS are women(5), and the ratio of female to male patients varies depending on different studies, from 20:1 to 9:1 in favour of the female gender. It most often occurs in patients who are in their 40s or 50s (1). The prevalence of secondary SS depends on the diseases with which it occurs. Thus, the prevalence of sSS in systemic lupus erythematosus varies from 6.5 to 19%, in rheumatoid arthritis from 4 to 31%, and in systemic sclerosis from 14 to 20.5%. In patients with rheumatoid arthritis, it usually occurs as a late manifestation of the disease, while in patients with systemic lupus erythematosus, SS precedes the diagnosis of lupus by about two years. It is not uncommon that sSS also occurs as part of autoimmune events specific to a particular organ, such as primary biliary cirrhosis and Graves' disease. (1).

Although the drugs used can relieve the symptoms and prevent the development of complications in this

UVOD

Sjögrenov sindrom (SS) je kronična sustavna autoimunosna upalna bolest koja je obilježena gustom limfocitnom infiltracijom egzokrinih žlijezda, ali i drugih tkiva i organa (1). Ovisno o tome radi li se o izoliranom entitetu ili entitetu u sklopu druge sustavne upalne bolesti, dijelimo ga na primarni (pSS) i sekundarni Sjögrenov sindrom (sSS) (1). Sjögrenov sindrom je bolest izrazito heterogene kliničke slike te varijabilnog tijeka i prognoze. Ne postoji jedan klinički, patološki ili radiološki znak koji bi služio kao „zlatni standard" za dijagnozu ili klasifikaciju bolesti. Zahvaćanje suznih žlijezda i žlijezda slinovnica te posljedična suhoća očiju i manjak sline ubrajaju se u najčešće kliničke manifestacije bolesti. Tijek i dugoročna prognoza bolesti kao i klinička slika ovise o distribuciji upalne aktivnosti. Simptomi suhoće, bol i umor su dobroćudne manifestacije bolesti koje su prisutne u većine oboljelih i značajno utječu na kvalitetu života, dok se u 20 – 40% bolesnika javljaju teške sustavne manifestacije, a dio bolesnika će se prezentirati i limfomom (2,3). SS je relativno česta autoimunosna bolest, druga po učestalosti nakon reumatoidnog artritisa (1,4). U više od 95% slučajeva oboljeli od primarnog SS-a su žene (5), a odnos ženskih i muških bolesnika varira ovisno o različitim studijama, od 20:1 do 9:1 u korist žena. Najčešće se javlja u 4. i 5. desetljeću života (1). Prevalencija sekundarnog SS-a ovisi o bolestima uz koje se javlja. Tako prevalencija sSS-a u sistemskom eritematoznom lupusu varira od 6,5% do 19%, u reumatoidnom artritisu od 4% do 31%, a u sistemskoj sklerozi od 14% do 20,5%. U bolesnika s reumatoidnim artritisom obično se javlja kao kasna manifestacija bolesti, dok u bolesnika sa sistemskim eritematoznim lupusom SS prethodi dijagnozi lupusa za oko dvije godine. Nerijetko se sSS javlja i u sklopu autoimunosnih zbivanja specifičnih za pojedini organ poput primarne bilijarne ciroze i Gravesove bolesti (1).

Iako primijenjeni lijekovi mogu olakšati simptome i spriječiti razvoj komplikacija u sklopu ove bolesti, često ne dovode do zadovoljavajuće remisije, odnosno izlječenja. Međutim, razvoj novih terapijskih opcija za liječenje raznih autoimunosnih bolesti pa tako i SS-a te

disease, they often do not lead to a satisfactory remission or cure. However, the development of new therapeutic options for the treatment of various autoimmune diseases, including SS, and numerous clinical trials have highlighted the need for a better definition and earlier recognition of this disease.

HISTORY OF SJÖGREN'S SYNDROME

Anecdotal records of the condition we know today as Sjögren's syndrome date back to the second half of the 19th century. In 1882, in his lecture "On the origin of retinal detachment", Thomas Leber described three patients with dry inflammation of the cornea and conjunctiva with the formation of filaments, and he called this condition filamentary keratitis (6). Although he did not associate it with ocular surface dryness, his observations played an important role in the later definition of SS. In the late 1880s, Hutchinson and Hadden independently published reports of patients with severe dry mouth and consequent oral complications. Hutchinson is the author of the term "xerostomia" (6–8). Polish surgeon Johann Mikulicz-Radecki was born in 1892. described the case of a patient with painless symmetrical enlargement of the lacrimal and salivary glands, and the histopathological record of the salivary gland samples today fits the clinical features of MALT lymphoma (mucosa-associated lymphoid tissue) infiltration. In the mid-20s of the 20th century, the dermatologist Gougerot described the cases of three patients with progressive and chronic dryness of the mouth due to atrophy of the salivary glands and associated dryness of the eyes, nose, larynx and vagina. At the end of the 1920s, Houwer described cases of patients with chronic and bilateral filamentary keratitis, and half of these patients also suffered from associated arthritis. (7,8).

Although numerous authors "paved the way" for Henrik Sjögren, he was the only one who concluded that it is a systemic disease and not just an ocular disorder in his 1933 doctoral dissertation "Zur Kenntnis der Keratoconjunctivitis Sicca Keratitis filiformis bei hypofunction der Tranendriisen". He came to the above conclusions based on the follow-up of 19 patients with keratoconjunctivitis, 13 of whom also had associated arthritis. (8).

The opinion that it is an autoimmune disease first appeared in the 1950s, and this position was supported by Alspaugh's discovery of anti-SSA (anti-Ro) and anti-SSB (anti-La) antibodies. Through the efforts of a working group led by Haralampos Moutsopoulos in the 1970s and 1980s, it was discovered that SS is a chronic autoimmune disease characterized by infiltration of exocrine glands with B and T-lymphocytes, that the risk of developing lymphoma is up to 44 times higher than in the general population, and that certain

brojna klinička ispitivanja istaknuli su potrebu boljeg definiranja i ranijeg prepoznavanja ove bolesti.

POVIJEST SJÖGRENOVOG SINDROMA

Anegdotalni opisi stanja koje danas poznajemo pod nazivom Sjögrenov sindrom datiraju iz druge polovice 19. stoljeća. Thomas Leber je 1882. godine u predavanju *O porijeklu ablacije retine* opisao i tri bolesnika sa suhom upalom rožnice i spojnice uz formiranje filamenata te je navedeno stanje nazvao filamentozni keratitis (6). Iako ga nije povezao sa suhoćom površine oka, njegova su zapažanja odigrala važnu ulogu u kasnijoj definiciji SS-a. Krajem 1880-ih Hutchinson i Hadden, neovisno jedan o drugom, objavili su prikaze bolesnika s teškom suhoćom usta i posljedičnim oralnim komplikacijama. Hutchinson je autor pojma „kserostomija" (6–8). Poljski je kirurg Johann Mikulicz-Radecki 1892. godine opisao slučaj bolesnika s bezbolnim simetričnim povećanjem suznih i slinovnih žlijezda, a patohistološki opis uzoraka slinovnica danas se uklapa u sliku infiltracije MALT limfomom (engl. *mucosa-associated lymphoid tissue*). Sredinom 20-ih godina 20. stoljeća dermatolog Gougerot je opisao slučajeve troje bolesnika s progresivnom i kroničnom suhoćom usta uslijed atrofije slinovnica te pridruženom i suhoćom očiju, nosa, grkljana i vagine. Krajem 1920-ih Houwer opisuje slučajeve bolesnika s kroničnim i obostranim filamentoznim keratitisom od kojih polovica ima i pridruženi artritis (7,8).

Iako su brojni autori „utrli put" Henriku Sjögrenu, tek je on u svojoj doktorskoj disertaciji *Zur Kenntnis der Keratoconjunctivitis Sicca Keratitis filiformis bei hypofunction der Tranendriisen* iz 1933. godine zaključio da je riječ o sustavnoj bolesti, a ne samo o okularnom poremećaju. Do navedenih je zaključaka došao temeljem praćenja 19 bolesnica s keratokonjunktivitisom sika od kojih je 13 imalo i pridruženi artritis (8).

Mišljenje da je riječ o autoimunosnoj bolesti prvi put se javlja 1950-ih, a ta postavka je potkrijepljena Alspaughovim otkrićem protutijela anti-SSA (anti-Ro) i anti-SSB (anti-La) protutijela. Naporima radne skupine pod vodstvom Haralamposa Moutsopulosa 1970-ih i 1980-ih godina otkriveno je da je SS kronična autoimunosna bolest karakterizirana infiltracijom egzokrinih žlijezda B i T-limfocitima, da je rizik razvoja limfoma i do 44 puta veći u odnosu na opću populaciju te da se može govoriti o primarnom i sekundarnom SS-u ovisno o prisutnosti ili odsutnosti pridružene sustavne kolagenoze (8).

POSTAVLJANJE DIJAGNOZE SJÖGRENOVOG SINDROMA

Raznolikost i kompleksnost kliničke slike SS-a otežava dijagnostički i terapijski proces. Postavljanje dija-

characteristics could point to a case of primary and secondary SS depending on the presence or absence of associated systemic collagenosis (8).

ESTABLISHING DIAGNOSIS OF SJÖGREN'S SYNDROME

The diversity and complexity of the clinical features of SS complicates the process of diagnosis and therapy. The diagnosis of SS is often delayed, and the disease is often misdiagnosed as another autoimmune disease, most often systemic lupus erythematosus or rheumatoid arthritis. Certain subtypes of the disease (especially those without sicca symptoms) are more challenging to establish an accurate diagnosis, and due to a lack of understanding of the entire spectrum, the disease may remain undiagnosed. The diagnosis of SS should be suspected in individuals with persistent symptoms of dry eyes or oral cavity, enlargement of the parotid glands, and pathological findings of serological tests (e.g. anti-SS-A, anti-SS-B, rheumatism factor, hyperglobulinemia)(9). Dryness of the mouth often leads to a significant worsening of cavities, especially in the area of chewing surfaces or tooth cervix, hyperlobulated tongue (Figure 1), chronic erythematous oral candidiasis.

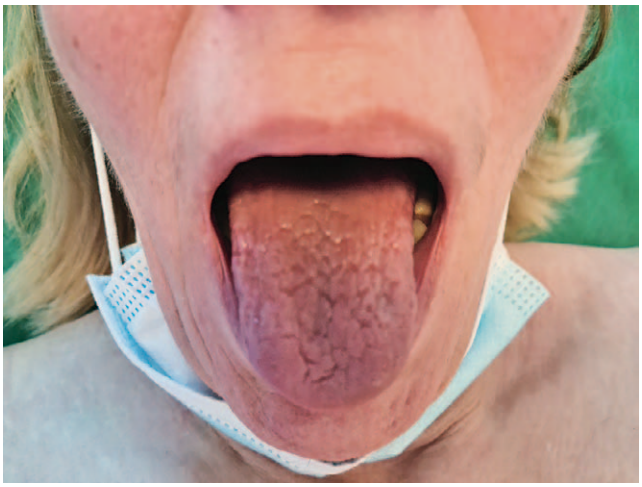


Figure 1 Dry mouth and hyperlobulated tongue in patient with primary Sjögren's syndrome (author's personal arhive)
Slika 1. Suhoća usta i hiperlobulirani jezik u bolesnice s primarnim Sjögrenovim sindromom (vlastita arhiva autora)

Making a diagnosis only on the basis of positive SS-A and SS-B antibodies is not advisable, considering that the said antibodies can be detected in other autoimmune diseases, but also in healthy individuals (10). Although medicine advances every day with the development of new diagnostic methods and tools, there is still no single diagnostic test that would confirm or exclude the diagnosis of SS, but it is established based on a combination of clinical and laboratory indicators.

gnoze SS-a često je zakašnjelo, a bolest se nerijetko pogrešno dijagnosticira kao druga autoimunosna bolest, najčešće sistemski eritematozni lupus ili reumatoidni artritis. Određeni podtipovi bolesti (pogotovo oni bez sika-simptoma) izazovniji su za postavljanje točne dijagnoze, a zbog nerazumijevanja cijelog spektra bolest može ostati i nedijagnosticirana. Na dijagnozu SS-a treba posumnjati kod pojedinaca s trajno prisutnim simptomima suhoće očiju ili usne šupljine, uvećanja parotidnih žlijezda te patoloških nalaza serološkim testova (npr. anti SS-A, anti-SS-B, reuma faktora, hiperglobobulinemije) (9). Suhoća usta nerijetko dovodi do izrazitog pogoršanja karijesa, posebice u području zagriznih ploha ili zubnih vratova, hiperlobuliranog jezika (slika 1) i kronične eritematozne oralne kandidijaze.

Postavljanje dijagnoze samo na temelju pozitivnih protutijela SS-A i SS-B protutijela nije uputno s obzirom na to da se navedena protutijela mogu detektirati kod drugih autoimunosnih bolesti, ali i kod zdravih osoba (10). Iako medicina svakodnevno napreduje uz razvoj novih dijagnostičkih metoda i sredstava, još uvijek ne postoji jedinstveni dijagnostički test kojim bi se potvrdila ili isključila dijagnoza SS-a, već se ona postavlja na temelju kombinacije kliničkih i laboratorijskih pokazatelja.

Dijagnoza SS-a postavlja se kod objektivnih pokazatelja suhoće oka i/ili usta ili oštećenja žljezdanog parenhima (nakon isključenja drugih mogućih uzroka) uz prisutnost serološkog ili histološkog dokaza autoimunosti. U pojedinim dobnim skupinama klasična klinička slika SS-a varira, pa je tako u djece znatno češća prisutnost rekurentnog parotitisa, dok objektivni pokazatelji suhoće očiju i usta nisu uvijek prisutni (11). Novija multicentrična studija na velikom broju bolesnika pokazala je da su mladi bolesnici (do 35. godine starosti) imali veću učestalost povećanja slinovnica, limfadenopatije, leukopenije, hipokomplementemije te hipergamaglobulinemije i limfoma u odnosu na kontrolnu populaciju bolesnika sa Sjögrenovim sidromom koji su bili srednje dobi. Stariji su bolesnici (dob iznad 65. godine) imali češće sika-simptome i intersticijsku patologiju pluća te također veću pojavnost limfoma (12). Poznato je da oko 20% bolesnika neće razviti sika-simptome, već će se prezentirati šarolikom paletom sustavnih manifestacija (2,4,5). Većina sustavnih manifestacija uključena je u *Indeks aktivnosti Sjögrenovog sindroma* (ESSDAI – prema engl. EULAR *Sjögren's syndrome disease activity index*). Nova istraživanja pokazuju da više od četvrtine bolesnika s pSS-om može imati manifestacije koje nisu obuhvaćene navedenim indeksom od kojih je najčešći Raynaudov sindrom koji je u nedavnom istraživanju bio prisutan u 15% bolesnika (5). Nadalje, brojni radovi pokazuju da se sustavne manifestacije mogu javiti i znatno prije sika-simptoma, što često značajno odgađa postavljanje točne dija-

Table 1 Questionnaire on dry mouth and eyes with suspected Sjögren's syndrome. (adapted according to reference No 16)
Tablica 1. Upitnik o suhoći usta i očiju kod sumnje na Sjögrenov sindrom (prilagođeno prema referenciji br. 16)

Questions about the symptoms of tear gland involvement / Pitanja o simptomima zahvaćanja suznih žlijezda	Questions about the symptoms of salivary gland involvement / Pitanja o simptomima zahvaćanja žlijezda slinovnica
1. Have you had daily, persistent, problematic dry eyes for > 3 months? / Jeste li imali svakodnevnu, trajnu, problematičnu suhoću očiju >3 mjeseca?	1. Have you had a daily feeling of dry mouth > 3 months? / Jeste li imali svakodnevni osjećaj suhoće usta >3 mjeseca?
2. Do you have a recurrent sensation of sand or gravel in the eyes? / Imate li ponavljajući osjećaj pijeska ili šljunka u očima?	2. Do you have to wake up at night to drink water because of dry mouth? / Morate li se buditi noću piti vodu zbog suhoće usta?
3. Do you use tear substitutes more than 3 times a day? / Koristite li umjetne suze?	3. Do you frequently drink liquids to aid in swallowing dry foods? / Pijete li često tekućinu za lakše gutanje hrane?
	4. Have you had recurrent or permanently swollen salivary glands as an adult? / Jeste li imali ponavljajuće ili trajno otečene žlijezde slinovnice u odrasloj dobi?

The diagnosis of SS is established with objective indicators of dry eyes and/or mouth or damage to the glandular parenchyma (after excluding other possible causes) with the presence of serological or histological evidence of autoimmunity. In certain age groups, the standard clinical features of SS varies, so the presence of recurrent parotitis is much more common in children, while objective indicators of dry eyes and mouth are not always present (11). A recent multicentre trial conducted on a large number of patients showed that young patients (up to 35 years of age) had a higher frequency of salivary gland enlargement, lymphadenopathy, leukopenia, hypocomplementemia, and hypergammaglobulinemia and lymphoma compared to a control population of middle-aged patients with Sjögren's syndrome. Older patients (over the age of 65) had more frequent sicca symptoms and interstitial lung pathology, as well as a higher incidence of lymphoma (12). It is known that about 20% of patients will not develop sicca-symptoms, but will present themselves with a colourful palette of systemic manifestations. (2,4,5). Most systemic manifestations are included in the Sjögren's syndrome disease activity index (ESSDAI, EULAR Sjögren's syndrome disease activity index). New research shows that more than a quarter of patients with pSS may have manifestations that are not covered by the mentioned index, the most common of which is Raynaud's syndrome, which was present in 15% of patients according to a recently conducted research (5). Furthermore, numerous works show that systemic manifestations can occur well before sicca symptoms, which often significantly delays the establishment of an accurate diagnosis (13). However, due to the non-specificity of systemic manifestations, the diagnosis can be made in the case of a positive finding of anti-SSA antibodies and other laboratory indicators characteristic of the disease.

Typical sicca symptoms will often be present in pSS at the time of diagnosis, and the percentage of patients varies between 86–95% in published studies (5,12). Other clinical manifestations that occur in more than 10% of

gnoze (13). Međutim, zbog nespecifičnosti sustavnih manifestacija dijagnoza se može postavi u slučaju pozitivnog nalaza antitijela anti-SSA te drugih laboratorijskih pokazatelja karakterističnih za bolest.

Klasični će sika-simptomi često biti prisutni u pSS-u u trenutku postavljanja dijagnoze, a postotak bolesnika varira u objavljenim studijama između 86 i 95% (5,12). Ostale kliničke manifestacije koje se javljaju u više od 10% bolesnika s pSS-om su zglobne (41%), plućne manifestacije (12%), limfadenopatija (11%), opći simptomi, umor te u 10% slučajeva kožne manifestacije poput palpabilne purpure potkoljenica (5,14). Zahvaćanje perifernoga živčanog sustava (periferna neuropatija) javlja se u 10% bolesnika, zahvaćanje bubrega u oko 5%, dok se kronični gastritis i disfagija pojavljuju u oko 2 – 3% bolesnika. Prema dostupnim studijama procjene zahvaćanja središnjega živčanog sustava značajno variraju, jer nema jasno postavljenih kriterija za dijagnozu (15).

Na simptome suhoće oka u sklopu sika-sindroma treba posumnjati kada bolesnici navode svakodnevne tegobe s očima u trajanju više od tri mjeseca, kontinuirano imaju osjećaj pijeska ili stranog tijela u očima te ako trebaju koristiti umjetne suze više od tri puta dnevno. Kserostomija i simptomi sijaloadenitisa suspektni su ako bolesnici navode osjećaj suhoće usta u trajanju više od tri mjeseca, buđenje noću kako bi popili vode, konzumaciju tekućine kako bi mogli jesti suhu hranu te epizodno ili konstantno oticanje u području slinovnica (16). U svrhu ispitivanja sika-simptoma napravljen je validirani upitnik (16) koji je prikazan u tablici 1.

Naravno, ovakve su tegobe subjektivne naravi te ih je za postavljanje dijagnoze nužno objektivizirati. Tri najčešće pretrage za objektiviziranje suhog oka jesu: Schirmerov test, test vremena pucanja suznog filma (TBUT – engl. *tear break-up time*) i ocjena bojenja površine oka (OSS – engl. *ocular staining test*) (9). OSS i Schirmerov test čine dva kriterija u zajedničkim kriterijima EULARA-a i ACR-a. iz 2016. godine (17). Kse-

patients with pSS are joint manifestations (41%), pulmonary manifestations (12%), lymphadenopathy (11%), general symptoms, fatigue and in 10% of cases skin manifestations such as palpable purpura of the lower legs (5,14). Involvement of the peripheral nervous system (peripheral neuropathy) occurs in 10% of patients, kidney involvement in about 5%, while chronic gastritis and dysphagia occur in about 2–3% of patients. According to the available studies, estimates of involvement of the central nervous system vary significantly, as there are no clearly established criteria for diagnosis (15).

Symptoms of dry eye as part of sicca syndrome should be suspected when patients report daily eye problems lasting more than 3 months, have a continuous feeling of sand or a foreign body in the eyes, and if they need to use artificial tears more than 3 times a day. Xerostomia and symptoms of sialoadenitis are suspected if patients report a feeling of dry mouth lasting more than 3 months, waking up at night to drink water, consuming liquids to be able to eat dry food, and episodic or constant swelling in the salivary gland area (16). For the purpose of examining sicca symptoms, a validated questionnaire (16) was created, which is shown in the Table 1.

Of course, these complaints are subjective in nature and it is necessary to objectivize them in order to establish a diagnosis. The three most common tests for the objectivization of dry eye: Schirmer's test, tear break-up time test (TBUT) and ocular staining test (OSS) (9). OSS and Schirmer's test are two criteria in the 2016 joint criteria of EULAR and ACR. (17). Xerostomia and salivary gland changes are objectivized by sialometry, imaging methods and biopsy (18). Sialometry is used to quantify or measure the amount of saliva produced. If 0.1 mL of saliva or less is secreted in one minute without stimulation, the criteria for xerostomia are met. The sensitivity of sialometry is 56%, and the specificity is 81%. (9). It should be kept in mind that sialometry is not valid if the patient is chronically taking drugs with anticholinergic effects such as some antihistamines, benzodiazepines, antidepressants. Technetium Tc-99m pertechnetate salivary scintigraphy and contrast sialography are no longer frequently used. The imaging methods that are preferred today are magnetic resonance imaging and easily available ultrasound, and they are supported by the specificity for SS greater than 90%, i.e. 93% and 92% respectively in the case of an ultrasound (19). The advantage of ultrasound is that it can be used in diagnosis, but also in disease follow-up. Moreover, salivary gland ultrasound has been shown to be a diagnostic tool comparable to salivary gland biopsy. Biopsy, i.e. histopathological analysis of small salivary glands (sensitivity 80%, specificity 82%) is still the gold standard in the diagnosis of SS, and in the 2016 classification criteria it has the highest number of points (17). Sialometry and biopsy are the only methods listed in the latest classification criteria for assessing salivary gland function (17). Laboratory, sero-

Table 2 Laboratory, serological, radiological and histopathological findings characteristic of the diagnosis of Sjögren's syndrome.

Tablica 2. Laboratorijski, serološki, radiološki i patohistološki nalazi karakteristični za dijagnozu Sjögrenovog sindroma

Laboratory findings / Laboratorijski nalazi: • ESR, CRP / **SE**, CRP • CBC, biochemical findings, urine / KKS, biokemijski nalazi, urin • **hypergammaglobulinemia**/hypogammaglobulinemia / **hipergamaglobulinemija**/hipogamaglobulinemija • C3, C4
Serological evidence of autoimmunity / Serološki dokaz autoimunosti: • **ANA** • **SSA** +/– SSB antibodies (50–70%) / **protutijela SSA** +/– SSB (50 – 70%) • RF (40–50%) • cryoglobulinemia / krioglobulinemija • anticentromere antibodies / anticentromerna protutijela
Objective evidence of dryness of the eyes or mouth or involvement of the glandular parenchyma / Objektivni dokaz suhoće očiju ili usta ili zahvaćanja žljezdanog parenhima • Schirmer test, TBUT, OSS, unstimulated salivation ≤0,1 mL/min / Schirmerov test, TBUT, OSS, nestimulirano lučenje sline ≤0,1 mL/min • MR or US evidence of gland parenchyma changes characteristic of SSj / MR ili UZV dokaz promjena parenhima žlijezda karakerističnih za SS • **salivary gland biopsy** with focal lymphocytic sialadenitis and focus score ≥ 1 focus / 4 mm^2 / **biopsija žlijezda slinovnica** s fokalnim limfocitnim sijaladenitisom i fokus skorom ≥ 1 fokus /4 mm^2

Legend / Legenda: ESR / SE – erythrocyte sedimentation rate / brzina sedimentacije eritrocita; CRP – C reactive protein / C-reaktivni protein; CBC / KKS – complete blood count / kompletna krvna slika; C3, C4 – complement / komplement; ANA – antinuclear antibodies / antinuklearna antitijela; RF – rheumatoid factor / reumatoidni faktor; TBUT – tear break-up time; OSS – ocular staining score / ocjena bojenja površine oka; MR – magnetic resonance imaging / magnetska rezonancija; US / UZV – ultrasound / ultrazvuk

rostomija i promjene slinovnica objektiviziraju se sijalometrijom, slikovnim metodama te biopsijom (18). Sijalometrija se koristi za kvantificiranje odnosno mjerenje količine proizvedene sline. Ako se bez stimulacije u jednoj minuti luči 0,1 mL sline ili manje od toga, ispunjeni su kriteriji za kserostomiju. Osjetljivost je sijalometrije 56%, a specifičnost 81%. (9). Treba imati na umu da sijalometrija nije mjerodavna ako bolesnik kronično uzima lijekove s antikolinergičkim djelovanjem poput nekih antihistaminika, benzodizepina, antidepresiva. Scintigrafija slinovnica tehnecij-pertehnetatom te kontrastna sijalografija više se ne koriste često. Slikovne metode koje se danas preferiraju jesu magnetska rezonancija te lako dostupan ultrazvuk, a u prilog im idu specifičnost za SS veća od 90%, tj. 93% odnosno 92% u slučaju ultrazvuka (19). Prednost ultrazvuka je to što se može koristiti u postavljanju dijagnoze, ali i u praćenju bolesti. Štoviše, ultrazvuk slinovnica se pokazao kao dijagnostičko sredstvo usporedivo s biopsijom

logical, radiological and histopathological findings characteristic for the diagnosis of Sjögren's syndrome are presented in Table 2.

To establish a diagnosis, after the objectivization of sicca-symptoms or in the case of systemic manifestations of the disease, it is necessary to perform an immunoserological test. It should be emphasized that testing for the presence of autoantibodies should be used to confirm a working diagnosis, and not be used as a screening test, considering that a healthy part of the population may have a positive finding of autoantibodies. Therefore, in the context of objectivized sicca-symptoms and a negative finding of antinuclear antibodies (ANA), it is unlikely that this is a patient with SS. In addition to autoantibodies (ANA positive in over 85% of cases, anti-SSA in 50 to 70%, rheumatoid factor (RF) in 50 to 60%, anti-SSB in 33 to 50%), there are other laboratory indicators indicative of SS such as which are accelerated erythrocyte sedimentation rate in 80 to 90% of cases, hypergammaglobulinemia in 80%, anaemia of chronic disease in a quarter of cases and leukopenia in 10% of cases. Thrombocytopenia is rarely present. A rare serological finding is anticentromeric antibodies that can be detected in up to 5% of cases, without or only with some clinical characteristics for systemic sclerosis, and anti-CCP without other elements for rheumatoid arthritis (20). New research shows the importance of new antibodies in predicting certain disease manifestations and long-term complications, which could have great clinical significance in the future (21).

Part of the patients will be diagnosed in the stage of developed lymphoproliferative disease, considering that compared to other systemic inflammatory diseases, SS has the highest risk for the development of lymphoma, according to the standardized incidence of 9 to 44 or 5 to 15, depending on whether these were published before the year 2000 or in the later period. The most common histological subtype of lymphoma are MALT lymphomas (2). Certain clinical and laboratory characteristics are associated with an increased risk of developing lymphoma. Due to the large clinical spectrum of this disease, the differential diagnosis of Sjögren's syndrome is very broad and includes other systemic autoimmune diseases (primarily systemic lupus erythematosus and rheumatoid arthritis), infections (hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), various non-autoimmune causes of dry mouth or eyes (age, medications), IgG4-related disease, sarcoidosis, amyloidosis, lymphoma, Graft vs. Host Disease (GVHD) and other diseases.

CLASSIFICATION CRITERIA OF SJÖGREN'S SYNDROME

Classification criteria that were originally developed and validated for the purpose of standardizing cohorts

slinovnica. Biopsija, odnosno patohistološka analiza malih žlijezda slinovnica (osjetljivost 80%, specifičnost 82%) i dalje je zlatni standard u postavljanju dijagnoze SS-a te u klasifikacijskim kriterijima iz 2016. nosi najveći broj bodova (17). Sijalometrija i biopsija su jedine od svih nabrojanih metoda za procjenu funkcije žlijezda slinovnica sadržane u najnovijim klasifikacijskim kriterijima (17). Laboratorijski, serološki, radiološki i patohistološki nalazi karakteristični za dijagnozu Sjögrenovog sindroma prikazani su u tablici 2.

Za postavljanje dijagnoze, nakon objektivizacije sika-simptoma ili u slučaju sustavnih očitovanja bolesti potrebno je učiniti imunoserološko testiranje. Potrebno je naglasiti da testiranje prisutnosti autoantitijela treba koristiti za potvrdu radne dijagnoze, a ne koristiti kao probirni test s obzirom na to da zdravi dio populacije može imati pozitivan nalaz autoantitijela. Stoga je u kontekstu objektiviziranih sika-simptoma i negativnog nalaza antinuklearnih antitijela (ANA) malo vjerojatno da je riječ o bolesniku sa SS-om. Osim autoantitijela (ANA pozitivna u više od 85% slučajeva, anti-SSA u 50 – 70%, reumatoidni faktor (RF) u 50 – 60%, anti-SSB u 33 – 50%), postoje i drugi laboratorijski pokazatelji indikativni za SS kao što su ubrzana sedimentacija eritrocita u 80 – 90% slučajeva, hipergamaglobulinemija u 80%, anemija kronične bolesti u četvrtini slučajeva i leukopenija u 10% slučajeva. Trombocitopenija je rijetko prisutna. Rijedak serološki nalaz jesu anticentromerna protutijela koja se mogu detektirati u do 5% slučajeva, bez kliničkih karakteristika za sistemsku sklerozu ili tek s nekima od njih, te anti-CCP bez drugih elemenata za reumatoidni artritis (20). Nova istraživanja pokazuju važnost novih protutijela u predviđanju pojedinih manifestacija bolesti te dugoročnih komplikacija, što bi moglo imati velik klinički značaj u budućnosti (21).

Dijelu bolesnika dijagnoza će biti postavljena u fazi razvijene limfoproliferativne bolesti, s obzirom na to da SS u usporedbi s drugim sistemskim upalnim bolestima ima najviši rizik za razvoj limfoma i to prema standardiziranoj incidenciji od 9 do 44 odnosno od 5 do 15, ovisno je li riječ o studijama prije ili poslije 2000. godine. Najčešći histološki podtip limfoma jesu MALT limfomi (2). Pojedine kliničke i laboratorijske karateristike povezane su s povećanim rizikom razvoja limfoma. Diferencijalna dijagnoza Sjögrenovog sidroma vrlo je široka zbog velikoga kliničkog spektra ove bolesti i obuhvaća druge sustavne autoimune bolesti (prvenstveno sistemski eritematozni lupus i reumatoidni artritis), infekcije (virus hepatitisa C [HCV], virus humane imunodeficijencije [HIV – prema engl. *human immunodeficiency virus*], citomegalo virus [CMV]), različite neautoimune uzroke suhoće usta ili očiju (starost, lijekovi), bolest IgG4, sarkoidozu, amiloidozu, limfom, bolest presatka protiv primatelja (GVHD – prema engl. *graft versus host disease*) i drugo.

of patients for inclusion in clinical trials and studies, often serve as an aid in clinical practice when establishing a diagnosis. Given the extremely heterogeneous clinical features of SS, it is understandable why more than eleven different classification criteria for SS have been proposed over the years since 1960. Figure 2 shows the development of individual classification criteria for Sjögren's syndrome throughout history.

The classification criteria that were developed until 1993 were mostly based on the clinical experience of leading experts or on the data of individual centres, and therefore none of them were accepted by the wider scientific community (22,23). When it comes to the older criteria for the diagnosis of SS, the most used were: the San Francisco criteria (proposed in 1975 and subsequently revised in 1984), the Copenhagen criteria (proposed in 1976) and the Japanese criteria (published in 1978), as well as the Greek and the Californian criteria proposed in 1986. (22–27). The Japanese criteria have been updated several times, the last time being in 1999.

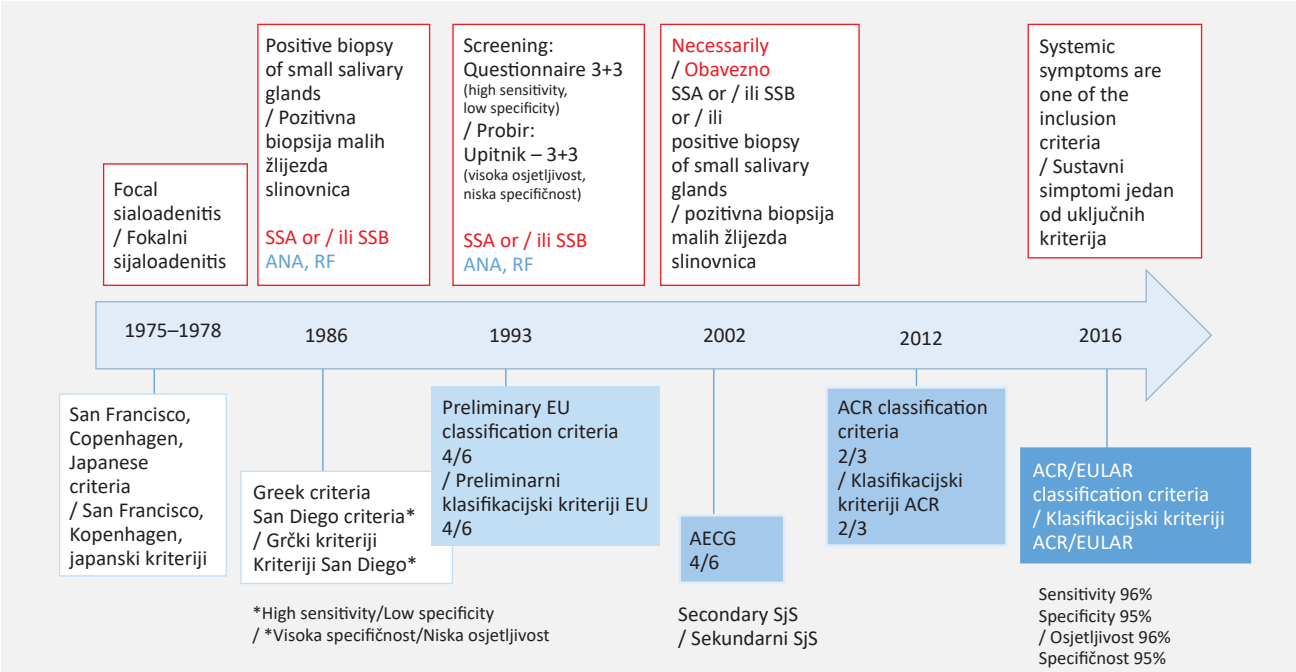
In the San Francisco criteria that were proposed in 1965, the introduction of a new diagnostic criterion was recommended – the presence of focal sialoadenitis in the biopsy samples of the minor salivary glands to determine the presence of the oral component of Sjögren's syndrome instead of the subjective assessment of xerostomia based on the presented research conducted on 100 patients (22). The criteria were revised in 1984, when it was confirmed in 362 patients that focal sialoadenitis in an adequate sample is an objective criterion specific for SS (23). The Copenhagen criteria required at least two pathological objective tests for the assessment of dry eye and mouth for classification (24). The first Japanese criteria were published in 1978 and were used in Japan for over 20 years. For classification, it was necessary to have a subjective feeling of dry mouth or eyes and at least one of the following: a) two pathological eye tests, b) focal sialoadenitis or c) abnormal sialography/scintigraphy (25). In the last revised Japanese criteria from 1999, which were formed as a result of the work of the Japanese working group for SS, it was not necessary to have subjective symptoms of dryness for classification, and serological findings and stimulated sialometry were introduced as criteria for assessing saliva secretion. These classification criteria contained four major components: histology, oral tests (sialography/scintigraphy/stimulated sialometry), ocular tests (Schirmer's test + Rose Bengal staining test/fluorescein) and serology (SS-A or SS-B). For classification, it was necessary to have at least two of the four criteria (28). According to the data recorded on 900 patients, it was estimated that the criteria have a sensitivity of 96%, a specificity of 90.5% and an accuracy for the diagnosis of SS of 94.5%. (28). These latest Japanese criteria were quite similar to the preliminary European classification criteria published 6 years

KLASIFIKACIJSKI KRITERIJI SJÖGRENOVOG SINDROMA

Klasifikacijski kriteriji koji su prvotno razvijeni i validirani u svrhu standardiziranja kohorti bolesnika za uključivanje u klinička ispitivanja i studije često služe kao pomoć u kliničkoj praksi pri postavljanju dijagnoze. S obzirom na izrazito heterogenu kliničku sliku SS-a razumljivo je zašto je tijekom godina predloženo više od jedanaest različitih klasifikacijskih kriterija za SS od 1960. godine. Na slici 2. prikazan je razvoj pojedinih klasifikacijskih kriterija za Sjögrenov sindrom kroz povijest, do 1993. god.

Klasifikacijski kriteriji koji su bili razvijeni do 1993. godine većinom su se bazirali na kliničkom iskustvu vodećih eksperata ili na podatcima pojedinih centara te stoga niti jedan od njih nije bio prihvaćen u široj znanstvenoj zajednici (22,23). Od kriterija starijeg datuma za dijagnozu SS-a najviše su se koristili: kriteriji San Francisco (predloženi 1975. i naknadno revidirani 1984. godine), kopenhagenski (predloženi 1976.) te japanski (objavljeni 1978.), grčki i kalifornijski kriteriji koji su predloženi 1986. godine. (22–27). Japanski kriteriji su u nekoliko navrata ažurirani, zadnji put 1999. godine.

U kriterijima San Francisco koji su predloženi 1965. godine preporučeno je uvođenje novog dijagnostičkog kriterija – prisutnost fokalnog sijaloadenitisa u uzorcima biopsije malih žlijezda slinovnica za utvrđivanje prisutnosti oralne komponente Sjögrenovog sindroma umjesto subjektivne procjene kserostomije na temelju prikazanog istraživanja provedenog na 100 bolesnika (22). Kriteriji su revidirani 1984. godine, kada je na 362 bolesnika potvrđeno da je fokalni sijaloadenitis u adekvatnom uzorku objektivan kriterij specifičan za SS (23). Kopenhagenski kriteriji za klasifikaciju su tražili najmanje dva patološka objektivna testa za procjenu suhoće oka i usta (24). Prvi japanski kriteriji objavljeni su 1978. godine i koristili su se u Japanu preko 20 godina. Za klasifikaciju je bilo potrebno imati subjektivan osjećaj suhoće usta ili očiju te najmanje jedno od slijedećeg: a) dva patološka očna testa, b) fokalni sijaloadenitis ili c) abnormalnu sijalografiju/scintigrafiju (25). U posljednjim revidiranim japanskim kriterijima iz 1999., koji su formirani kao rezultat rada japanske radne skupine za SS, za klasifikaciju nije bilo nužno imati subjektivne simptome suhoće, a kao kriterij uvedeni su serološki nalazi te stimulirana sijalometrija kao metoda procjene izlučivanja sline. Ti klasifikacijski kriteriji sadržavali su četiri velike komponente: histologiju, oralne testove (sijalografija/scintigrafija/stimulirana sijalometrija), očne testove (Schirmerov test + test Rose Bengal/florescein) te serologiju (SS-A ili SS-B). Za klasifikaciju je bilo potrebno imati najmanje dva od četiri kriterija (28). Prema podatcima napravljenim na 900 bolesnika procijenjeno je da kriteriji imaju osjetlji-



Legend /Legenda: ANA – antinuclear antibodies / antinuklearna antitijela; RF – rheumatoid factor / reumatoidni faktor; AECG – American-European Consensus Group / American-European Consensus Group; ACR – American Rheumatological Society / Američko reumatološko društvo; EULAR – European Association of Rheumatology Associations / Europski savez udruga za reumatologiju; SS – Sjögren's syndrome / Sjögrenov sindrom

Figure 2 Development of classification criteria for Sjögren syndrome throughout history
Slika 2. Razvoj klasifikacijskih kriterija za Sjögrenov sindrom kroz povijest

earlier. The Greek criteria published in 1986 were based on a study of 52 patients with sicca symptoms. According to them, for classification it was necessary to have focal sialoadenitis (≥2 focus/4 mm2) with one of the following criteria: a) subjective dryness of the eye plus a pathological finding of the Schirmer's test plus a pathological finding of the Rose Bengal staining test, b) anamnestic or current enlargement of the parotid glands and c) sensation of dry mouth and pathological finding of stimulated sialometry (26). The Californian criteria, also called the San Diego criteria, also published in 1986, are criteria of a more restrictive nature. According to these criteria, for the diagnosis it was necessary to have focal sialoadenitis (≥2 foci/4 mm2), a feeling of dry mouth with a pathological finding of stimulated and non-stimulated sialometry, a pathological finding of the Schirmer's test and one of the dye tests (Rose Bengal staining or fluorescein test) and a positive finding of one of the serological tests (IgM-RF [titer ≥ 160] or ANA [titer ≥ 160] or SS-A or SSB antibodies) (27). Exclusion criteria (lymphoma, chronic Graft vs. Host Disease – GVHD), acquired immunodeficiency syndrome, sarcoidosis are also listed in them for the first time. The differences and similarities of individual criteria up to 1993 are presented in Table 3.

In 1993, preliminary European classification criteria for SS were proposed (7). They were widely used for the next ten years, both in clinical practice and in ob-

vost 96%, specifičnost 90,5% te točnost za dijagnozu SS-a 94,5% (28). Ovi najnoviji japanski kriteriji dosta su sličili preliminarnim europskim klasifikacijskim kriterijima objavljenim šest godina ranije. Grčki kriteriji objavljeni 1986. godine napravljeni su na istraživanju 52 bolesnika sa sika-simptomima. Prema njima za klasifikaciju je bilo nužno imati fokalni sijaloadenitis (≥2 fokus/4 mm^2) uz neki od slijedećih kriterija: a) subjektivnu suhoću oka plus patološki nalaz Schirmerovog testa plus patološki nalaz Rose bengal testa, b) anamnestički ili trenutno povećanje parotidnih žlijezda i c) osjećaj suhoće usta i patološki nalaz stimulirane sijalometrije (26). Kalifornijski kriteriji koji se još nazivaju kriteriji San Diego, objavljeni također 1986., restriktivnije su naravi. Prema tim kriterijima za dijagnozu je bilo potrebno imati fokalni sijaloadenitis (≥2 fokus/4 mm^2), osjećaj suhoće usta uz patološki nalaz stimulirane i nestimulirane sijalometrije, patološki nalaz Schirmerovog testa i nekog od testa s bojama (Rose Bengal ili floresceinskog testa) te pozitivan nalaz nekog od seroloških testova (IgM-RF [titar ≥ 160] ili ANA [titar ≥ 160] ili SS-A ili SSB antitijela) (27). U njima su također po prvi put navedeni i isključni kriteriji (limfom, kronična bolest presatka protiv primatelja – GVHD, sindrom stečene imunodeficijencije, sarkoidoza). Razlike i sličnosti pojedinih kriterija do 1993. prikazane su u tablici 3.

Table 3 Differences and similarities of classification criteria proposed up to 1993 (adapted according to reference No 27)
Tablica 3. Razlike i sličnosti klasifikacijskih kriterija predloženih do 1993. godine (prilagođeno prema referenciji br. 27).

	San Francisco (1975, 1984)	Copenhagen (1976)	Japanese (1978)	Japanese (1999)	Greek (1986)	San Diego (1986)
References / Referenca	(22,23)	(24)	(25)	(28)	(26)	(27)
Subjective dryness of the eyes / Subjektivna suhoća oka	–	–	required / obvezna	–	+	–
Subjective dryness of the mouth / Subjektivna suhoća usta	–	–	required / obvezna	–	+	+
History of parotid gland swelling / Anamneza oticanja parotida	–	–	–	–	+	–
Ocular tests / Očni testovi:						
Schirmer's test / Schirmerov test	+ (< 10 mm /5 min)	+ (≤10 mm /5 min)	+ (≤10 mm /5 min)	+ (≤5 mm /5 min)	+ (≤5 mm /5 min)	+ (<9 mm /5 min)
Break-up time	+	+(≤10 s)	–	–	–	–
Rose Bengal	+	+(≥4)	+ (≥2)	+ (≥3)	+ (≥4)	+ (≥4)
Florescein test / Test floresceinom	–	–	+	+	–	+
Oral tests / Oralni testovi:						
Unstimulated whole saliva / Nestimulirano izlučivanje sline	+	+	–	–	–	+
Stimulated salivary flow / Stimulirano izlučivanje sline	–	–	+	+	+	+
Scintigraphy / Scintigrafija	–	+	–	+	–	–
Sialography / Sijalografija	–	–	+	+	–	–
Biopsy of small salivary glands / Biopsija malih žlijezda slinovnica	≥1 focus on 4 mm^2 / ≥1 fokus na 4 mm^2	≥1 focus / fokus /4 mm^2	≥1 focus on the lobe / ≥1 fokus po lobusu	≥1 focus / fokus /4 mm^2	≥2 focus / fokus /4 mm^2	≥2 focus / fokus /4 mm^2
Biopsy of small salivary gland mandatory criterion / Biopsija malih žlijezda slinovnica obvezan kriterij	Yes / Da	No / Ne	No / Ne	No / Ne	Yes / Da	Yes / Da
ANA	–	–	–	–	–	+
Anti-SSA	–	–	–	–	–	+
Anti-SSB	–	–	–	+	–	+
IgM-RF	–	–	–	+	–	+
pSS/sSS terminology / Terminologija pSS/sSS	+	+	–	–	+	–

Legend / Legenda: ANA – antinuclear antibodies / antinuklearna antitijela; IgM-RF – rheumatoid factor – imunoglobulin M / reumatoidni faktor imunoglobulin M; pSS – primary Sjögren's syndrome / primarni Sjögrenov sindrom; sSS – secondary Sjögren's syndrome / sekundarni Sjögrenov sidrom

servational and interventional studies. During the development of the classification criteria in 1993, a questionnaire on dry eyes and mouth was designed and validated, which is used in a minimally modified form in the current classification criteria. Three questions for dry eye and three questions for dry mouth were chosen, which had high sensitivity and low specificity and so well discriminated patients from controls and served as screening (Table 1) (7). For the classification of primary SS, the patient had to have four out of six criteria present. In addition to symptoms of dry eyes and mouth, the criteria included an objective finding of dry eye (Schirmer's test ≤ 5 mm/5 min, Rose Bengal

Godine 1993. predloženi su preliminarni europski klasifikacijski kriteriji za SS (7). Oni su se uvelike koristili sljedećih deset godina, kako u kliničkoj praksi, tako i u opservacijskim i intervencijskim studijama. Tijekom razvoja klasifikacijskih kriterija 1993. godine osmišljen je i validiran upitnik o suhoći oka i usta koji se u minimalno izmijenjenom obliku koristi i u trenutnim klasifikacijskim kriterijima. Izabrana su tri pitanja za suhoću oka te tri pitanja za suhoću usta koja su imala visoku osjetljivost i nisku specifičnost te tako dobro distingvirala bolesnike od kontrola i služila kao probir (tablica 1) (7). Bolesnik je za klasifikaciju primarnog SS-a trebao imati prisutna četiri od šest kriterija. Osim

score ≥ 4), then histological evidence of salivary gland involvement, one of the objective tests of salivary gland involvement (salivary gland scintigraphy, parotid sialography and unstimulated saliva secretion (≤ 1.5 ml/15 min) and serological proof of autoimmunity (presence of SSA or SSB antibodies, ANA or RF). Table 4 shows the differences and similarities of the classification criteria published from 1993 until today. Although the above classification criteria were widely accepted, they had several problems. A combination of ocular and oral symptoms and dry eye tests and salivary gland involvement tests could also be found in patients with sicca symptoms who did not necessarily have SS. Patients with true primary SS, but without subjective sicca-symptoms, could just as easily be omitted from the classification.

These criteria were subsequently revised by the American-European Consensus Group (AECG) and published new revised criteria in 2002 (8). In order to correct the problems with the earlier criteria, the patient had to have one of the following two findings characteristic of the disease for classification: a) positive antibodies characteristic of the disease (SSA or SSB) or b) a positive biopsy of minor salivary glands. These classification criteria, unlike the previous ones, introduced the classification of sSS in patients with another autoimmune disease with the presence of sicca symptoms and with two additional criteria from the group (III, IV or V). In 2012, the new, somewhat modified classification criteria of the ACR were published, which did not bring major news or diagnostic advances (30). For classification, it was necessary to have at least two of the three criteria: 1. serological criterion (positive anti SSA and/or anti SSB antibodies or positive rheumatism factor and ANA in a titer greater than 1:320), 2. ophthalmological criterion (ocular staining score, OSS ≥ 3), 3. presence of lymphocytic sialedenitis in the biopsy of minor salivary glands. In a study that compared the classification criteria AECG and ACR, matching results of these two sets of criteria were shown, and no clear evidence was presented for the increased value of the new ACR criteria compared to the old AECG criteria from a clinical perspective (31).

The joint criteria of ACR and EULARA from 2016 are currently used to classify the disease. They can be used in patients with at least one symptom of dry eyes or mouth according to the AECG questionnaire or in suspected systemic disease. The new parameter in the current criteria is that each criterion does not have the same weight, that is, it does not signify the same number of points. The classification is based on the weighted sum of five criteria: positive SSA antibodies and focal lymphocytic sialoadenitis with focus sum ≥1 focus/4 mm2, consisting of three points each, then Schirmer's test and OSS ≥5 for the objectivization of dry eyes and unstimulated salivation ≤0, 1 mL/min

simptoma suhoće očiju i usta, u kriterije su ulazili objektivni nalaz suhoće oka (Schirmerov test ≤ 5 mm/5 min, zbroj Rose Bengal ≥ 4), zatim histološki dokaz zahvaćanja žlijezda slinovnica, jedan od objektivnih testova zahvaćanja žlijezda slinovnica (scintigrafija žlijezda slinovnica, sijalografija parotida i nestimulirano lučenje sline [≤ 1,5 ml/15 min] te serološki dokaz autoimunosti [prisutnost antitijela SSA ili antitijela SSB, ANA ili RF]). Tablica 4 prikazuje razlike i sličnosti klasifikacijskih kriterija objavljenih od 1993. godine do danas. Iako su navedeni klasifikacijski kriteriji bili naširoko prihvaćeni, imali su nekoliko problema. Kombinacija okularnih i oralnih simptoma te testova suhoće očiju i testova zahvaćanja slinovnica mogla se također naći i u bolesnika sa sika-simptomima koji nisu morali imati SS. Isto tako, lako se moglo ispustiti iz klasifikacije bolesnike s pravim primarnim SS-om, ali bez subjektivnih sika-simptoma.

Ove kriterije naknadno je revidirala američko-europska skupina (AECG – prema engl. *American-European Consensus Group*) i 2002. godine objavila nove revidirane kriterije (8). Da bi se ispravili problemi s ranijim kriterijima, bolesnik je za klasifikaciju morao obvezno imati jedan od sljedeća dva nalaza karakteristična za bolest: a) pozitivna protutijela karakteristična za bolest (SSA ili SSB) ili b) pozitivnu biopsiju malih žlijezda slinovnica. Ovi klasifikacijski kriteriji za razliku od prethodnih uveli su klasifikaciju i sSS u bolesnika s prisutnom drugom autoimunosnom bolesti uz prisutnost sika-simptoma te uz dodatna dva kriterija iz grupe (III, IV ili V). Godine 2012. objavljeni su novi ponešto izmijenjeni klasifikacijski kriteriji ACR-a koji nisu donijeli velikih novosti niti dijagnostičke pomake (30). Za klasifikaciju bilo je potrebno imati najmanje dva od tri kriterija: 1. serološki kriterij (pozitivna protutijela anti-SSA i/ili anti-SSB ili pozitivan reuma faktor i ANA u titru većem od 1:320), 2. oftalomološki kriterij (OSS ≥ 3), 3. prisutnost limfocitnog sijaledenitisa u bioptatu malih žlijezda slinovnica. U studiji koja je uspoređivala klasifikacijske kriterije AECG i ACR pokazani su podudarni rezultati ovih dvaju skupova kriterija te nisu predočeni jasni dokazi za povećanu vrijednost novih kriterija ACR-a u odnosu na stare kriterije AECG-a iz kliničke perspektive (31).

Za klasifikaciju bolesti trenutno se koriste zajednički kriteriji ACR-a i EULARA-a iz 2016. godine. Oni se mogu koristiti u bolesnika s najmanje jednim simptomom suhoće očiju ili usta prema upitniku AECG-a ili kod sumnje na sustavnu bolest. Ono što je novo u trenutnim kriterijima jest da svaki kriterij nema istu težinu, odnosno ne nosi isti broj bodova. Klasifikacija se temelji na ponderiranom zbroju pet kriterija: pozitivna antitijela SSA i fokalni limfocitni sijaloadenitis s fokus zbrojem ≥1 fokus/4 mm^2, svaki nosi po tri boda, zatim Schirmerov test i OSS ≥5 za objektivizaciju suhoće oči-

Table 4 Differences and similarities of classification criteria published between 1993 and 2016.
Tablica 4. Razlike i sličnosti klasifikacijskih kriterija objavljenih 1993. – 2016. godine

	Classification criteria / Klasifikacijski kriteriji	Preliminary european (1993) / Preliminarni europski (1993.) (16)	AECG (2002) / AECG (2002.) (29)	ACR (2012) / ACR (2012.) (30)	ACR/EULAR (2016) / ACR/EULAR (2016.) (17)	
	Number of criteria for classification / Kriterij za klasifikaciju	4/6 criteria / 4/6 kriterija	4/6 criteria – mandatory criterion 4. or 6. 3/4 objective criteria (3., 4., 5., ili 6.) / 4/6 kriterija – obvezan kriterij 4. ili 6. 3/4 objektivna kriterija (3., 4., 5., ili 6.)	2/3 criteria / 2/3 kriterija	≥ 4 points in patients with sicca symptomes or ESSDAI ≥1 / ≥ 4 boda u bolesnika sa sika simptomima ili ESSDAI ≥1	
1.	Eye dryness / Suhoća oka	+	+	+	–	
2.	Oral symptoms / Oralni simptomi	+	+	–	–	
3.	Eye tests / Očni testovi	Schirmer's test (≤ 5 mm/ 5 min) or / Schirmer test (≤ 5 mm/ 5 min) ili Rose Bengal ≥4 / Rose Bengal zbroj ≥4	Schirmer's test (≤ 5 mm/5 min) or / Schirmer test (≤ 5 mm/5 min) ili van Bijsterveld ≥4 / van Bijsterveld zbroj ≥4	OSS ≥ 3	OSS ≥ 5 Schirmer's test (≤ 5 mm / 5 min) / Schirmer test (≤ 5 mm / 5 min)	1 point / 1 bod 1 point / 1 bod
4.	Biopsy of small salivary glands / Biopsija malih žlijezda slinovnica	≥ 1 focus / fokus / 4 mm^2	≥ 1 focus / fokus / 4 mm^2	≥ 1 focus / fokus / 4 mm^2	≥ 1 focus / fokus / 4 mm^2	3 points / 3 boda
5.	Involvement of salivary glands / Zahvaćanje žlijezda slinovnica	salivary gland scintigraphy or parotid sialography or unstimulated salivary flow (≤ 1.5 ml in 15 min) / scintigrafija žlijezda slinovnica ili sijalografija parotida ili nestimuliran protok sline (≤ 1,5 ml u 15 min)	salivary gland scintigraphy or parotid sialography or unstimulated saliva flow (≤ 1.5 ml in 15 min) / scintigrafija žlijezda slinovnica ili sijalografija parotida ili nestimuliran protok sline (≤ 1,5 ml u 15 min)	–	unstimulated saliva flow (≤ 0.1 ml in 1 min) / nestimuliran protok sline (≤ 0,1 ml u 1 min)	1 point / 1 bod
6.	Antibodies / Antitijela	SSA or SSB or ANA or RF / SSA ili SSB ili ANA ili RF	SSA and/or SSB / SSA i/ili SSB	SSA or SSB or RF and ANA titer >1:320 / SSA ili SSB ili RF i ANA titar >1:320	SSA	3 points / 3 boda
	Exclusion criteria / Isključni kriteriji	lymphoma, AIDS, sarcoidosis, GVHD / limfom, AIDS, sarkoidoza, GVHD	Previous head and neck radiotherapy, HCV infection, AIDS, lymphoma, sarcoidosis, GVHD, use of anticholinergics / Prethodna radioterapija glave i vrata, infekcija HCV, AIDS, limfom, sarkoidoza, GVHD, korištenje antikolnergika	Previous head and neck radiotherapy, HCV, AIDS, sarcoidosis, amyloidosis, GVHD, IgG4 – related disease / Prethodna radioterapija glave i vrata, infekcija HCV AIDS, sarkoidoza, amiloidoza,GVHD, IgG4 – vezana bolest	Previous radiotherapy of the head and neck, HCV AIDS, amyloidosis, GVHD, IgG4 – related disease / Prethodna radioterapija glave i vrata, infekcija HCV, AIDS, amiloidoza, GVHD, IgG4 – vezana bolest	
	Terminology pSS / sSS / Terminologija pSS/sSS		+		–	

Legend / Legenda: ANA – antinuclear antibodies / antinuklearna antitijela; RF – rheumatoid factor / reumatoidni faktor; TBUT – tear break-up time; OSS – ocular staining score / ocjena bojenja površine oka; AIDS –aquired immunodeficiency syndrome / sindrom stečene imunodeficijencije; GVHD – graft versus host disease / kronična bolest presatka protiv primatelja; HCV – hepatitis C virus / virus hepatitisa C; IgG4 – immunoglobulin G4 / imunoglobulin G4.

consisting of one point each. The patient must have 4 or more points in order for the classification to be successful. Positive SSB antibodies in the absence of SSA antibodies are no longer a criterion, and ANA and RF have also been dropped from the criteria. The reason for this decision was that a very small number of patients who met the ACR criteria had negative SSA and SSB antibodies, and positive ANA and RF (21).

A comparison of the AECG classification criteria from 2002 and the latest ACR/EULAR classification criteria showed excellent agreement between them (κ = 0.92). (32). However, the ACR/EULAR classification criteria were still more sensitive and additionally classified patients without sicca symptoms, who had systemic manifestations as pSS, which once again confirms the importance of including systemic manifestations in the classification criteria. This study showed that the sensitivity of the new ACR/EULAR criteria is 87.4%, and the specificity is 95.4% when the physician's diagnosis is taken as the standard. (32). It has also been shown that the inclusion of salivary gland ultrasound in the ACR/EULAR criteria can further increase their sensitivity (32). Summary of main features of classification criteria from 1993 to 2016 are presented in table 4.

CONCLUSION

Over the years, significant progress has been made in the understanding of Sjögren's syndrome as a systemic disease. This is especially outlined in the latest ACR/EULAR classification criteria from 2016, where the classification includes patients with systemic manifestations of the disease without sicca symptoms. However, the complexity of the clinical features of this disease still makes timely diagnosis and early recognition difficult. Therefore changes are not expected in a future in this field.

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ju te nestimulirano lučenje sline ≤0,1 mL/min nose svaki po jedan bod. Za klasifikaciju bolesnik treba imati četiri ili više bodova. Pozitivna antitijela SSB u odsutnosti antitijela SSA više nisu kriterij, a također su iz kriterija izbačeni ANA i RF. Razlog za ovu odluku bio je taj što je vrlo mali broj bolesnika koji su ispunili kriterije ACR imao negativna protutijela SSA i SSB, a pozitivna ANA i RF (21).

Usporedba klasifikacijskih kriterija AECG iz 2002. godine i najnovijih klasifikacijskih kriterija ACR/EULAR-a pokazala je odličnu suglasnost među njima (κ = 0,92) (32). Međutim, klasifikacijski kriteriji ACR/EULAR-a bili su ipak osjetljiviji i klasificirali su dodatno bolesnike bez sika-simptoma, koji su imali sustavne manifestacije kao pSS, što ponovno potvrđuje važnost uključivanja sustavnih manifestacija u klasifikacijske kriterije. Ova studija je pokazala da je osjetljivost novih kriterija ACR/EULAR-a 87,4%, a specifičnost 95,4% kada se dijagnoza liječnika uzme kao standard (32). Također, pokazano je da uključenje ultrazvuka žlijezda slinovnica u kriterije ACR/EULAR-a može dodatno povećati njihovu osjetljivost. (32). Sažetak glavnih obilježja kriterija od 1993. do 2016. godine je prikazan na tablici 4.

ZAKLJUČAK

Tijekom godina je napravljen značajan pomak u razumijevanju Sjögrenovog sindroma kao sustavne bolesti. To se posebno ocrtava u najnovijim klasifikacijskim kriterijima ACR/EULAR-a iz 2016. godine, gdje su klasifikacijom obuhvaćeni i bolesnici sa sustavnim manifestacijama bolesti bez sika-simptoma. No, kompleksnost kliničke slike ove bolesti i dalje otežava pravovremenu dijagnozu i rano prepoznavanje. Stoga ne očekuju promjene u ovom području.

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