Revista Colombiana de
REUMATOLOGÍA
www.elsevier.es/rcreuma

Review Article

Questions as regards the recognition of elderly-onset primary Sjögren's syndrome: Where we are and where we would rather be

Ciro Manzo

Internal and Geriatric Medicine Department, Azienda Sanitaria Locale Napoli 3 sud, Geronthorheumatologic Outpatient Clinic, poliambulatorio "Mariano Lauro", Sant'Agnello, Naples, Italy

ARTICLE INFO

Article history:
Received 12 November 2019
Accepted 5 May 2020

Keywords:
Primary Sjögren's syndrome
Elderly-onset primary Sjögren's syndrome
Elderly patients
Drug-induced sicca syndrome
Classification criteria

ABSTRACT

Several epidemiological studies have suggested that the prevalence of the onset of primary Sjögren's Syndrome in the elderly (EOpSS) is significantly higher (between five to eight times) than in other age groups. However, when a literature review was performed, the number of patients with EOpSS was much lower than epidemiologically expected. An evaluation was performed on Sjögren (sicca) syndrome, including immunological markers, labial salivary glands biopsy, and some extra-glandular manifestations. These could be confounding factors in the elderly patients, much more so than in other age groups, and lead to a misdiagnosis of EOpSS. This article presents a review of the most common difficulties that may be present in the recognition of EOpSS, and highlights the lack of elderly patient-centred studies as the most important unmet need.

© 2020 Asociación Colombiana de Reumatología. Published by Elsevier España, S.L.U. All rights reserved.

Preguntas sobre el reconocimiento del síndrome de Sjögren primario con inicio en la edad avanzada: ¿dónde estamos y dónde preferiríamos estar?

Palabras clave:
Síndrome de Sjögren primario
Síndrome de Sjögren primario con inicio en la edad avanzada
Pacientes de edad avanzada
Síndrome de sicca inducido por drogas
Criterios de clasificación

RESUMEN

Varios estudios epidemiológicos han sugerido que la prevalencia del síndrome de Sjögren primario (SSp) en la población de edad avanzada (Elderly-Onset primary Sjogren's Syndrome [EOpSS], según la clasificación inglés) es considerablemente mayor (entre 5 y 8 veces) que en grupos de edad diferente. Sin embargo, una revisión sistemática de la literatura mostró que el número de pacientes con EOpSS era mucho menor de lo que se esperaba epidemiológicamente. La evaluación del síndrome de sicca, los marcadores inmunológicos, la biopsia de las glándulas salivales labiales y algunas manifestaciones extraglandulares podrían convertirse en factores de confusión en pacientes de edad avanzada mucho más frecuentemente que en

E-mail addresses: cirmanzo@libero.it, manzoreumatologo@libero.it
https://doi.org/10.1016/j.rcreu.2020.05.006
0121-8123/© 2020 Asociación Colombiana de Reumatología. Published by Elsevier España, S.L.U. All rights reserved.

personas de otros grupos de edad, lo que favorecería un diagnóstico erróneo del EOpSS. En este artículo se revisan las principales dificultades que pueden afectar al reconocimiento del EOpSS, destacando la falta de estudios centrados en el paciente anciano como la necesidad insatisfecha más importante.

© 2020 Asociación Colombiana de Reumatología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

Elderly-onset primary Sjögren's syndrome (EOpSS) has an estimated overall prevalence of approximately 3%, but epidemiological data are very heterogeneous and prevalence depends on variables such as geographic areas, simple sizes, and diagnostic criteria.[1,2] The age used to define the population is itself a variable: more than 60 years, more than 65, more than 70, according to different researchers. First data were presented by Drosos et al. in 1988[3]: in 62 healthy volunteers with a mean age of 81 years (range: 67–95 years), EOpSS was confirmed in 4.83% of the study group. In another study conducted in 2008, Haugen et al. showed that in an elderly group (aged 71–74 years) EOpSS was confirmed in 3.39% according to the 1993 European Community Study Group (ECGS) classification criteria, and in 1.40% according to the revised 1996 European classification criteria. In this study, the prevalence of pSS in the younger group (aged 40–44 years) was lower, totaling 0.44% and 0.22%, respectively.[4] In general, epidemiological studies highlighted that the prevalence of pSS in the elderly population is higher (between five to eight times) than in other age groups.[5–7]

Classification criteria

All principal cohorts in literature are based on the classification criteria proposed by ECGS in 1993 and by American European Consensus Group (AECG) in 2002. As known, these criteria were designed for entry into clinical trials. The target population consisted of persons with signs and symptoms suggestive of SS. In particular, the AECG criteria considered six items, two of which were subjective (ocular and oral symptom complaints by the patients) and four based on objective findings (Table 1).

In patients without any potentially associated disease, pSS may be defined as the presence of four of the aforementioned six items (histopathology and autoantibodies are mandatory) or presence of three of the four objective criteria.[8]

At the end of 2016, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) presented jointly established pSS diagnostic criteria. Unlike the AECG criteria, these criteria were based on objective tests, taking into account symptoms as inclusion criteria. Of all the laboratory tests, diagnostic importance was attributed only to SSA/Ro autoantibodies (3 points). Positive serology for anti-SSB/La without positive serology for anti-SSA/Ro, and positivity for antinuclear antibodies (ANA) and rheumatoid factor were no longer considered. Histopathological examination of labial salivary gland (LSG) biopsies with the assessment of FS remained an important element (FS > 1 gives 3 points).[9] The diagnosis is made if a patient presents with a sum of ≥4 points, but a cut-off of 5 points instead of 4 raises the specificity of the criteria from 89% to 98%.[10]

Both in AECG criteria and in ACR/EULAR criteria, established exclusion criteria must be evaluated: head and neck radiation treatment, active hepatitis C virus infection (confirmed using PCR), acquired immune deficiency syndrome, sarcoidosis, amyloidosis, graft versus host disease, and immunoglobulin G4-related disease. Additionally, in the evaluation of dry eye symptoms, patients using eye drops for glaucoma daily and those who have had corneal surgery or cosmetic eyelid surgery in the last 5 years are scored 0 points.[8,9]

What happens when these criteria are applied to the elderly population? In the real world, the application of these proposed criteria to the elderly comes up against a whole series of criticalities.

1. *Sicca syndrome*: Both in the criteria proposed by the AECG and those by the ACR/EULAR collaborative group, reported symptoms of ocular and/or buccal dryness are the first step. These symptoms are common among the elderly, and their prevalence may reach up to 30% in persons over the age of 65 years.[11] However, when these symptoms are evaluated through objective tests, a weak confirmation is found.[12] Diagnostic tests have several confusing elements in the elderly. For example, older age is associated with a reduction of tear and/or saliva production,[13,14] and this reduction may affect the results of Schirmer test or the assessment of unstimulated whole saliva flow rate. In two population-based survey of health elderly people, the prevalence of an abnormal Schirmer test ranged from 12 to 58%.[13,15] So, Schirmer's test may be less useful than ocular staining score as a confirmation test for keratoconjunctivitis sicca in EOpSS patients.[16]

Furthermore, multimorbidity and polypharmacy (including over-the-count drugs) are very common in elderly patients.[17–20] Some drugs reduce the secretion of tears or saliva.[21,22] These drugs include anticholinergics, antidepressants (tricyclic or selective serotonin reuptake inhibitors), antihypertensives (terazosin, prazosin, clonidine, and atenolol), antihistamines, antireflux drugs, diuretics, benzodiazepines (Table 2). Among these, anticholinergic drugs are the most important confounding factors, so that patients who are normally taking these drugs should be evaluated for objective signs of salivary hypofunction and eye dryness after a sufficient time of their withdrawal.

Table 1 – AECG criteria.

Subjective findings

1. Ocular symptom complained by the patient;
2. Oral symptom complained by the patient.

Objective findings

3. Schirmer's test < 5 mm/5 min at least one eye or Rose Bengal score according to the van Bijsterveld score;
4. Minor salivary biopsy with a focus score (FS) > 1 (FS means no less than 50 mononuclear cells per 4 mm^2 of the glandular section);
5. Objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests: (a) unstimulated whole salivary flow < 1.5 mL in 15 min; (b) parotid sialography showing the presence of diffuse sialectasis (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts; (c) salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of trace.
6. Presence in the serum of antibodies to Ro (SSA) or La (SSB) antigens, or both.

AECG: American European Consensus Group; FS: Focus Score.

Table 2 – Categories of drugs that can induce xerostomia and/or xerophtalmia.

Antihistamines
Decongestants
Antidepressants
Antipsychotics
Antihypertensive
Anticholinergics
Opioids
Diuretics
Anticholinesterases and memantina.
Protease inhibitors
Benzodiazepine

Table 3 – Tarpley's grading system for LSG biopsies.[35]

Grade	Description gland tissue
0	Normal
1	1 or 2 aggregate
2	>3 aggregates
3	Diffuse infiltrate with partial destruction of acinar tissue with or without fibrosis
4	Diffuse infiltrate with or without fibrosis destroying the lobular architecture complete.

LSG: Labial Salivary Gland.

2. *LSG biopsy*: As well-known, a focal lymphocytic sialadenitis (FLS) with >50 mononuclear cells in a peri-ductal or peri-vascular localization is considered the most specific histopathological finding. The term FLS refers to the histopathological pattern of the presence of one or more foci in the biopsies, while the tissue surrounding the foci is composed mainly of unaffected parenchyma. Given the heterogeneous distribution of the inflammatory infiltrate and glandular damage, analysis of four to seven glands from each patient is suggested in order to obtain a reasonably sized sample, and analysis of a glandular surface area of at least 8 mm^2 is recommended.[23,24]

In all ages of life, the evaluation of LSG biopsies is far from easy and straightforward. Vivino et al. reported that a second expert evaluation of 58 LSG re-analysed by a single centre led to revision of the initial diagnosis in 53% of the patients.[25] More recently, Costa et al. reported a multicenter cohort study in which minor salivary gland biopsies were analyzed with a standard blinded assessment by two different pathologists at 2-month interval. The analysis included the measurement of FLS and detection of germinative centres (GC)-like structures. The inter-observer variability comparison revealed poor agreement for the detection and calculation of focus score and detection of FLS, lack of concordance for the presence of duct dilation and (less for) fibrosis. In more than 12% of the cases, the second evaluation by trained pathologists led to a diagnosis change.[26] Moreover, some life habits may be confusing factors. For example, cigarette smoking is negatively associated with FS > 1 in lower lip biopsy in patients with pSS, and may also negatively influence the presence of anti-SSA/Ro antibodies in circulating blood.[27] A protocol published in 2011[28] by the Sjögren's International Clinical Collaborative Alliance (SICCA) highlighted that these foci must occur adjacent to normal appearing acini.

According to literature review, LSG biopsy is performed less frequently in EOpSS patients than in adults, and in some studies it has been not reported.[6,29] In older persons, the presence of age-related biopsy findings may realize confounding features. For example, some investigators found that acinar atrophy and fibrosis is possible in healthy individuals aged over 65 years, FS was higher in older age groups, and the increased area of fat tissue in the LSG biopsies is not specific associated with pSS but is a selective feature of ageing.[14,30–33] On the other hand, Kihuchi et al. highlighted that, while there were significant differences in frequency of acinar atrophy between the sublingual and submandibular salivary glands of subjects younger and older than 75, the labial glands showed no such variation.[34] The use of a grading score taking the destruction of acinar tissue and fibrosis into account (such as the one proposed by Tarpley et al. and listed in Table 3) may be of greater usefulness in the elderly patient when pSS is suspected.

Compared to healthy controls, the LSG biopsies of pSS patients show more acinar atrophy and fibrotic changes.[36,37] More recently, the Sjögren's histopathology workshop performed by the EULAR Sjogren's Syndrome Experimental and Translational Investigative Alliance (ESSENTIAL) study group provided a consensus guidance for the use of LSG histopathology in clinical trials. The diagnostic importance of foci that are adjacent to normal parenchyma was emphasized and several recommendations were proposed. However, the level of these recommendations is low.[38]

Table 4 – The most common extraglandular manifestations of pSS.

Organ or system	Signs and symptoms
Joints	Arthralgia and arthritis.
Skin	Annular erythema, palpable purpura (vasculitis and cryoglobulinaemia), xerosis.
Haematologic	Leucopenia, neutropenia, thrombocytopenia, anaemia, cryoglobulinaemia, monoclonal proteins, MGUS, and mucosa-associated lymphoid tissue lymphoma.
Muscle	Myalgia and myositis.
Ears, nose, and throat	Otitis media, nosebleeds, crusting damage, poor sense of smell, impeded swallowing, and hearing loss.
Bronchi	Recurrent bronchitis, bronchiolites, bronchial hyper-reactivity, and dry cough.
Lung	Interstitial lung disease (NSIP, LIP, UIP, and OP), pleurisy, and pleural effusion.
Peripheral nervous system	Sensory and combined sensory-motor neuropathy, mononeuropathy with cranial nerve involvement, mononeuropathy, multiple mononeuropathy (mononeuritis multiplex) and demyelinating syndromes, including Smith-Magenis-like syndrome and autonomic neuropathies, and restless leg syndrome.
Central nervous system	Focal lesions, changes with pyramidal symptoms, encephalopathy, changes typical for aseptic meningitis, transverse myelitis, optic neuropathy, and demyelinating symptoms (Smith–Magenis-like syndrome). Cognitive impairment.
Kidney	Interstitial nephritis with distal renal tubular acidosis, glomerulonephritis with coexisting cryoglobulinaemia, and urolithiasis.
Gastrointestinal tract	Gastro-oesophageal reflux, gastritis, primary biliary cirrhosis,* autoimmune hepatitis,* and cholelithiasis.
Cardiovascular system	Vasculitis (leukocytoclastic vasculitis), purpura, livedo reticularis, Raynaud's phenomenon, pericarditis, carditis, pleuritis, and pulmonary arterial hypertension.
Other	Autoimmune thyroiditis[a]

MGUS: monoclonal gammopathy of undetermined significance; NSIP: nonspecific interstitial pneumonia; LIP: lymphocytic interstitial pneumonia; UIP: usual interstitial pneumonia; .OP: organizing pneumonia.

[a] Autoimmune diseases commonly accompanying primary Sjögren's syndrome.

As these data highlight, there is a strong need to achieve a consensus among experts on how to differentiate pSS lesions from the age-related degenerative and atrophic lesions of salivary glands. Other histopathological markers besides FS have been proposed, but whether and how these markers may contribute to classification and diagnosis of EOpSS remains unclear. In the same way, salivary gland ultrasonography to the diagnosis of pSS showed very promising results, but data regarding EOpss are little more than anecdotal.[39,40]

3. *Immunological markers*: The antibodies most frequently present in pSS are antibodies against the small ribonucleoproteins SSA/Ro and SSB/La. In 1999, some invetigators highlighted that patients diagnosed before 45 years of age have higher anti-SSA and SSB autoantibody concentrations (62.5%) than patients with EOpSS (20.8%).[41] More recently, a lower frequency of anti-SSA and anti-SSB was confirmed in patients with an elderly diagnosis (>70 years) from the Big Data International Sjögren Cohort.[42,43]

The absence of the auto-antibodies included in classification criteria in biopsy-proven patients characterizes the seronegative subset of pSS by definition. Seronegative pSS is not uncommon. According to data from Sjögren Big Data Project, approximately 20% of pSS patients are seronegative.[44] In comparison with seropositive pSS, seronegative patients have an older age at diagnosis, a higher frequency of fatigue and pain, a lower frequency of systemic manifestations, a lower risk of lymphoma. No significant differences in results of signs and symptoms of glandular involvement are present.[44–47] In particular, the possibility that one-third of patients with chronic fatigue syndrome having sicca symptoms fulfil criteria for SS,[45] and that the frequency of fatigue and chronic pain could favour the diagnosis of so-called "functional somatic syndromes"[43] in older patients with seronegative pSS, deserve to be highlighted for the implications they may have in clinical practice.

4. *Extraglandular manifestations*: Beyond sicca syndrome, pSS is a complex systemic disease. The most common extraglandular manifestations are listed in Table 4.

As known, both AECG and ACR/EULAR criteria emphasized the importance of the impairment of the salivary and lachrymal functions, and did not adequately considered the extraglandular manifestations of pSS. In the clinical practice, some patients may have systemic manifestations unrelated to sicca syndrome.[48] This seems particularly frequent in patients with EOpSS. In the largest reported cohort, these patients showed a higher risk for presenting activity at articular, pulmonary, muscular and peripheral nervous system domains.[43] When LSG biopsy is performed, an association between severe systemic manifestations and high FS is usually found, while association between systemic manifestations and immunological markers is more weak.[49–52]

Literature review

A comprehensive literature search was conducted in Medline and PubMed bibliographic databases in order to identify all the studies on cohorts of patients with EopSS. This systematic review was made on 31 October 2019 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following main search terms were used: primary Sjogren syndrome AND/OR elderly onset Sjogren syndrome. References from all of the selected studies were also examined, while reviews, abstracts, and studies on secondary Sjogren's syndrome were excluded.

Table 5 – Data in the four literature studies on EOpSS patients.

Study	Patients (NO.)	Criteria	ANA Test (%)	ANTISSA	Positive LSG biopsy
Tishler et al.[29]	17	San Diego criteria	36	12	NR
Garcia-Carrasco et al.[53]	43	ECSG, 1993	65	23	76[a]
Botsios et al.[54]	21	AECG, 2002	85.7	66.7	52.3[b]
Chebbi et al.[6]	18	AECG, 2002	44.4	33.3	NR

Xerostomia (%)	Xeropthalmia (%)	Articular (%)	Neurological (%)	Pulmonary (%)	Haematological (%)
100	94	94	16	NR	NR
98	91	23	12	16	NR
71.4	76.1	66.7	4.7	4.7	14.2
100	100	88.8	44.4	11.1	5.5

NR: non reported; ECSG: European Community Study Group.
[a] LSG biopsy was performed only in 25 patients.
[b] LSG biopsy was performed in all 21 patients.

Four studies were identified, reporting on cohorts of patients with EopSS, totaling 99 patients.[6,29,53,54] In these studies, disease onset was determined based on the occurrence of symptoms strongly suggestive of pSS; in three of the studies, elderly onset was set at age 65 years, but in the García-Carrasco et al. study, it was set at 70 years. Each study used the diagnostic criteria commonly being used at the time of publication. The most significant data of these four studies are listed in Table 5.

A high percentage of patients with ANA positivity presented in the Botsios et al. cohort; this was only partially confirmed in the other three studies. With the exception of Chebbi et al. data, the presence of anti-SSA and anti-SSB was similar in all the studies. Differences between studies were found in clinical characteristics of patients, with neurological and pulmonary involvement more often observed in the Chebbi et al. cohort and Raynaud's phenomenon more frequently observed in the Botsios et al. LSG biopsies were performed in two cohorts. Lastly, when the authors compared older-group data with younger-group data, differences were only highlighted in the study by Chebbi et al. In this study, pulmonary involvement was more frequent in the older group (although not statistically significant), whereas the difference in levels of ANA, anti-SSA, and anti-SSB was statistically higher in the younger group. In the other three studies, clinical and laboratory results of EOpSS patients were quite similar to those in younger patients. Demographic factors and differences in genetic predisposition have a potential role in explaining these differences.

In the last five years, the Sjögren Big Data Project created a multicentre registry that today includes nearly 12,000 patients from the 5 continents.[55] Until today, according to our best knowledge, this consortium has not yet published final figures regarding EOpSS patients.[42,43]

Discussion and conclusions

As this review article highlighted, diagnosis of EOpSS has several unmet needs.

Firstly, although some epidemiological studies have suggested that the prevalence of pSS in the elderly population is significantly higher (between five to eight times) than in other age groups, it is possible that these suggestions are misleading. Indeed, cardinal sicca symptoms, which are the hallmark of the disease, may be attributed to ageing and/or medications.[56] On the other hand, it is well-known that some age-related immunological, test and histopathological findings may represent confounding factors in the clinical practice. For example, seronegative pSS seems more frequent in elderly patients than in other age groups. In these patients, the lack of LSG biopsy can favour completely different diagnoses, functional somatic syndromes among these. On the other hand, the same LSG biopsy can give false-positive results in healthy persons or not always easily decipherable findings in elderly patients with EOpSS.

Secondly, specificity and sensitivity of AECG and ACR/EULAR classification criteria should be validated also in patients with EOpSS, even taking into account that some extra-glandular manifestations when associated with specific serological or histopathological findings may be expression of EOpSS, although sicca syndrome is absent.

Finally, our review of the literature highlighted that studies focused on patients with EOpSS are scarce. In an ageing world, these studies should be much more numerous than those available. In the absence of more extensive case studies, many of the doubts and criticalities regarding the correct diagnostic process in patients with suspicion of EOpSS remain entirely entrusted to the experience of the clinician.

Founding source

None.

Conflict of interest

The author declares no conflict of interest.

REFERENCES

1. Moerman RV, Bootsma H, Kroese FG, Vissink A. Sjögren's syndrome in older patients: aetiology, diagnosis and management. Drugs Aging. 2013;30:137–53.

2. Manzo C, Maslinska M. Primary Sjögren's Syndrome in the elderly: does age of onset make a difference? EMJ Rheumatol. 2018;5:75–82.
3. Drosos AA, Andonopoulos AP, Costopoulos JS, Papadimitriou CS, Moutsopoulos HM. Prevalence of primary Sjögren's syndrome in an elderly population. Br J Rheumatol. 1988;27:123–7.
4. Haugen AJ, Peen E, Hultén B, Johannessen AC, Brun JG, Halse AK, et al. Estimation of the prevalence of primary Sjögren's syndrome in two age-different community-based populations using two sets of classification criteria: the Hordaland Health Study. Scand J Rheumatol. 2008;37:30–4.
5. Maciel G, Crowson CS, Matteson EL, Cornec D. Prevalence of primary sjögren's syndrome in a US population-based cohort. Arthritis Care Res (Hoboken). 2017;69:1612–6.
6. Chebbi W, Ben Salem W, Klii R, Kessomtini W, Jerbi S, Sfar MH. Primitive Sjögren syndrome in the elderly: clinical and immunological characteristics. Pan Afr Med J. 2015;20:8.
7. Patel R, Shahane A. The epidemiology of Sjögren's syndrome. Clin Epidemiol. 2014;6:247–55.
8. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: a revised version of the european criteria proposed by the American-European consensus group. Ann Rheum Dis. 2002;61:554–8.
9. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 ACR-EULAR classification criteria for primary Sjogren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheumatol. 2017;69:35–45.
10. Vitali C, Del Papa N. Classification and diagnostic criteria in Sjogren's syndrome: a long-standing and still open controversy. Ann Rheum Dis. 2017;76:1953–4.
11. Baer AN, Walitt B. Sjogren's syndrome and other causes of sicca in the older adult. Clin Geriatr Med. 2017;33:87–103.
12. Hay EM, Thomas F, Pal B, Hajeer A, Chambers H, Silman AJ. Weak association between subjective symptoms or and objective testing for dry eyes and dry mouth: results from a population based study. Ann Rheum Dis. 1998;57:20–4.
13. Schein OD, Munoz B, Tielsch JM, Bandeen-Roche K, West S. Prevalence of dry eye among the elderly. Am J Opthalmol. 1997;124:723–8.
14. Syrjanen S. Age-related changes in structure of labial minor salivary glands. Age Ageing. 1984;13:159–65.
15. Lin PY, Tsai SY, Cheng CY, Liu JH, Chou P, Hsu WM. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shilpai Eye study. Opthalmology. 2003;110:1096–101.
16. Maslinska M, Manzo C. Sindrome di Sjogren primaria nell' anziano: l' età di insorgenza realizza differenze? G It Reumatol Clin. 2018;1:31–44.
17. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev. 2011;10:430–9.
18. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, et al. Prevalence, determinants and patterns of multimorbidity in primary care. A systematic review of observational studies. PLOS ONE. 2014;9:e102149.
19. Menewer K, Akdeniz M, Kavukcu E. Assessment of comorbidity and use of prescription and non prescription drugs in patients over 65 years attending family medicine outpatient clinics. Gerontol Geriatr Med. 2019:5, http://dx.doi.org/10.1197/233372149874274.
20. Rankin A, Cadogan CA, Hughes C. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev. 2018:CD008165.
21. Smidt D, Torpet LA, Nauntofte B, Heegaard KM, Pedersen AM. Association between labial and whole salivary flow rates, systemic diseases and medications in a sample of older people. Community Dent Oral Epidemiol. 2010;38:422–35.
22. Wolff A, Joshi RK, Ekström J, Aframian D, Pedersen AM, Proctor G, et al. A guide to medications inducing salivary gland dysfunction, xerostomia, and subjective sialorrhea: a systematic review sponsored by the World Workshop on Oral Medicine VI. Drugs R D. 2017;17:1–28.
23. Barone F, Campos J, Bowman S, Fisher BA. The value of histopathological examination of salivary gland biopsies in diagnosis, prognosis and treatment of Sjögren's Syndrome. Swiss Med Wkly. 2015;16:145, http://dx.doi.org/10.4414/smw.2015.14168, w14168.
24. Kroese FGM, Haacke EA, Bombardieri M. The role of salivary gland histopathology in primary Sjogren's syndrome: promises and pitfalls. Clin Exp Rheumatol. 2018;36 Suppl. 112:S222–33.
25. Vivino FB, Gala I, Hermann GA. Change in final diagnosis on second evaluation of labial minor salivary gland biopsies. J Rheumatol. 2002;29:938–44.
26. Costa S, Quintin-Roue I, Lesourd A, Jousse-Joulin S, Berthelot JM, Hachulla E, et al. Reliability of histopathological salivary gland biopsy assessment in Sjogren's syndrome: a multicenter cohort study. Rheumatology (Oxford). 2015;54:1056–64.
27. Manthorpe R, Benoni C, Jacobsson L, Kirtava Z, Larsson A, Liedholm R, et al. Lower frequency of focal lip sialadenitis (focus score) in smoking patients. Can tobacco diminish the salivary gland involvement as judged by histological examination and anti-SSA/Ro and anti-SSB/La antibodies in Sjögren's syndrome? Ann Rheum Dis. 2000;59:54–60.
28. Shiboski SC, Shiboski CH, Criswell LA, Baer A, Challacombe S, Lanfranchi H, et al. American College of Rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the SICCA cohort. Arthritis Care Res (Hoboken). 2012;64:475–87.
29. Tishler M, Yaron I, Shirazi I, Yaron M. Clinical and immunological characteristics of elderly onset Sjögren's syndrome: a comparison with younger onset disease. J Rheumatol. 2001;28:795–7.
30. Radfar L, Kleiner DE, Fox PC, Pillemer SR. Prevalence and clinical significance of lymphocytic foci in minor salivary glands of health volunteers. Arthritis Rheum. 2002;47: 520–4.
31. Lindahl G, Hedfors E:. Focal lymphocytic infiltrates of salivary glands are not confined to Sjögren's syndrome. Scand J Rheumatol Suppl. 1986;61:52–5.
32. Vered M, Buchner A, Boldon P, Dayan D:. Age-related histomorphometric changes in labial salivary glands with special reference to the Acinar component. Exp Gerontol. 2000;35:1075–84.
33. Leehan Km, Pezant Np, Rasmussen A, Grundahl K, Moore JS, Radfar L, et al. Fatty infiltration of the minor salivary glands is a selective feature of aging but not Sjögren's syndrome. Autoimmunity. 2017;50:451–7.
34. Kihuchi M, Inagaki T, Ogawa K, Banno S, Mastumoto Y, Ueda R, et al. Histopathological investigation of salivary glands in the asymptomatic elderly. Arch Gerontol Geriatr. 2004;38:131–8.
35. Tarpley Tm Jr, Anderson Lg, White Cl:. Minor salivary gland involvement in Sjögren's syndrome. Oral Surg Oral Med Oral Pathol. 1974;37:64–74.
36. Leehan Km, Pezant Np, Rasmussen A, Grundahl K, Moore JS, Radfar L, et al. Minor salivary gland fibrosis in Sjögren's syndrome is elevated associated with focus score and not solely a consequence of aging. Clin Exp Rheumatol. 2018;36 Suppl. 112:80–8.
37. Llamas-Gutiérrez FJ, Reyes E, Martínez B, Hernández-Molina G. Histopathological environment besides the focus score in Sjögren's syndrome. Int J Rheum Dis. 2014;17:898–903.
38. Fisher BA, Jonsson R, Daniels T, Bombardieri M, Brown RM, Morgan P, et al. Standardisation of labial salivary gland

histopathology in clinical trials in primary Sjögren's syndrome. Ann Rheum Dis. 2017;76:1161–8.
39. Cornec D, Jousse-Joulin S, Pers JO, Marhadour T, Cochener B, Boisramé-Gastrin S, et al. Contribution of salivary gland ultrasonography to the diagnosis of Sjögren's syndrome. Arthritis Rheum. 2013;65:216–25.
40. Takagi Y, Nakamura H, Sumi M, Shimizu T, Hirai Y, Horai Y, et al. Combined classification system based on ACR/EULAR and ultrasonographic scores for improving the diagnosis of Sjögren's syndrome. PLOS ONE. 2018;13:e0195113.
41. Haga HJ, Jonsson R. The influence of age on disease manifestations and serological characteristics in primary Sjögren's syndrome. Scand J Rheumatol. 1999;28:227–32.
42. Retamozo S, Brito-Zerón P, Zeher M, Sivils KL, Seror R, Mandl T, et al. Epidemiologic subsets drive a differentiated clinical and immunological presentation of primary Sjögren Syndrome: analysis of 9302 patients from the Big Data International Sjögren Cohort. Arthritis Rheumatol. 2017;69:209.
43. Brito-Zeron P, Retamozo S, Ramos-Casals M. Phenotyping Sjogren's syndrome: towards a personalised management of the disease. Clin Exp Rheumatol. 2018;36 Suppl. 112:S198–209.
44. Brito-Zeron P, Acar-Denizli N, Zeher M, Rasmussen A, Seror R, Theander E, et al. How does primary Sjögren's syndrome present in biopsy-proven patients without circulating Ro/La autoantibodies? Characteristics at diagnosis of 2073 patients from the Sjögren big data project. Arthritis Rheumatol. 2016;68(S10):2682.
45. Nishikai M, Akiya K, Tojo T, Onoda N, Tani M, Shimizu K. "Seronegative" Sjögren's syndrome manifested as a subset of chronic fatigue syndrome. Br J Rheumatol. 1996;35:471–4.
46. Quartuccio L, Baldini C, Bartoloni E, Priori R, Carubbi F, Corazza L, et al. Anti-SSA/SSB-negative Sjögren's syndrome shows a lower prevalence of lymphoproliferative manifestations, and a lower risk of lymphoma evolution. Autoimmun Rev. 2015;14:1019–22.
47. Brito-Zeron P, Acar-Denizli N, Ng WF, Zeher M, Rassmussen A, Mandl T, et al. How imunological profile drives clinical phenotype of primary Sjogren's syndrome at diagnosis: analysis of 10,500 patients (Sjogren Big Data Project). Clin Exp Rheumatol. 2018;36 Suppl. 112:S102–12.
48. Brito-Zeron P, Theander E, Baldini C, Seror R, Retamozo S, Quartuccio L, et al. Early diagnosis of primary Sjögren's syndrome: Eular-SS task force clinical recommendations. Expert Rev Clin Immunol. 2016;12:137–56.
49. Daniels TE, Whitcher JP. Association of patterns of labial salivary glands inflammation with keratoconjunctivitis sicca Analysis of 618 patients with suspected Sjogren's syndrome. Arthritis Rheum. 1994;6:869–77.
50. Carubbi F, Alunno A, Cipriani F, Di Benedetto P, Ruscitti P, Berardicurti O, et al. Is minor salivary gland biopsy more than a diagnostic tool in primary Sjogren's syndrome? Association between clinical, histopathological, and molecular features: a retrospective study. Semin Arthritis Rheum. 2014;44:314–24.
51. Risselada AP, Hair MDE, Kruize AA, Bijlsma JWJ, van Roon JAG. Lymphocytic focus score as a prognostic tool. Ann Rheum Dis. 2015;74:e31.
52. Bouma HR, Bootsma H, van Nimwegen JF, Haacke EA, Spijkervet FK, Vissink A, et al. Aging and immunopathology in Primary Sjögren's Syndrome. Curr Aging Sci. 2015;8:202–13.
53. García-Carrasco M, Ramos-Casals M, Rosas J, Pallarés L, Calvo-Alen J, Cervera R, et al. Primary Sjögren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore). 2002;81:270–80.
54. Botsios C, Furlan A, Ostuni P, Sfriso P, Andretta M, Ornetto F, et al. Elderly onset of primary Sjögren's syndrome: clinical manifestations, serological features and oral/ocular diagnostic tests. Comparison with adult and young onset of the disease in a cohort of 336 Italian patients. Joint Bone Spine. 2011;78:171–4.
55. Acar-Denizli N, Kostov B, Ramos-Casals M. The Big Data Sjögren Consortium: a project for a new data science era. Clin Exp Rheumatol. 2019;37 Suppl. 118:19–23.
56. Al-Hashimi I. Xerostomia secondary to Sjögren's syndrome in the elderly: recognition and management. Drugs Aging. 2005;22:887–99.