ARP Rheumatology 2022;4:268-270

EDITORIAL

Diagnosing Sjögren's disease in 2023: what is new?

Bandeira M[1,2], Romão VC[1,2,3]

Sjögren's Disease (SjD) is a complex systemic rheumatic disease targeting primarily exocrine glands, particularly salivary and lacrimal glands. Its hallmark is ocular and oral dryness, present in around 98% of patients, with 89% reporting both[1]. Arthralgia and fatigue are also commonly observed, followed by salivary gland swelling, whereas systemic extra-glandular involvement including neurological, renal, vascular or pulmonary manifestations have been considered to be present in up to one third of patients[1]. Nonetheless, this figure has recently been questioned, as thorough clinical assessment often reveals a number of extra-glandular features not previously recognized as part of SjD[2]. Chronic fatigue is a complex complaint present in up to 80% of patients with SjD. It is multidimensional, different from ordinary lethargy and has a significant impact on health-related quality of life[3]. A recent study showed pain and fatigue as the major predictors of decreased quality of life in SjD patients, independent of disease activity, age, literacy, disability and fibromyalgia[4]. Recently published evidence also suggests metabolic factors as important mediators for high symptom burden in SjD[5].

SjD affects mainly middle-aged women (female: male ratio of 9:1). It has been classically considered one of the most frequent inflammatory RMDs, but this notion has been recently questioned[6]. In fact, the estimated prevalence of SjD has been of is 39 in 100 000 individuals (0.04%), a figure below the rare disease threshold[6]. This remains a question to be answered and a relevant one, as rare orphan diseases tend to have distinct features for patient support and benefits.

In order to measure outcomes in SjD, disease activity scores were developed by the EULAR Sjögren's task force. The EULAR SjD Disease Activity Index (ESSDAI) evaluates systemic disease activity, and a few studies have met the primary endpoint using this outcome measure. Nonetheless, ESSDAI is poorly related with EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), and other PROs such as the Profile of Fatigue and Discomfort-Sicca Symptoms Inventory (PROFAD-SSI), thus limiting the scope of disease evaluation from the patient perspective. The cause for this discrepancy is elusive to this date and deserves further study. In order to overcome this issue, STAR was proposed as a composite outcome measure that provides a comprehensive, multidimensional overview of SjD impact[7].

Notably, SjD not only seems to be underdiagnosed but may currently have a delayed diagnosis based on its non-specific symptoms and the common misuse of classification criteria, that require low-functioning glands, for diagnosis. Sicca symptoms and dryness objective scores may be a sign of long-lasting untreated inflammatory glandular involvement. It has been shown that sicca symptoms are more frequent in patients diagnosed later in life, with the frequency of oral dryness increasing according to the age of diagnosis[8,9]. Age seems to influence SjD expression, with a lower prevalence of glandular and lymph node involvement and higher frequency of pulmonary and peripheral nerve disease in older patients at diagnosis[8]. There is, in fact, growing evidence on the recognition of different disease patterns. There has been a definition of four subgroups regarding symptoms: low symptom burden, high symptom burden, dryness dominant with fatigue, and pain dominant with fatigue; which seem to have meaningful repercussions in treatment response[10]. Stratification of patients has been studied vastly for the past few years. It is currently also recognized that there is a non-sicca subgroup that seems to consist of younger, predominantly anti-SSA-positive patients who tend to have more systemic disease, mainly with a higher frequency of activity in the constitutional, cutaneous, renal, haematological and biological ESSDAI domains[9,11]. This subgroup is of particular importance, we believe, as patients are less likely to meet classification criteria and, conversely, may significantly benefit from timely and adequate diagnosis and treatment.

The hallmark histologic feature of SjD is salivary and lacrimal glands lymphocytic infiltration which helps to establish the diagnosis. The diagnosis of SjD is thus based on clinical features, specific autoantibodies (anti-Ro/SSA, anti-La/SSB) and salivary gland evaluation, both by minor salivary gland biopsy as well as salivary gland ultrasound (SGUS). In fact, many advances have been made in SGUS as of late. SGUS seems to

[1] Rheumatology Department, CHULN, Centro Académico de Medicina de Lisboa (CAML); [2] Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, CAML; [3] Clínica Universitária de Reumatologia, Faculdade de Medicina, Universidade de Lisboa, CAML.

Correspondence to Matilde Bandeira
E-mail: bandeira.matilde@gmail.com

be a valuable tool in SjD diagnosis, with a potential to replace other factors in SjD classification criteria[12]. When added to the current classification criteria, ultrasonography increased the criteria's sensitivity and seemed to perform similarly when replacing the ocular staining score, Schirmer's test, or unstimulated whole saliva flow[12]. There are other novelties within imaging currently being studied with some interesting results such as shear-wave elastography of major salivary glands[13] and ultra-high frequency ultrasonography of minor salivary glands[14] that may potentially also have good diagnostic value, but need additional testing. Furthermore, ultrasonographic evaluation of the salivary glands may raise suspicion of lymphoma and be used as guidance for additional assessment of this diagnosis such as ultrasound-guided parotid biopsy. This biopsy has, indeed, been proven to be a rather safe and well-tolerated procedure, which may be the foundation for new studies on its utility for SjD diagnosis[15]. Ultrasound may also play a role in monitoring SjD activity and treatment efficacy[16]. Curiously, there is also some evidence showcasing SGUS as a method to stratify SjD patients, considering a positive SGUS correlated with longer disease duration, higher ESSDAI, anti-SSA and anti-SSB antibodies and higher levels of both IgG and rheumatoid factor[17].

The most severe complication of SjD is lymphoma, which happens in around 5-10% of patients, making malignancies one of the leading causes of death in SjD, along with cardiovascular diseases and infections. Despite these comorbidities, there doesn't seem to be an increased risk of all-cause mortality in primary SjD except for older patients with extra-glandular involvement, hypocomplementemia, cryoglobulinemia or parotid swelling, that require closer follow-up[18]. Recent evidence, however, shows an increased risk for other non-hematologic neoplastic diseases in SjD patients[19].

There are specific autoantibodies that are considered immunological markers for SjD. Up to 75% of patients are anti-Ro/SSA positive and up to 50% anti-La/SSB positive[11]. The presence of anti-Ro/SSA and anti-La/SSB antibodies correlated with earlier disease onset, more severe glandular manifestations and extra-glandular systemic involvement[11]. Anti-Ro52, specifically, seems to correlate to some clinical features such as ESSDAI, hypergammaglobulinemia and focus score>1. In a recent study, a linear correlation between anti-Ro52 concentration and ESSDAI was observed[20]. Antinuclear antibodies and rheumatoid factor are also common serological findings in these patients and may be prognostic markers. For instance, rheumatoid factor has been associated with a more severe disease course and was defined as a risk factor for lymphoma[21]. Antinuclear antibodies-positive patients seem to be younger and also have a higher ESSDAI[11].

Some other antibodies have been studied in order to provide supplementary aid for the diagnosis of SjD in patients negative for both SSA and SSB, the so-called 'seronegative' SjD. Anti-NuMA antibodies, despite uncommon, have been associated mainly with SjD and systemic lupus erythematosus, and seem to confer a good prognosis[22]. Anti-NOR90 have also been, in some series, associated with SjD, although particularly in overlap syndromes such as SjD-rheumatoid arthritis and SjD-systemic sclerosis. Antibodies anti-muscarinic type 3 receptor seem to further enhance sensitivity and specificity for SjD diagnosis[23]. Furthermore, their titres correlated with ocular dryness, glandular dysfunction and ESSDAI, particularly the haematological and biological domains.

Despite there being some novel therapies under investigation, SjD diagnosis and treatment are still a challenge. The successful management of sicca complaints and fatigue are two of the most important unmet needs for the patient's quality of life[24]. A timely diagnosis is thus crucial for the institution of treatment. This requires a high suspicion level when facing typical organ involvements, never forgetting the different phenotypes of this disease, including the possibility of the lack of sicca symptoms. That being said, the present is exposing great innovation and research in SjD and the future is incredibly promising in terms of improving our ability to assist SjD patients.

REFERENCES

1. Mariette X, Criswell LA. Primary Sjögren's Syndrome. N Engl J Med. 2018;378(10):931-939. doi:10.1056/NEJMcp1702514
2. Retamozo S, Acar-Denizli N, Rasmussen A, et al. Systemic manifestations of primary Sjögren's syndrome out of the ESSDAI classification: prevalence and clinical relevance in a large international, multi-ethnic cohort of patients. Clin Exp Rheumatol. 2019;37 Suppl 1(3):97-106.
3. Mengshoel AM, Norheim KB, Omdal R. Primary Sjögren's syndrome: fatigue is an ever-present, fluctuating, and uncontrollable lack of energy. Arthritis Care Res (Hoboken). 2014;66(8):1227-1232. doi:10.1002/acr.22263
4. Dias LH, Miyamoto ST, Giovelli RA, de Magalhães CIM, Valim V. Pain and fatigue are predictors of quality of life in primary Sjögren's syndrome. Adv Rheumatol (London, England). 2021;61(1):28. doi:10.1186/s42358-021-00181-9
5. Pucino V, Turner JD, Nayar S, et al. Sjögren's and non-Sjögren's sicca share a similar symptom burden but with a distinct symptom-associated proteomic signature. RMD open. 2022;8(1). doi:10.1136/rmdopen-2021-002119
6. Cornec D, Chiche L. Is primary Sjögren's syndrome an orphan disease? A critical appraisal of prevalence studies in Europe. Ann Rheum Dis. 2015;74(3):e25. doi:10.1136/annrheumdis-2014-206860
7. Seror R, Baron G, Camus M, et al. Development and preliminary validation of the Sjögren's Tool for Assessing Response (STAR): a consensual composite score for assessing treatment effect in primary Sjögren's syndrome. Ann Rheum Dis. Published online April 2022. doi:10.1136/annrheumdis-2021-222054

8. Retamozo S, Acar-Denizli N, Horváth IF, et al. Influence of the age at diagnosis in the disease expression of primary Sjögren syndrome. Analysis of 12,753 patients from the Sjögren Big Data Consortium. Clin Exp Rheumatol. 2021;39 Suppl 1(6):166-174. doi:10.55563/clinexprheumatol/egnd1i
9. Chatzis LG, Koulouri V, Baldini C, et al. Clinical and laboratory findings of primary Sjögren's syndrome patients without sicca symptoms. Clin Exp Rheumatol. Published online October 2022. doi:10.55563/clinexprheumatol/gqvyus
10. Jessica R T*, Nadia H-T*, Dennis W L*, et al. Symptom-based stratification of patients with primary Sjögren's syndrome: multi-dimensional characterisation of international observational cohorts and reanalyses of randomised clinical trials. Lancet (London, England). Published online 2019. doi:https://doi.org/10.1016/S2665-9913(19)30042-6
11. Brito-Zerón P, Acar-Denizli N, Ng W-F, et al. How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren Big Data Project). Clin Exp Rheumatol. 2018;36 Suppl 1(3):102-112.
12. van Nimwegen JF, Mossel E, Delli K, et al. Incorporation of Salivary Gland Ultrasonography Into the American College of Rheumatology/European League Against Rheumatism Criteria for Primary Sjögren's Syndrome. Arthritis Care Res (Hoboken). 2020;72(4):583-590. doi:10.1002/acr.24017
13. Prata AR, Freitas JP, Marques ML, et al. Shear-Wave Elastography Evaluation of Major Salivary Glands in Primary Sjögren's Syndrome. ARP Rheumatol. 2022;1(ARP Rheumatology, no3 2022):197-204.
14. Ferro F, Izzetti R, Vitali S, et al. Ultra-high frequency ultrasonography of labial glands is a highly sensitive tool for the diagnosis of Sjögren's syndrome: a preliminary study. Clin Exp Rheumatol. 2020;38 Suppl 1(4):210-215.
15. Zabotti A, Pegolo E, Giovannini I, et al. Usefulness of ultrasound guided core needle biopsy of the parotid gland for the diagnosis of primary Sjögren's syndrome. Clin Exp Rheumatol. 2022;40(12):2381-2386. doi:10.55563/clinexprheumatol/5n49yj
16. Fisher BA, Everett CC, Rout J, et al. Effect of rituximab on a salivary gland ultrasound score in primary Sjögren's syndrome: results of the TRACTISS randomised double-blind multicentre substudy. Ann Rheum Dis. 2018;77(3):412-416. doi:10.1136/annrheumdis-2017-212268
17. Mossel E, van Nimwegen JF, Stel AJ, et al. Clinical Phenotyping of Primary Sjögren Syndrome Patients Using Salivary Gland Ultrasonography: Data From the RESULT Cohort. J Rheumatol. 2021;48(5):717-727. doi:10.3899/jrheum.200482
18. Singh AG, Singh S, Matteson EL. Rate, risk factors and causes of mortality in patients with Sjögren's syndrome: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford). 2016;55(3):450-460. doi:10.1093/rheumatology/kev354
19. Zhong H, Liu S, Wang Y, et al. Primary Sjögren's syndrome is associated with increased risk of malignancies besides lymphoma: A systematic review and meta-analysis. Autoimmun Rev. 2022;21(5):103084. doi:10.1016/j.autrev.2022.103084
20. Nakamura H, Morimoto S, Shimizu T, Takatani A, Nishihata S-Y, Kawakami A. Clinical manifestations in anti-Ro52/SS-A antibody-seropositive patients with Sjögren's syndrome. Immunol Med. 2021;44(4):252-262. doi:10.1080/25785826.2021.1919342
21. Nocturne G, Virone A, Ng W-F, et al. Rheumatoid Factor and Disease Activity Are Independent Predictors of Lymphoma in Primary Sjögren's Syndrome. Arthritis Rheumatol (Hoboken, NJ). 2016;68(4):977-985. doi:10.1002/art.39518
22. Arcani R, Bertin D, Bardin N, et al. Anti-NuMA antibodies: clinical associations and significance in patients with primary Sjögren's syndrome or systemic lupus erythematosus. Rheumatology (Oxford). 2021;60(9):4074-4084. doi:10.1093/rheumatology/keaa881
23. Mona M, Mondello S, Hyon JY, et al. Clinical usefulness of anti-muscarinic type 3 receptor autoantibodies in patients with primary Sjögren's syndrome. Clin Exp Rheumatol. 2021;39(4):795-803. doi:10.55563/clinexprheumatol/gy6udz
24. Romão VC, Talarico R, Scirè CA, et al. Sjögren's syndrome: state of the art on clinical practice guidelines. RMD open. 2018;4(Suppl 1):e000789. doi:10.1136/rmdopen-2018-000789