Original article

PRIMARY SJÖGREN'S SYNDROME: CLINICOPATHOLOGIC REVIEW OF 20 CASES USING THE ACR/EULAR CRITERIA

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ABSTRACT

OBJECTIVE: Sjögren's Syndrome (SS) is a systemic autoimmune disorder that may present a diagnostic challenge in low and middle-income settings. The American College of Rheumatologists (ACR) and European League against Rheumatism (EULAR) in 2016 developed diagnostic criteria. However, a dearth of literature exists on the clinico-pathologic pattern and the diagnostic criteria used to diagnose primary Sjögren's syndrome in Nigeria.

METHODOLOGY: This is a single-center retrospective review of 20 cases seen at the Oral Medicine clinic that underwent an evaluation for suspected primary Sjogren's Syndrome (pSS). We report the clinical and histopathology of the 20 cases, and evaluated these cases based on the diagnostic criteria by the ACR/EULAR.

RESULTS: The survey revealed a series of 20 cases. There were 14 females and 6 males with F: M ratio of 2.3:1. The study participants were from 18 to 78 years, with a mean age of 46.9 (± 15.9). Of all the cases reviewed, about 35% (n=7) met the ACR/EULAR criteria, and oral symptoms of dry mouth, 19(95%), was the most common symptom seen. Symptoms of persistent dry eyes and a feeling of gritty sensations in the eyes were equally common symptoms in the ocular region in 9(45%). Atypical symptoms in form of cough and sore throat resulting from dry mucosa were also reported in 15% (n=3) of cases reviewed.

CONCLUSION: Oral symptoms appear to be relatively common in the cases reviewed, while the ACR/EULAR criteria confirmed diagnosis in a third of the cases evaluated.

Keywords: Sjögren's syndrome, ACR/ EULAR criteria, Xerostomia, Xerophthalmia

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INTRODUCTION

Sjögren's Syndrome (SS) is a systemic autoimmune disorder that involves progressive destruction of exocrine glands leading to dryness of the eyes and mouth and B-cell hyperactivity.[1,2] The resulting inflammation is characterised by focal lymphocytic infiltration marked by a broad spectrum of clinical and serological manifestations.[3]

Sjögren's syndrome can be categorised into two types; primary and secondary SS. The primary type (pSS) typically presents with only ocular and oral symptoms, while the secondary type occurs with other systemic autoimmune diseases such as Rheumatoid arthritis, Systemic lupus erythematosus, or Scleroderma.[4] Primary SS is more commonly seen among middle-aged women, with a mean age of 56 years.[5,6] Likewise, it has been reported in middle-aged men,[6] but other reports have detailed a higher rate of onset in elderly men from age 65 years and above.[5,7,8] Major salivary gland swellings may accompany an oral presentation of SS.[2,9] Dryness of the nasal, tracheal, vaginal mucosa and skin can also be present.[2,9] Sjögren's syndrome can be complicated with the development of lymphoma in 5 to 10% of secondary SS cases.[1,10]

Based on the European League Against Rheumatism (EULAR) SS Patient Reported Index (ESSPRI), the most common clinical presentation of pSS are dry eyes (keratoconjunctivitis sicca), dry mouth (xerostomia) with fatigue.[2,11] The broadly accepted diagnostic criteria for pSS was recently developed by the American College of Rheumatologists (ACR) and European League against Rheumatism (EULAR) in 2016.[12] The ACR/EULAR criteria are used to diagnose pSS based on the sum of 5 weighted items. They include an anti-SSA(Ro) antibody positivity with a score of 3; focal lymphocytic sialadenitis from a labial gland biopsy with a minimum focus of 1 foci/mm^2, also with a score of 3; positive ocular staining score ≥5 (or van Bijsterveld score ≥4)[10] with a score of 1; Schirmer test of ≤5mm/5min in at least one eye, also with a score of 1 and an unstimulated salivary flow rate at 0.1ml/min, which gives another score of 1. Patients with a total score of four out of the five items meet the diagnostic criteria for Primary SS.[12]

Primary Sjögren's syndrome is a relatively rare condition with an incidence ratio (IR) of 6.92 per 100 000 person-years at risk.[5] Studies from Asia detailed relatively higher IR than other regions globally, ranging from 6.0 to 11.8 per 100 000 person-years. In Europe, incidence ratios for pSS range from 3.9 to 5.3, while in North America, the reported IR is estimated at 3.9, which is suggested to be the lowest IR of primary SS found worldwide.[5] However, incidence ratios and prevalence rates in Africa, Oceania, and South America are unknown.[5]

A dearth of literature exists on Sjögren's syndrome in Africa and Nigeria.[5] Research is needed to identify the pattern of clinical presentation and possible diagnostic criteria for primary SS in Nigeria and other low and middle-income settings. The purpose of this study is to describe the clinicopathological pattern of Primary Sjögren's syndrome presenting at a tertiary health facility in Nigeria using the ACR/EULAR 2016 criteria, which is widely accepted.[12] Our findings will contribute to the body of knowledge on the variety of ways in which Sjögren's syndrome presents and can help identify approaches to encourage early diagnosis and management of patients who present with Primary Sjögren's syndrome.

MATERIALS AND METHODS

Study design*:* This was a retrospective study using a cohort of 20 cases who presented at the Oral Medicine clinics of the Lagos State University Teaching Hospital, Ikeja.

Study population: De-identified data was obtained from records of clinically diagnosed Sjogren's syndrome over 5 years between 2015 and 2019 from the Oral Medicine Clinic at the Lagos State University Teaching Hospital by the investigators.

Case selection*:* Inclusion criteria were based on suspected cases of Sjogren's syndrome based on clinical assessment of signs and symptoms and the ACR/EULAR pSS diagnostic criteria.[12] Patients who responded positively to any of the questions stated in section a and the diagnostic tests in section b were included. Section a. questions consisted of: have you had daily, persistent, troublesome dry eyes for more than three months? do you have a recurrent sensation of sand or gravel or gritty sensation in the eyes? have you had a daily feeling of dry mouth for more than three months? do you frequently drink liquids to aid in swallowing food? Section b

information consisted of: labial salivary gland with focal lymphocytic sialadenitis measured following a biopsy; anti-SSA (Ro) antibody test; Schirmer of 5 mm/5min or less in at least one eye; positive ocular staining score ≥5 (or van Bijsterveld score ≥4),[13] unstimulated whole saliva flow rate of 0.1 ml/min or less.

Exclusion criteria: The study excluded participants with a positive history of either of the following: head and neck radiation treatment, active hepatitis C infection with positive polymerase chain reaction test, acquired immunodeficiency syndrome, sarcoidosis, amyloidosis, graft versus host disease IgG4-related disease and those with no biopsy or laboratory reports.[12]

Independent variable measures*:* The following variables were applied to participants who met the ACR/EUCR inclusion criteria: demographic information (age, sex), oral and ocular symptoms, time to diagnosis (first onset of symptoms to working diagnosis by an Oral Medicine specialist)

Outcome measures*:* The primary outcome measure was Primary Sjögren's syndrome. Only cases who met the ACR/EUCR criteria of a score of 4 from the 5 items were definitively diagnosed as pSS in the analysis.[9] Secondary outcome variable was time to the diagnosis of pSS, measured in months.

Statistical analysis: Demographic variables and case characteristics were described in tables and charts, using frequencies and percentages. Stata 15.0 (Stata Statistical Software: College Station, TX: Stata Corp LP) was used for data analysis. Pearson correlation chi-square was used. Statistical significance was set at p values < 0.05.

Ethics: Ethical approval was obtained from the Lagos State University Teaching Hospital Health Research Ethics Committee with reference number LREC/06/10/1338.

RESULTS

Demographic

This study reviewed a series of 20 cases of Sjogren's syndrome. There were 14 females and 6 males with a female to male ratio of 2.3:1 (Table 1). The age of the participants was from 18 to 78 years, with a mean age of 46.9 (± 15.9). Sixty-five percent were above 40 years. The total number of patients that presented at the oral medicine clinic within the study period was 731. Therefore, an estimated prevalence of 2.74% was obtained using the formula: number of cases/ total population at risk x 100 (20/731 X 100).

The majority, 19(95%) of participants presented with one or more oral symptoms, while 9(45%) reported ocular symptoms. Atypical symptoms indicating dryness of the respiratory mucosa, such as episodes of cough and dry throat was reported by 3(15%) of the study participants. The median time to diagnosis for all 20 cases was 4 weeks (IQR: 1-9 weeks) (Table1).

Table 1. Socio-demographic data and clinical characteristics

Case characteristic	n (%)
Age	N=20
<40 years	7(35.0)
≥40years	13(65.0)
Gender	N= 20
Male	6 (30.0)
Female	14(70.0)
Ocular symptoms [Present]	N= 20
Have you had daily, persistent, troublesome dry eyes for more than 3 months	9 (45.0)
Do you have a recurrent sensation of sand or gravel or gritty sensation in the eyes	9 (45.0)
Photophobia	1 (0.05)
Oral symptoms [Present]	N= 20
Have you had a daily feeling of dry mouth for more than 3 months	19(95.0)
Do you frequently drink liquids to aid in swallowing food	14(70.0)
Other signs [Present]	N= 20
*Symptoms of dry respiratory mucosa	3 (15.0)
Joint pain	6 (30.0)

*symptoms of dry respiratory mucosa: reported episodes of cough, dry throat.

ACR/EULAR Criteria

Based on the ACR/EULAR criteria, about 45% of study participants had an unstimulated whole saliva flow rate of 0.1 ml/min or less when the spitting method was used, while 20% had a Schirmer's test result suggestive of Sjogren's in at least one eye. Anti-SSA (Ro) antibody test

was positive in 15% of the study participants, 30% had positive histologic findings, 30% had van Bijsterveld score ≥4, and 35% were positive for primary Sjogren's syndrome based on the ACR/EULAR criteria (Table 2 and Table 3).

Histologic findings

Labial minor salivary gland biopsy showed a focal perivascular and periductal lymphoplasmacytic infiltration with basal cell hyperplasia, which stains deeply on hematoxylin and eosin tissue staining (Figures 1 and 2).

Table 2. Clinical characteristics based on 2016 ACR-EULAR Classification Criteria[5]

Criteria	Score	n=20(100%)
An unstimulated whole saliva flow rate of 0.1 ml/min or less	1	9 (45.0)
Schirmer 5 mm/5min or less in at least one eye	1	4 (20.0)
Ocular van Bijsterveld test	1	6 (30.0)
Anti-SSA (Ro) antibody test	3	3 (15.0)
*Histology: focal lymphocytic sialadenitis	3	6 (30.0)
Cases with Score ≥ 4		7 (35.0)

Notes: Findings from fluorescein staining (≥ 5 in Ocular Staining Score or ≥ 4 in van Bijsterveld Score). * Focus score ≥ 1 focus/4 mm², 1 focus = 50 lymphocytes/4 mm²

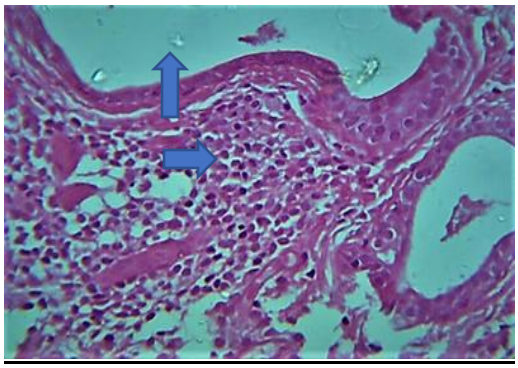

Figure 1: Labial gland biopsy report. Focal periductal lymphoplasmacytic infiltrates, acinar atrophy and ductal dilatation seen on a labial gland biopsy. Haematoxylin and Eosin staining x100 magnification.

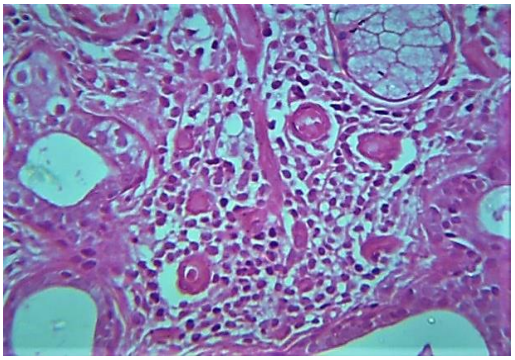

Figure 2: **Labial gland biopsy report**. Focal perivascular and periductal lymphoplasmacytic infiltration with basal cell hyperplasia observed on a labial gland biopsy. Hematoxylin and Eosin staining x100 magnification.

DISCUSSION

The current study assessed the clinicopathologic pattern of twenty suspected cases of pSS in a tertiary health facility in Nigeria. Of the 20 cases reviewed, thirty-five percent met the ACR/EULAR 2016 criteria for pSS. A majority presented with oral symptoms compared to ocular. Unstimulated salivary flow reduction was a more common finding than reduced tear flow assessed using Schirmer's test. These findings are supported by Lacombe *et al.*, who detailed a similar clinical presentation of pSS.[14]

In this study, the majority of the participants were female and middle-aged. This finding is comparable with the epidemiology of Sjogren's in other populations.[15-18] Furthermore, xerophthalmia was seen in nine cases reviewed, while xerostomia was seen in nineteen out of the twenty cases. This finding agrees with Garcia-Carrasco *et al*., where the commonality of these cardinal symptoms has been detailed.[19] Xerostomia and xerophthalmia are the main clinical features associated with accompanying symptoms such as difficulty with mastication, speaking and swallowing, foreign body sensation in the eyes, itchiness and grittiness in the eyes.[19] In addition, xerophthalmia may result in photophobia following photosensitivity as exhibited by a participant in this study. This finding is due to the irritation and destruction of the cornea or associated ocular infections.[20]

Further, atypical findings, as seen in three cases in this report and other studies, such as non-productive cough, [18,20,21] can significantly reduce patients' quality of life with pSS.[18,20] Other studies have reported these findings in association with both primary and secondary Sjogren's and general symptoms such as fatigue, which is two-fold worse in patients with pSS compared to controls.[22,23]

A multidisciplinary team was crucial in the diagnosis of the cases reviewed. For instance, specialised human resources, the ophthalmologist and the oral pathologist were very important so that the ACR/EULAR can be applied. Overall, the management of the cases reviewed was consistent with prior literature. All cases were managed based on signs and symptoms arising from the disease. They were counselled and supporting therapies such as sialagogues and tear substitutes were administered to improve their quality of life.

The disproportionate representation of research on Sjogren's syndrome, mainly from Asia and Europe[5] limits the generalizability of the existing literature to certain populations, particularly in sub-Saharan Africa. Hence the need for more studies on Sjogren's syndrome from populations in Africa.

In conclusion, the current report details a series of pSS cases using symptomatology and the ACR/EULAR classification. Of the 20 cases reviewed, seven met the ACR/EULAR criteria for diagnosing pSS. While the ACR/EULAR classification was developed primarily to standardise the recruitment of primary Sjogren's cases into clinical trials,[12] it may also be applicable for non-research purposes. However, this classification may be limited in our setting due to the laboratory-dependent indices of the criteria, which might not be readily available or affordable. Nevertheless, the current study provides early evidence on the symptomatology and clinical presentation of Sjogren's cases seen at a single centre in a developing country, Nigeria.

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Table 3: Clinical and pathological characteristic of cases reviewed

Case	Ocular symptoms	Oral symptoms	Salivary flow rate	Schirmer's test	Anti-SSA (Ro) antibody test	van Bijsterveld ocular test	Histology
1	+	+	0	0	0	0	0
2	+	+	+	0	0	0	0
3	0	+	+	+	0	+	+
4	0	+	0	0	0	0	0
5	0	+	0	+	0	0	0
6	+	0	0	0	+	0	0
7	+	+	0	0	0	0	0
8	0	+	0	0	+	0	0
9	0	+	0	0	0	0	0
10	0	+	0	0	0	0	0
11	0	+	+	+	0	0	0
12	+	+	0	0	0	0	0
13	+	+	+	0	0	+	+
14	+	+	+	0	0	0	0
15	+	+	0	0	0	0	0
16	+	+	0	+	+	0	0
17	+	+	+	0	0	+	+
18	0	+	+	0	0	+	+
19	+	+	+	0	0	+	+
20	0	+	+	0	0	+	+

Note: +: Positive finding. 0: Negative finding.

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REFERENCES

1. Mavragani CP, Moutsopoulos HM. The geoepidemiology of Sjögren's syndrome. Autoimmun Rev 2010; 9: A305-310.
2. Seror R, Ravaud P, Mariette X, Bootsma H, Theander E, Hansen A, et al. EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjogren's syndrome. Ann Rheum Dis. 2011;70(6):968–972.
3. Bolstad AI, Skarstein K. Epidemiology of Sjögren's Syndrome- From an Oral Perspective. Curr Oral Health Rep 2016;3:328–336.
4. Thorne I, Sutcliffe N. Sjögren's syndrome. British J Hosp Med. 2017;78(8):438-442.
5. Qin B, Wang J, Yang Z, et al. Epidemiology of primary Sjögren's syndrome: a systematic review and meta analysis. Ann Rheum Dis 2015;74:1983–1989.
6. Napeñas JJ, Rouleau TS. Oral complications of Sjögrens syndrome. Oral Maxillofac Surg Clin North Am 2014;26(1):55–62.
7. Voulgarelis M, Ziakas PD, Papageorgiou A, et al. Prognosis and outcome of non-Hodgkin lymphoma in primary Sjögren syndrome. Medicine (Baltimore) 2012;91:1-9.
8. Argyropoulou OD, Valentini E, Ferro F, Leone MC, Cafaro G, Bartoloni E, Baldini C. One year in review 2018: Sjögren's syndrome. Clin Exp Rheumatol 2018;36(112):S14-S26.
9. Shiboski CH, Shiboski SC, Seror R, Criswell LA,Labetoulle M, Lietman TM, et al. American College of Rheumatology/European League against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol. 2017; 69(1):35-45.
10. van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. Archives of ophthalmology. 1969; 82(1):10-14.
11. Lacombe, V., Lacout, C., Lozac'h, P. *et al.* Unstimulated whole saliva flow for diagnosis of primary Sjögren's syndrome: time to revisit the threshold?Arthritis Res Ther. 2020: 22; 38.
12. Vivino FB. Sjogren's syndrome: Clinical aspects. Clinical Immunology 2017;182:48-54.
13. Thomas E, Hay E, Hajeer A, Silman, Sjogren's syndrome: a community-based study of prevalence and impact, Br J Rheumatol 1998; 37:1069-1076.
14. Stefanski AL, Tomiak C, Pleyer U, Dietrich T, Burmester G, Dörner T. The diagnosis and treatment of Sjögren's syndrome. Dtsch Arztebl Int 2017;114: 354–61.
15. Jadhav S et al. Sjögren's Syndrome: A Case Study. J Int Oral Health. 2015; 7(3): 72-74.
16. Garcia-Carrasco M, Mendoza-Pinto C, Jimenez Hernandez C et al, Serologic features of primary Sjögren's syndrome: clinical and prognostic correlation. J Clin Rheumtol. 2012; 7(6):651-659.
17. Both T, Dalm VA, van Hagen PM, van Daele PL. Reviewing primary Sjögren's syndrome: beyond the dryness - From pathophysiology to diagnosis and treatment. Int J Med Sci. 2017 Feb 23;14(3):191-200.
18. 18. Provost TT, Watson R. Cutaneous manifestations of Sjogren's syndrome. Rheum Dis Clin North Am. 1992;18: 609-616
19. ampey J, Corruble E, Gottenberg JE, Buhl C, Meyer, Caudmont C, et al. Quality of life and psychological status in patients with primary Sjogren's syndrome and sicca symptoms without autoimmune features. Arthritis Rheum. 2006; 55: 451-457.
20. Segal B, Thomas W, Rogers T, Leon JM, Hughes P, Patel D, et al. Prevalence, severity, and predictors of fatigue in subjects with primary Sjogren's syndrome. Arthritis Rheum. 2008; 59: 1780-1787.