Research article

Sjogrens syndrome in Nigerians with rheumatoid arthritis

Oguntona SA[1], Otulana TO[2]

[1]Department of Medicine, Olabisi Onabanjo University/ Teaching Hospital, Sagamu, Ogun State, Nigeria
[2]Department of Surgery, Olabisi Onabanjo University/ Teaching Hospital, Sagamu, Ogun State, Nigeria

Corresponding author: Dr SA Oguntona, PO Box 231, Sagamu, Ogun State, Nigeria. Email: oguntonasa@yahoo.com

Abstract

Background: Sjogren's Syndrome (SS) is a systemic autoimmune disorder, characterized by lymphocytic infiltration and malfunction of the exocrine glands. When it presents alone, it is referred to as primary Sjorgren's syndrome and secondary when presented in the context of an underlying connective tissue disease. The main clinical symptoms are dry eyes and xerostomia. A number of auto-antigens and auto-antibodies have been described which may play a central role in the pathogenesis of the disease.

Methodology: This was a retrospective study of all the rheumatology cases over a three year (January 2011-December 2013) period. The records of cases suggestive of Sjogren's syndrome were retrieved for further study. Necessary information was derived from cases that met the diagnosis of Sjogren's syndrome. Diagnosis was made based on symptomatology of dry eyes and dry mouth and the Ophthalmologist's assessment in patients with an established diagnosis of connective tissue disorder.

Results: Six patients met the diagnosis of Sjogren's syndrome out of the 472 rheumatology cases seen, constituting 1.27% of the total cases of rheumatology seen over the study period.There were 5 females (83.3%) and a male (16.7%). Twenty one were cases of rheumatoid arthritis of which six developed dry mouth and eyes suggestive of Sjogren's syndrome.

Conclusion: Sjogren's syndrome is not a common disorder in our clinic; it is preponderant in females and related to rheumatoid arthritis, it should also be considered in patients with other types of connective tissue disorders when they present with eye and mouth symptoms.

Introduction

Sjogren's Syndrome (SS) is a multi-systemic disorder characterized by the destruction of lacrimal and salivary glands–glandular tissues resulting into keratoconjuctiva Sicca (KCS), (dry eyes) and Xerostomia (dry mouth) respectively (Sicca syndrome)[1]. Primary SS presents in isolation with KCS and Xerostomia. Secondary SS is commonly associated with Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), and Systemic Sclerosis (SSc)[2,3].

SS affects all age groups with onset usually in the middle age. In Western studies, it has a prevalence of 4 per 100,000 populations and affects mostly females with a male to female ratio of 1:9[4]. The prevalence in African population is unknown.

The aetiology and pathophysiology are unknown. In primary SS, antibodies to ribonucleoproteins Ro (SS-A) and La (SS-B) are found in 90% of patients[5]. Viral infections have been implicated in its aetiology, including Epstein-Barr virus, hepatitis C virus, and cytomegalovirus[5]. Diffuse Idiopathic Infiltrative Lymphocytic Syndrome (DILS) is an important Sjogren mimic associated with Human immunodeficiency virus-1.

Clinical features of SS include decreased tear and saliva secretion, leading to dry eye and dry mouth. Salivary and extra-salivary B cell lymphomas have been found to be associated with SS. Systemic involvement may include the skin, respiratory, renal, hepatic, neurologic, and vascular system[6].

The purpose of this study was to establish the prevalence of the Sicca syndrome in Nigerian patients with rheumatic disease.

Materials and Methods

We retrospectively reviewed the records of all 472 patients with rheumatic disorders seen at the medical outpatient clinic of Olabisi Onabanjo University Teaching Hospital (OOUTH) from January 2011 to December 2013. All RA patients were evaluated for evidence of SS according to the 2002 revised international classification criteria. For all patients, the diagnosis of RA was ascertained using established classification criteria[7] and the disease onset and duration noted.

The following features were retrieved from the case records: arthritis, fever, rash, lymphadenopathy, parotid gland enlargement, xerostomia, xerophthalmia,

pulmonary symptoms, renal symptoms, nervous system involvement, hypertension and diabetes mellitus.

Laboratory and radiological findings: All patients had serological evaluations, including Antinuclear Antibody (ANA), anti-SSA and anti-SSB antibodies, Rheumatoid Factor (RF) in addition to full blood count (definition of terms are: anaemia (Hb<10 g/dl), leucopenia (white blood cell count <4000/µl), thrombocytopenia (platelet count <100, 000/µl), electrolyte, urea and creatinine, chest-X- ray, and blood sugar estimation. Erythrocyte sedimentation rate was also checked. There was however no materials to detect the objective reduction in salivary secretion.

Case definition: The American-European consensus group criteria of 2002 for SS consist of six items which are:

- Ocular symptoms of inadequate tear production
- Ocular signs of corneal damage due to inadequate tearing
- Oral symptoms of decreased saliva production
- Salivary gland histopathology demonstrating foci of lymphocytes
- Tests indicating impaired salivary gland function
- Presence of auto-antibodies (anti-Ro/SSA and/or anti-La/SSB)

Primary SS was defined as patients with no associated connective tissue disease who have four of the above items (presence of auto-antibody is mandatory). Secondary SS was defined as the presence of any connective tissue disease in the presence of any four of the above items.

Rheumatoid Arthritis (RA): RA was defined according to the 1987 classification criteria of the American College of Rheumatology[7].

Results

Six patients fulfilled the criteria for SS among the 21 RA patients identified (4.4% of total rheumatology cases). All had developed SS following the onset of RA.

There were five females (83.3%) and one male. The age range of the patients was 35 to 53 years. All the patients presented with dry eyes and dry mouth. Other clinical features presented by our patients are as shown in Figure 1. Tear Break Up Time (TBUT) was 5 and 6 seconds respectively in 2 patients, 9 seconds in 3 patients and 10 seconds in one patient.

Laboratory: All patients had an elevated ESR, two had a significantly raised ANA titre and one a positive RoSSA/LaSSB. All the six patients had leucopenia, thrombocytopenia, and anaemia. Interstitial lung disease was seen in a female, two showed laboratory results in support of renal involvement (elevated creatinine and urea levels and two positive proteinuria) but none develop renal failure. None of the patients had diabetes mellitus.

Medications: Response to artificial tear (tear natural, Ivymoicell), artificial saliva, and muscarinic agent was uniformly good except for two patients who reacted to pilocarpine with diarrhoea and tremor respectively. The diarrhoea got better with continuation of the drug while tremor responded to dosage reduction.

Figure 1: Other clinical presentations of SS in our patients

Ocular	Oral
Irritation of the eye	Difficulty in swallowing solid foods
Grittiness/ sandy feeling in the eyes	Dental carries
Foreign body sensation	Inability to speak for a long time without sipping water
Itchy eyes	
Abnormal tear break up time	

Discussion

Sjogren's Syndrome (SS) often coexists with other systemic autoimmune diseases, including RA and systemic lupus erythematosus. In 1933, Sjogren described clinical and histological findings in nineteen women with dry mouth and dry eyes, thirteen of the patients had probable RA[8]. Since 1965, there have been several studies that have focused on RA associated with SS[9]. Subsequent studies demonstrated significant differences in the clinical features of SS patients with and without RA[10-11]. In our study 28.6% of the 21 rheumatoid arthritis patients fulfilled the SS criteria, a value in agreement with earlier studies in other populations[10,11].

All the six RA/SS patients in this study presented with ocular manifestations. Early diagnosis of ophthalmic disease in patients with RA is very important because of the need for timely management of potentially serious and sight-threatening complications. The presence of ocular disease may also be an indication of on-going systemic disease activity[12].

The clinical course of ocular disease in RA is quite variable. Keratoconjuctivitis Sicca (KCS) due to SS is the most common ophthalmic manifestation of RA, occurring in as many as 15-25% of patients[13]. Symptomatic and objective signs of KCS are central to the diagnosis of SS. Patients with SS often complain of dryness, foreign body sensation, burning, or photophobia[6] and ocular examination usually reveal an abnormal tear break up time[14]. Severe dry eye may however exist independently from severe articular disease and should be evaluated in all patients with RA regardless of extra-articular manifestations[15].

Sicca symptoms are much more common than SS in older adults. It was estimated that approximately 35% of older subjects have the sensation of dry eyes and dry mouth[16]. This has been adduced to various medications

prescribed for the elderly patients; however, only about 10% of these subjects have objective evidence of reduced tear or saliva production[16]. Evidence of severe dry eye existed in 33% of the patients in this study. This finding is at variance with the finding in elderly patients, because the cohorts in this study were patients that are much younger and had secondary SS.

Other ocular manifestations seen in RA patients apart from KCS include episcleritis, scleritis, corneal inflammation and corneal infection[6]. These clinical findings were however not established in our patients.

The diagnosis of dry/sicca symptom was confirmed by the Ophthalmologists in our patients with slit lamp evidence of abnormal tear break up time. Other ocular tests to confirm the sicca symptoms include Schirmer's and Rose Bengal tests[17] which were not done in our centre.

All the patients also presented with oral dryness (xerostomia) with difficulty in swallowing dry food without drinking liquids. Two patients had tooth extraction as a result of dental carries. Dry mouth is common particularly in older patients, but objective evidence of reduced salivary flow is less frequent[18]. Salivary gland biopsy is not necessary in all patients for the confirmation that symptoms of dryness are due to SS[21]. The presence of a connective tissue disease with diagnosis of KCS is enough to establish the diagnosis of secondary SS in patients with dry mouth symptoms[19].

All the six secondary SS patients had haematological abnormalities. They all presented with pan-cytopenia. Primary SS patients and RA without Sjogren's, and RA with SS patients can present with a variety of haematologic abnormalities, including anaemia, leucopenia and thrombocytopenia[20]. Earlier studies found that RA/SS patients had a longer duration of disease than those with RA only.

Patients with RA/SS have a more severe form of arthritis, and that the incidence of anaemia was higher in RA/SS patients than in RA patients[21]. Leucopenia and thrombocytopenia in RA without SS is often associated with drug toxicity. Leucopenia and thrombocytopenia are frequently seen in RA/SS and primary SS, but seldom in RA only. Generally, the incidence of haematological system abnormality is much higher in RA/SS patients than in those without[21].

The six patients were treated with Disease Modifying Anti-Rheumatic Drugs (DMARD), and in addition were also placed on treatment for the Sicca symptoms. There is however no consistently effective treatment for SS. The current therapy is primarily symptomatic[22].

Non-pharmacological modalities of treatment instituted for the ocular symptoms in our patients included avoidance of medications that can cause dryness and reduced exposure to environments that exacerbate dryness. Pharmacological therapies instituted include the use of artificial tear, occasional use of topical steroid during intense inflammation, and the use of pilocarpine. The symptoms of dry mouth were treated with frequent sips of water, intense oral hygiene, prevention and treatment of oral infections, and local and systematic stimulation of salivary secretion by the use of muscarinic agonist (pilocarpine).

People with xerostomia often have a very high rate of tooth decay and mucosal infection. Referral to the dentist should be early for recognition and treatment of dental carries. Proper brushing, flossing and use of alcohol-free mouthwashes should be recommended[23,24].

The good response observed in our patients with the use of muscarinic agonist may also in part be explained by the fact that all the patients were placed on hydroxyl-chloroquine for the treatment of RA. Hydroxy-chloroquine has been shown to some extent to be beneficial for dry mouth[27]. None of the patients however developed hydroxy-chloroquine induced maculopathy. A study of forty patients who received hydroxy-chloroquine (6-7mg/kg/day) for 24-48 months were shown to develop improvement in oral dryness compared with baseline values[25].

In conclusion, SS may be primary or secondary. RA is the most common underlying condition in secondary disease. Treatment should be a collaborative effort involving the ophthalmologists, dentists, and the rheumatologists.

References

1. Pillimer SR. Sjogren's syndrome. In: Klippel JH, Crofford LJ, Stone JH, Weyand CM, editors. Primer on the rheumatic diseases. Atlanta: Arthritis Foundation; 2001. p. 377-384.
2. Dawson LJ, Fox PC, Smith PM. Sjogren's syndrome-The non apoptic model of glandular hypofunction. *Rheumatology*. 2006; **45**: 792-798.
3. Theander E, Jacobsson LTH. Relationship of Sjogren's syndrome to other connective tissue and autoimmune disorders. *Rheum Dis Clin North Am*. 2008; **34**:935-947.
4. Sanchez-Guerrero J, Pérez-Dosal MR, Cárdenas-Velázquez F, Perz-Reguera A, Celis-Aguilar E, Soto-Rojas AE. Prevalence of Sjögren's syndrome in ambulatory patients according to the American-European Consensus Group criteria. *Rheumatology* (Oxford). 2005; 44:235 -240.
5. Ramos-Casals R, Font J. Primary Sjögren's syndrome: current and emergent aetiopathogenic concepts. *Rheumatology*. 2005; **44**:1354-1367.
6. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. *Arch Intern Med.* 2004; **164**:1275-1284.
7. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988; **31**: 315-324.
8. Sjogren H, Zur Kenntnis der. Keratoconjunctivitis sicca. *Acta Ophthalmol.* 1933; **11**(suppl II):1.68.

9. Carmona L, Gozalez-Alvaro I, Balsa A, Angel Belmonte M, Tena X, Sanmarti R. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. *Ann Rheum Dis*. 2003; **62**:897-900.
10. Young A, Koduri G. Extra-articular manifestations and complications of rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2007; **21**:909-927.
11. Wolfe F, Michaud K. Prevalence, risk and risk factors for oral and ocular dryness with particular emphasis on rheumatoid arthritis. *J Rheumatol*. 2008; **35**:1023-1030.
12. Price EJ, Venables PJ. Dry eyes and mouth syndrome: a subgroup of patients presenting with sicca symptoms. *Rheumatology* (Oxford). 2002; **41**:416-422.
13. Mohammed K, Pope J, Le Riche N, Brintnell W, Cairns E, Coles R, *et al.* Association of severe inflammatory polyarthritis in primary Sjogren's syndrome: clinical, serologic, and HLA analysis. *J Rheumatol*. 2009; **36**: 1937-1942.
14. Kalk WW, Mansour K, Vissink A, Spijkervet FK, Bootsma H, Kallenberg CG, *et al.* Oral and ocular manifestations in Sjogren's syndrome. *J Rheumatol*. 2002; **29**: 924-930.
15. Schein OD, Hochberg MC, Munoz B,Tielsch JM, Bandeen-Roche K, Provost T. Dry eye and dry mouth in the elderly: a population-based assessment. *Arch Intern Med.* 1999;**159**:1359-1363.
16. Srinivasan S, Slomovic AR. Sjogren's disease. *Compr Ophthalmol Update.* 2007; **8**: 205-212.
17. Hochberg MC, Tielsch J, Munoz B, Bandeen-Roche K, West SK, Schein OD. Prevalence of symptoms of dry mouth and their relationship to saliva production in community dwelling elderly: the SEE project. Salisbury Eye Evaluation. *J Rheumatol.* 1998; **25**:486-491.
18. Fox RI. Sjogren's syndrome. *Lancet.* 2005; **366**:321-331.
19. Lee M, Rutka JA, Slomovic AR, McComb J, Baily DT, Bookman AAM. Establishing guidelines for the role of minor salivary gland biopsy in clinical practice for Sjogren's syndrome. *J Rheumatol.* 1998; **25**:247-253.
20. Roy CN. Anemia of inflammation. *Haematology Am Soc Hematol Educ Program.* 2010; **2010**:276-280.
21. Ramakrishna R, Chaudhuri K, Sturgess A,Manoharan A. Haematological manifestations of primary Sjogren's syndrome: a clinicopathological study. *Q J Med*. 1992; **83**: 547-554.
22. Mavragani CP, Moutsopoulos NM, Moutsopoulos HM. The management of Sjogren's syndrome. *Nat Clin Pract Rheumatol.* 2006; **2**:252-262.
23. Wu AJ. Optimizing dry mouth treatment for individuals with Sjogren's syndrome. *Rheum Dis Clin North Am.* 2008; **34**:1001-1010.
24. Furness S, Worthington HV, Bryan G, Birchenough S, McMillan R. Interventions for the management of dry mouth: topical therapies. *Cochrane Database Syst Rev*. 2011; (12):CD008934.
25. Rihl M, Ulbricht K, Schmidt RE, Witte T. Treatment of sicca symptoms with hydroxychloroquine in patients with Sjogren's syndrome. *Rheumatology*. 2009; **48**:796 -799.