A STUDY ON THE PREVALENCE OF SICCA SYNDROME IN PATIENTS WITH RHEUMATOID ARTHRITIS

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CERTIFICATE

This is to certify that this dissertation titled "**A STUDY ON THE PREVALENCE OF SICCA SYNDROME IN PATIENTS WITH RHEUMATOID ARTHRITIS"** submitted by **Dr. AMRITA RAMASWAMI** to the faculty of General Medicine, **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the requirement for the award of MD degree **Branch I General Medicine**, is a bonafide research work carried out by her under our direct supervision and guidance.

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DECLARATION

I**, Dr. AMRITA RAMASWAMI** solemnly declare that the dissertation titled "**A STUDY ON THE PREVALENCE OF SICCA SYNDROME IN PATIENTS WITH RHEUMATOID ARTHRITIS"** has been prepared by me.

This is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** in partial fulfillment of the rules and regulations for the award of MD degree **(Branch I) General Medicine.**

Place: Madurai

Date: **Dr. AMRITA RAMASWAMI**

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CONTENTS

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, affecting 0.5% to 1% of the general population worldwide. Although the prevalence is constant across the globe, regardless of geographic location and race, there are some exceptions. In China, the occurrence of RA is lower (about 0.3%), whereas it is substantially higher in other populations, such as the Pima Indians in North America (about 5%). Because of its prevalence and the ready accessibility of joint samples for laboratory investigation, RA has served as a useful model for the study of many inflammatory and immune-mediated diseases[1]. As such, the information gleaned from these studies has provided new and unique insights into the mechanisms of normal immunity.

Although RA is properly considered a disease of the joints, abnormal immune responses can cause a variety of extra-articular manifestations. In some cases, production of rheumatoid factor (RF) with the formation of immune complexes that fix complement contributes to extra-articular findings. RA is a systemic disease with a variety of extra-articular manifestations. It is estimated that as many as 40% of patients may have extra-articular manifestations and in 15% these are severe.

On occasion, extra-articular manifestations may be the major evidence of disease activity and source of morbidity and require management per se[2].Although the frequency of patients with severe extra-articular manifestations appears to be declining, these patients have an increased mortality compared to other persons with RA or age- matched normal controls.

Some of the notable extraarticular manifestations are:

1. Rheumatoid vasculitis
2. Pleuropulmonary manifestations
3. Cardiovascular disease
4. Neurologic manifestations
5. Eye involvement in the form of episcleritis and scleritis
6. Sjogren's syndrome
7. Felty's syndrome
8. Osteoporosis
9. Development of Lymphomas

From 15 – 20% of patients with RA may develop Sjogren's syndrome with attendant keratoconjunctivitis sicca[2].

This study was undertaken to screen rheumatoid arthritis patients for the presence of sicca symptoms, look for objective evidence of sicca and estimate the prevalence of sicca syndrome in these patients.

REVIEW OF LITERATURE

RHEUMATOID ARTHRITIS:

INTRODUCTION:

Rheumatoid arthritis is a symmetric inflammatory arthritis that mainly affects the small joints of the hands and feet. Larger joints can be involved, usually in a symmetric fashion.

Cartilage destruction and bone erosions are common, especially in rheumatoid factor–positive or anticitrullinated protein antibody–positive patients.

Uncontrolled synovitis can lead to severe deformities, loss of function, and increased mortality.

Early aggressive therapy seems to improve long-term outcomes in rheumatoid arthritis.

Systemic manifestations include pulmonary disease, vasculitis, nodules, and eye disease.

EPIDEMIOLOGY AND BURDEN OF THE DISEASE

In past years, most investigators accepted a prevalence of rheumatoid arthritis (RA) in most populations of around 1%, with an

incidence in women twice that in men. This number was based on many studies of population samples that varied among the surveys from 0.3% to 1.5% [3-5]. This figure of 1% prevalence of RA in most populations may be changing, however, as incidence rates in different decades are studied.

CLINICAL SYNDROMES OF EARLY RHEUMATOID ARTHRITIS:

There are distinctive patterns of onset of rheumatoid arthritis. They are

1. Insidious onset
2. Acute or intermediate onset

Insidious Onset

RA has an insidious, slow onset over weeks to months in 55% to 65% of cases[6]. The initial symptoms may be systemic or articular. In some individuals, fatigue, malaise, swollen hands, and diffuse musculoskeletal pain may be the first nonspecific complaints, with joints becoming involved later.

Morning stiffness is a cardinal sign of inflammatory arthritis that can appear even before pain and may be related to the accumulation of edema fluid within inflamed tissues during sleep. The morning stiffness dissipates as edema and products of inflammation are absorbed by

lymphatics and venules and returned to the circulation by motion accompanying the use of muscles and joints. To be specific for joint inflammation, morning stiffness (e.g., “difficulty moving around”) should persist for at least 30 to 45 minutes before disappearing. A similar “gel” phenomenon can occur if a patient is inactive for a period during the day.

Acute or intermediate onset:

Of patients, 8% to 15% have an acute onset of symptoms that peak within a few days. Rarely, a patient can pinpoint the onset of symptoms to a specific time or activity.

SIGNS AND SYMPTOMS OF THE DISEASE:

Articular Involvement

The joints most commonly involved first in RA are the metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, metatarsophalangeal joints, and wrists (Table 1)[7] . Larger joints generally become symptomatic after small joints.

Table -1 -- Distribution of Joints Involved in Attacks Based on a Cumulative Experience with 227 Patients[1]

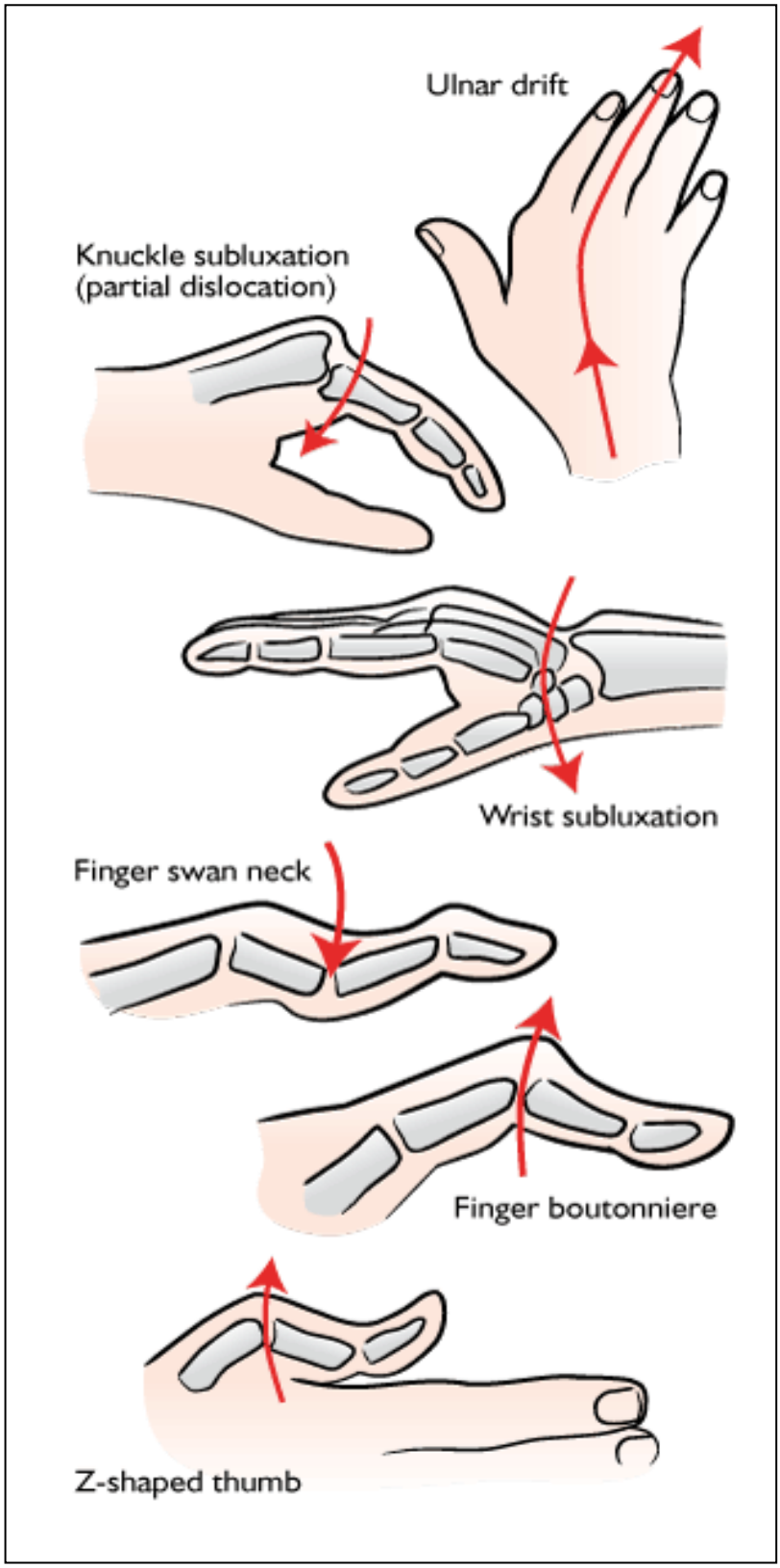
Joint Involvement	% Patients (Mean)	% Patients (Range)
MCP, PIP	91	74-100
Wrists	78	54-82
Knees	64	41-94
Shoulders	65	33-75
Ankles	50	10-67
Feet	43	15-73
Elbows	38	13-60
Hips	17	0-40
Temporomandibular	8	0-28
Spine	4	0-11
Sternoclavicular	2	0-6
Para-articular sites	27	20-29

Pain, swelling and tenderness may initially be poorly localized to the joints. Pain in affected joints, aggravated by movements is the most common manifestation of rheumatoid arthritis. Morning stiffness of more than 1 hour duration is an almost invariable feature of inflammatory arthritis.

With persistent inflammation, a variety of characteristic joint changes develop. These can be attributed to a number of pathologic events, including laxity of supporting soft tissue structures; damage or weakening of ligaments , tendons and the joint capsule; cartilage degradation: muscle imbalance; and unopposed physical forces associated with the use of affected joints. Characteristic changes of the hand include (1) radial deviation of the wrist with ulnar deviation of the digits (“Z” deformity);(2)Hyperextension of the proximal interphalangeal joints with compensatory flexion of the distal interphalangeal joints.(swan-neck deformity);(3)flexion contracture of the proximal interphalangeal joint and extension of the distal interphalangeal joints (boutonniere deformity)

In the foot, hallux valgus , widening of the forefoot, lateral deviation and dorsal subluxation of the toes can occur.

DEFORMITIES OF THE HAND AND FINGERS IN RHEUMATOID ARTHRITIS



Extra-articular Complications of Rheumatoid Arthritis

Generally, the number and severity of extra-articular features vary with the duration and severity of the disease. Several of these features may be related to extra-articular foci of an immune response[8]. These patients with systemic immune responses have true rheumatoid disease, not just RA. Other unusual proteins and protein complexes in the circulation of patients with active rheumatoid disease include antiphospholipid antibodies, circulating immune complexes, and cryoglobulins. Extra-articular manifestations of RA are associated with excess mortality.[9]

SKELETON

The skeleton has two anatomically and functionally separate components, cortical and trabecular bone, which respond differently to systemic and local diseases and to drugs. RA can be associated with generalized osteopenia and osteoporosis owing to the effects of drugs (especially corticosteroids). The risk of hip fracture and vertebral compression fracture can be quite high. Bone densitometry should be performed routinely in patients with RA, and treatment with bisphosphonates should be considered as an adjunct to therapy.

MUSCLE

Clinical weakness is common in RA, but is it caused by muscle involvement in the rheumatoid inflammation, or is it a reflex weakness response to pain? Most rheumatoid patients have muscle weakness, but few have muscle tenderness or elevated muscle enzymes in the blood.

More recent studies have pointed to at least five different types of muscle disease in RA, although clinically relevant active myositis is uncommon[10]:

1. Diminution of muscle bulk with atrophy of type II fibers
2. Peripheral neuromyopathy, usually due to a mononeuritis multiplex
3. Steroid myopathy
4. Active myositis and muscle necrosis with foci of endomysial mononuclear cell infiltration
5. Chronic myopathy resembling a dystrophic process, probably the end stage of inflammatory myositis

SKIN

The most frequently recognized skin lesion in RA is the rheumatoid nodule, but there are several other manifestations as well. “Senile” purpura resulting from skin atrophy and capillary fragility is especially common in patients treated with glucocorticoids. Palmar erythema is common, but Raynaud's syndrome is rare.

EYE

Virtually all ocular manifestations of RA can be considered complications of the disease. Keratoconjunctivitis sicca is a component of Sjögren's syndrome. More directly related to the rheumatoid process and seen in the synovium and within rheumatoid nodules are scleritis and episcleritis. The highly differentiated connective tissues in the eye make rheumatoid manifestations particularly interesting and, when they occur in aggressive form, very serious.

The episclera of the eye is highly vascular compared with the dense sclera. Scleritis, episcleritis, or both occur in less than 1% of rheumatoid patients.

In episcleritis, the eye becomes red and, in contrast to conjunctivitis, results in no discharge other than tearing in response to the gritty discomfort. Loss of vision does not occur as a direct result of the episcleritis, but a keratitis or cataract developing secondarily can cause visual loss.

Scleritis causes severe ocular pain and a dark red discoloration. No discharge is present. Depending on the intensity of the process, scleritis can be localized and superficial or generalized, with or without granulomatous resorption of the sclera down to the uveal layer; when this complication occurs, it is termed *scleromalacia perforans*.

Patients with RA who have an associated keratoconjunctivitis sicca secondary to Sjögren's syndrome have pruritic and painful eyes, sometimes leading to chronic blepharitis.

INFECTION

The incidence of infections as a complication of RA has paralleled the use of glucocorticoids, biologics, and immunosuppressive agents. TNF blockers are especially noteworthy because they have been associated with reactivation of tuberculosis and other opportunistic

infections such as histoplasmosis. Pulmonary infections, skin sepsis, and pyarthrosis are among the most common infections in RA. [11,12]

CANCER

There is an increased risk for malignancy in RA patients, with an increased risk for lymphoma in certain patient subsets. Interstitial fibrosis may be a risk factor for lung carcinoma, particularly of the bronchoalveolar variety.[13] One exception is cancer of the gastrointestinal tract, for which there seems to be a reduced risk for RA patients.[14] It is possible that nonsteroidal anti-inflammatory drugs (NSAIDs) lower the risk of this form of cancer, as supported by evidence that these drugs can diminish the occurrence and numbers of colonic polyps.

RA patients are at a two to three times higher risk of Hodgkin's disease, non-Hodgkin's lymphoma, and leukemia than the normal population; this is independent of immunosuppressive therapy.

HEMATOLOGIC ABNORMALITIES

Most patients with RA have a mild normocytic normochromic anemia that correlates with ESR elevation and the activity of the disease. Anemia has mixed causes in RA. One deficiency may mask evidence of

others. A useful guide is that three quarters of rheumatoid patients with anemia have the anemia of chronic disease, whereas one quarter respond to iron therapy. Patients in both groups may have superimposed vitamin B_{12} or folate deficiencies.

RENAL DISEASE

The kidney is rarely involved directly in RA, but often is compromised indirectly by therapy. Amyloidosis is an unusual complication of chronic RA. AA amyloidosis, along with vasculitis and sepsis, is one of the most important life-threatening complications of RA.

PULMONARY DISEASE

There are at least six forms of lung disease in RA, as follows:

- Pleural disease
- Interstitial fibrosis
- Nodular lung disease
- Bronchiolitis obliterans with organizing pneumonia
- Arteritis, with pulmonary hypertension

CARDIAC COMPLICATIONS

Cardiac disease in RA can take many forms. It has become apparent that the increased risk of premature death in RA is due largely to an increased incidence of cardiovascular disease, primarily myocardial infarction and congestive heart failure. Advances in echocardiography have made the diagnosis of pericarditis and endocardial inflammation easier and more specific. Myocardial biopsy through vascular catheters has facilitated diagnosis and classification of myocarditis.

DIAGNOSIS

Criteria to establish the diagnosis of RA are based on an effective clinical history and physical examination, laboratory tests, and exclusion of other diagnoses. No single feature or laboratory test is sufficient for a definite diagnosis. The 1988 American College of Rheumatology criteria for classification usually are not used in individual cases for diagnosis; however, the requirement that objective evidence for synovitis must be present for at least 6 weeks is an important one especially because many transient forms of synovitis are observed in primary care settings .

Table 2 -- 1988 Revised American Rheumatism Association Criteria for Classification of Rheumatoid Arthritis[1]

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints lasting at least 1 hr before maximal improvement
2. Arthritis of ≥3 joint areas	At least 3 joint areas simultaneously having soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician (the 14 possible joint areas are [right or left] PIP, MCP, wrist, elbow, knee, ankle, and MTP joints)
3. Arthritis of hand joints	At least 1 joint area swollen as above in wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as in criterion 2) on both sides of the body (bilateral involvement of PIP, MCP, or MTP joints is acceptable without absolute symmetry)
5. Rheumatoid	Subcutaneous nodules over bony prominences or

Criterion	Definition
nodules	extensor surfaces, or in juxta-articular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method that has been positive
7. Radiographic changes	Changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

The history and physical examination are the most sensitive and specific tools for diagnosis of RA. Initial laboratory tests often show the results in the following list .

- Normal white blood cell count and differential
- Thrombocytosis

- Mild anemia (hemoglobin 10 g/dL), normochromic and either normocytic or microcytic
- Normal urinalysis
- ESR 30 mm/hr or greater and C-reactive protein level greater than 0.7 pg/mL
- Normal renal, hepatic, and metabolic tests
- Normal serum uric acid level
- Positive RF test (about 70% to 80% of patients; present in many normal individuals, patients with other rheumatic diseases, and individuals with chronic infections)
- Anticitrullinated protein antibody (about 80% to 90% of patients; can be seen in other diseases, including active tuberculosis) (especially useful in early synovitis)

SJOGREN'S SYNDROME :

In 1933, Sjögren described the association of filamentary keratitis with arthritis. Previously, in 1882, Leber had described filamentary keratitis, and in 1888, Mikulicz had described a patient with bilateral

lacrimal and parotid gland enlargement. Biopsy of these glands revealed extensive round cell infiltration. In 1953, Morgan and Castleman[13] noted the similarity between the glandular enlargement described by Mikulicz and the keratitis described by Sjogren. Subsequently, these disorders were considered to be variants of the same process, and the term *Sjögren's syndrome* (SS) became more widely used.[14]

DEFINITIONS :

Primary SS is best defined as dry eyes and dry mouth secondary to autoimmune dysfunction of the exocrine glands. Secondary SS is the same disease in the presence of another autoimmune connective tissue disorder. Until relatively recently (1980), the terms *sicca syndrome* and *sicca complex* were used interchangeably with SS in the literature, and their routine use in clinical settings persists today.

CAUSE AND PATHOGENESIS

Animal models of SS have provided some important insights regarding the immunopathogenesis of this disease: (1) SS has a strong immunogenetic component, (2) the inflammatory infiltrate is largely T cell driven, (3) autoimmune sialadenitis can be triggered by viral

infection, (4) relatively specific autoantibodies are produced, and (5) genes regulating apoptosis influence the chronicity of lymphocytic infiltration and are candidates for therapeutic manipulation.

CLINICAL MANIFESTATIONS

OCULAR

Although the most prominent ocular manifestation of SS is dry eye, patients are often unaware of dryness as a presenting symptom. Instead, they may complain of a foreign body–type sensation manifested by scratchiness, grittiness, or irritation from a "grain of sand." Other common symptoms of dry eye include photophobia, redness, and ocular fatigue. Thick mucous strands may cause blurring of vision, and the eyelids may be encrusted, especially on awakening. If the condition persists and is untreated, symptoms may reflect complications of xerophthalmia, including pain, intense photophobia indicative of corneal abrasion, and discharge, possibly indicative of infection. Infections threaten sight and are most often caused by gram-positive bacteria.

ORAL

In contrast to dry eye, patients often complain of a dry mouth. Physicians caring for SS patients are accustomed to seeing them carry plastic water bottles because they require a constant supply of moisture to be comfortable. The dry-mouth patient describes a parched feeling in the mouth, often extending to the throat. Eating is often difficult without supplemental liquids. Owing to a reduction in salivary volume and the subsequent loss of the antibacterial properties of saliva, tooth decay is accelerated. In fact, unexplained rampant dental caries may be the first sign of dry mouth.

OTHER XEROSES

Dry nose is common and may lead to inflammation with subsequent congestion, crusting, and epistaxis. Xerotrachea may result in a chronic dry cough. Dry skin may lead to pruritus and excoriation. Rarely, secondary infection may occur. Vaginal dryness may lead to pruritus, irritation, and dyspareunia. Although the most common cutaneous manifestation of SS is dryness, little is known about the precise cause or whether cutaneous dryness is truly part of the autoimmune exocrinopathy of SS. Sweat volume is reduced in SS patients,[15] and a skin biopsy

revealed lymphocytic infiltrates surrounding eccrine glands and ducts in one patient suffering from severe anhidrosis.[16]

Table 3 -- Systemic Manifestations Associated with Sjögren's Syndrome

Musculoskeletal Arthralgias Myalgias
Cutaneous Dry skin Hyperglobulinemic purpura Vasculitis
Pulmonary Xerotrachea Pulmonary infiltrate Micronodules
Gastrointestinal Esophageal dysmotility Pancreatitis Hepatitis

Renal Renal tubular acidosis Interstitial nephritis
Neurologic Peripheral neuropathy Cranial neuropathy (especially fifth cranial nerve) Central nervous system disease
Hematologic Leukopenia Anemia Lymphoma

SECONDARY SJÖGREN'S SYNDROME

Although secondary SS is defined as xerostomia and xerophthalmia in the presence of an autoimmune connective tissue disease, it is important to note that secondary SS is not monolithic. In other words, the characteristics of SS may vary among the different connective tissue disorders. Additionally, SS is a common accompaniment of autoimmune disorders not generally considered to be connective tissue diseases, such

as thyroiditis, primary biliary cirrhosis, and MS. Thus, signs of SS should not be overlooked in these contexts.

Clinical SS affects approximately 20% of patients with RA. Thirty-one percent have positive MSG biopsies.[17] SS-A antibodies have been found in 4% to 23% of RA patients.[17,18,19] These patients are more likely to have severe sicca complaints and positive MSG biopsies.

CLINICAL OUTCOMES

When followed over a 10-year period, approximately one third of patients with sicca complaints eventually fulfilled the criteria for SS. [20,21] Development of disease and severity of sicca symptoms correlate with the presence of autoantibodies, particularly ANA and SS-A, and the serum IgG level.

DIAGNOSIS AND WORKUP:

The modalities used for the workup of SS are the basis for most of the criteria proposed for the classification of SS. Thus, the evaluation of a patient with suspected SS often requires cooperation among the rheumatologist, ophthalmologist, and dental specialist. The workup of SS

is based on the American-European Consensus Group modification of the European Community criteria shown in Table 3.

Table 4 -- AEC Criteria for Sjögren's Syndrome

I. Symptoms of dry eye Patients must have a positive response to at least one of the following: Have you had daily, persistent, troublesome dry eyes for more than 3 months? Do you have a recurrent sensation of sand or gravel in the eyes? Do you use tear substitutes more than three times a day?
II. Oral symptoms Patients must have a positive response to at least one of the following: Have you had a daily feeling of dry mouth for more than 3 months? Have you had recurrently or persistently swollen salivary

glands as an adult?

Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs

Patients must have objective evidence of ocular involvement, defined as a positive result from at least one of the following two tests:

Schirmer test performed without anesthesia (5 mm in 5 min)

Rose bengal score or other ocular dye score (4 according to van Bijsterveld's scoring system)

IV. Histopathology

This criterion is met if an expert histopathologist evaluates focal lymphocytic sialadenitis with a focus score of 1 in the patient's minor salivary glands (obtained through normal- appearing mucosa). The focus score is defined as the number of lymphocytic foci adjacent to normal-appearing mucous acini and containing more than 50 lymphocytes/4 mm^2 of glandular tissue.

V. Salivary gland involvement

Patient must have objective evidence of salivary gland involvement, defined by a positive result for at least one of the following diagnostic tests:

Unstimulated whole salivary flow (1.5 ml in 15 min)

Parotid sialography showing the presence of diffuse sialectasis (punctate, cavitary, or destructive pattern) without evidence of obstruction in the major ducts

Salivary scintigraphy showing delayed uptake, reduced concentration, delayed excretion of tracer, or some combination of these

VI. Autoantibodies

Patient must have the following autoantibodies present in serum:

antibodies to Ro (SS-A) or La (SS-B)
Definite Sjögren's syndrome requires the presence of four criteria, one of which must be either a positive biopsy or autoantibodies
Exclusions: prior head and neck radiation, hepatitis C infection, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), preexisting lymphoma, sarcoidosis, graft-versus-host disease, use of anticholinergic drugs

Serologies, particularly ANA and SS-A and SS-B, correlate with focus score on biopsy.[22] Serum IgG is the most specific predictor of a positive biopsy but has relatively low sensitivity.[23]A recent report of 41 patients tested for the presence of anti–SS-A and anti–SS-B and undergoing MSG biopsy showed a fairly high negative predictive value of anti–SS-A for MSG biopsy.[24] Anti–SS-B may be useful in identifying primary SS among patients presenting with xerostomia, xerophthalmia, and undifferentiated features of connective tissue disorder.[25]

TREATMENT

Therapy for SS has three phases. The first phase consists of external moisture replacement or capture. This approach can be applied to the oral cavity, eyes, nose, skin, and genital tract. The second phase consists of stimulation of endogenous secretions, which has proved effective mainly for xerostomia. This approach is currently under investigation for other xeroses, including the eyes and skin. Finally, patients with systemic manifestations, such as pulmonary disease, vasculitis and pseudolymphoma, may require corticosteriods, cytotoxic agents, or both.

AIMS AND OBJECTIVES

1. To evaluate the prevalence of the sicca syndrome in patients with rheumatoid arthritis
2. To estimate the prevalence of sicca symptoms in patients with rheumatoid arthritis and to look for correlation between the prevalence of sicca symptoms and disease duration and activity
3. To look for the presence of the primary sicca syndrome using antibody assay in patients who have objective evidence of sicca symptoms.

MATERIALS AND METHODS

Ours was a cross sectional study carried out for a period of 1 year. The setting was the Department of Medicine, Government Rajaji Hospital, Madurai. Approval was obtained from the ethical committee headed by the Dean, Govt Rajaji Hospital. Informed written consent was obtained from all patients. The study population consisted of patients attending the outpatient department of rheumatology who were randomly selected. The data obtained was analysed using EPI Info 2002 statistical software.

The study was carried out on 40 patients attending the Rheumatology out-patient department of Madurai Medical College with an established diagnosis of RA, as defined by the American College of Rheumatology 1987 criteria.

Patients were considered seropositive if the rheumatoid factor (Latex agglutination test) was positive (>8 IU/L) on atleast one occasion during the course of their disease.

All patients had been treated with nonsteroidal anti-inflammatory drugs (diclofenac, 100-150 mg/day) daily. Treatment with a DMARD was initiated when a diagnosis of RA was made. All the patients included in

our study were receiving one or more DMARDs including chloroquine, sulfasalazine and methotrexate. Some of them were on low dose steroids (5-15mg/day) depending on severity of symptoms.

INCLUSION CRITERIA :

- Patients who satisfied the American College of Rheumatology 1987 criteria.
- Age group - 17 to 60 years irrespective of the sex
- Any duration of illness

EXCLUSION CRITERIA

- Past head and neck irradiation treatment
- Hepatitis C infection
- AIDS
- Pre-existing lymphoma
- Use of anti-cholinergic drugs

A questionnaire prepared noted the duration of RA, duration of early morning joint stiffness, personal history including smoking, medications and occupation. The questionnaire also included questions on oral and ocular symptoms. The use of current and previous disease-

modifying drugs, corticosteroid use and analgesics was noted. Cigarette consumption was evaluated in pack years (1 pack yr = 20 cigarettes/day for 1 yr).

- A detailed clinical examination consisting of examination of the eyes and oral cavity ,salivary gland swelling, the number of tender and swollen joints and systemic examination was performed. All patients had venous blood taken for full blood count, renal function tests, erythrocyte sedimentation rate and immunological investigations including rheumatoid factor (latex agglutination test).
- All patients were made to undergo Schirmer's I test using test strips and only those patients who had symptoms and objective evidence of dry eye in the form of wetting of the test strips less than or equal to 5 mm in 5 minutes were subjected to antibody assay.
- The activity of the disease was assessed using DAS 28(Disease activity score).Disease activity score is a composite score using tender and swollen joint count, ESR and patients' global assessment activity using a 100 mm visual analogue scale.
- DAS28 = 0.56 √(no.of tender joints) + 0.28 √(no.of swollen joints) +0.70 log(ESR)+0.014 (global assessment in mm).

Classification

- Mild <3.2
- Moderate 3.2-5.1
- Severe >5.1 (Minimum score :0; Maximum score : 9)

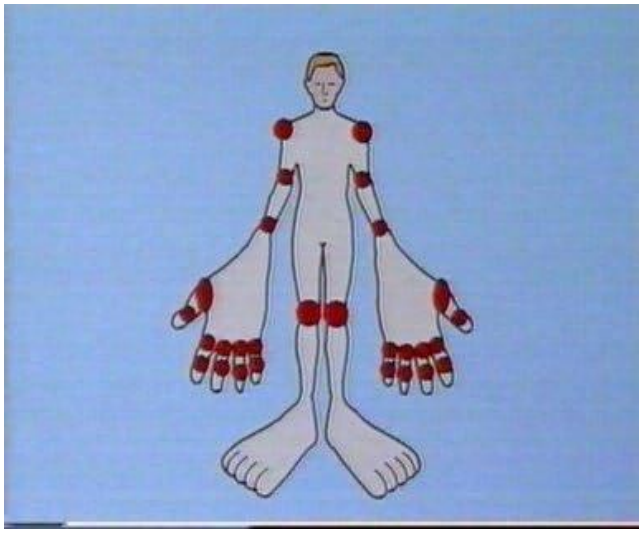
Parameters used in Disease activity score:

(1) Total 28 joint count for tenderness

(2) Total 28 joint for swelling

(3) ESR in mm in first hour

(4) Patient assessment of global health using a 100mm visual analogue scale ranging from 0(very good) to 100 (very poor).



Schirmer's test and auto antibody profile :

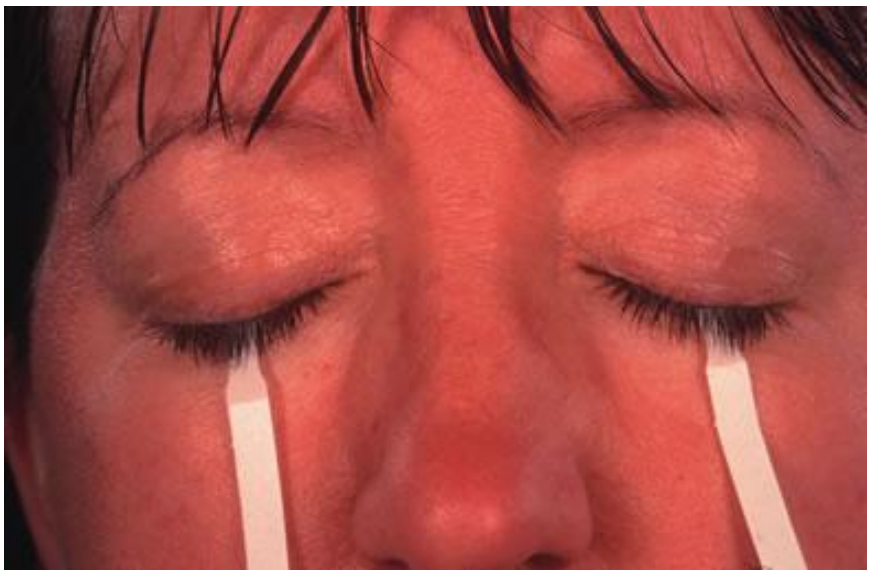
SCHIRMER – I TEST:

The test was performed according to published guidelines. Patients had not used tear substitutes for atleast one hour before examination. Patients dried their eyes carefully with a soft paper tissue ; then the test strips – always starting with the right eye – were placed between the medial and lateral parts of the lower eyelid, and removed after five minutes. Anaesthesia was not used. A positive test for reduced tear production was recorded if the strips were wetted 5 mm or less in one or both eyes, starting from the notch of the test strip corresponding to the inferior lid margin.

AUTO-ANTIBODY PROFILE:

Those patients who had oral and ocular sicca symptoms and a positive Schirmer's test in one eye were subjected to a blood profile for extractable nuclear antigens. The test kit used consisted of test strips with six antigens namely RNP, Smith antigen ,SS-A native , Ro – 52 recombinant , SS-B,Scl-70 , Jo-1 . Following this, the revised criteria were applied to estimate the prevalence of the sicca syndrome.

SCHIRMER'S TEST BEING PERFORMED ON A PATIENT



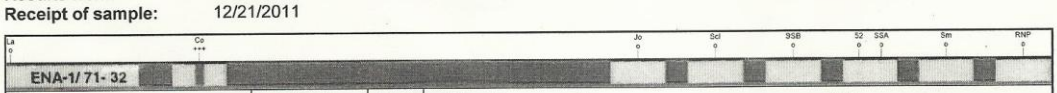
Madurai Arthritis and Rheumatism Centre

(Centre for comprehensive rheumatic care)

MARC

LABORATORY REPORT

Patients IDs:	Mrs.Armugam	**Test:**	Ena ProfilPlus 1 (6 Ag, SS-A und Ro52)
Name:	Mrs.Armugam	**Strip number:**	71-32
Testkit:	Ena1	**Lab number:**	5248/11
Date of receipt:	12/24/2011	**Number:**	1
Results from:	12/24/2011	**Sent from:**	Dr.P.S.Arulrajamurugan
Receipt of sample:	12/21/2011		



Antigen	Intensity	Class
RNP/Sm (RNP)	1	o
.m (Sm)	1	o
SS-A native (60 kDa) (SSA)	2	o
Ro-52 recombinant (52)	3	o
SS-B (SSB)	1	o
Scl-70 (Scl)	0	o
Jo-1 (Jo)	1	o
Control (Co)	102	+++
Label (La)		

o (+) + ++ +++

Class	Explanation
o	Negative
(+)	Borderline
+	Positive
++	Strong positive
+++	Strong positive

Signature: _____

Signature

ENA REPORT OF PATIENT SHOWING NEGATIVE RESULTS FOR

ALL SIX EXTRACTABLE NUCLEAR ANTIGENS

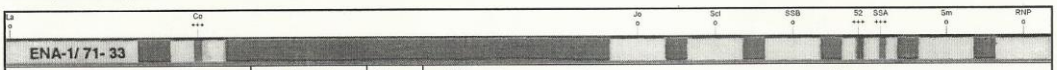
Madurai Arthritis and Rheumatism Centre

(Centre for comprehensive rheumatic care)

MARC

LABORATORY REPORT

Patients IDs:	Mrs.Kaleeswari	**Test:**	Ena ProfilPlus 1 (6 Ag, SS-A und Ro52)
Name:	Mrs.Kaleeswari	**Strip number:**	71-33
Testkit:	Ena1	**Lab number:**	2916/10
Date of receipt:	12/24/2011	**Number:**	1
Results from:	12/24/2011	**Sent from:**	Dr.P.S.Arulrajamurugan
Receipt of sample:	12/21/2011		



Antigen	Intensity	Class
RNP/Sm (RNP)	1	o
.n (Sm)	0	o
SS-A native (60 kDa) (SSA)	96	+++
Ro-52 recombinant (52)	114	+++
SS-B (SSB)	4	o
Scl-70 (Scl)	1	o
Jo-1 (Jo)	1	o
Control (Co)	98	+++
Label (La)		

o (+) + ++ +++

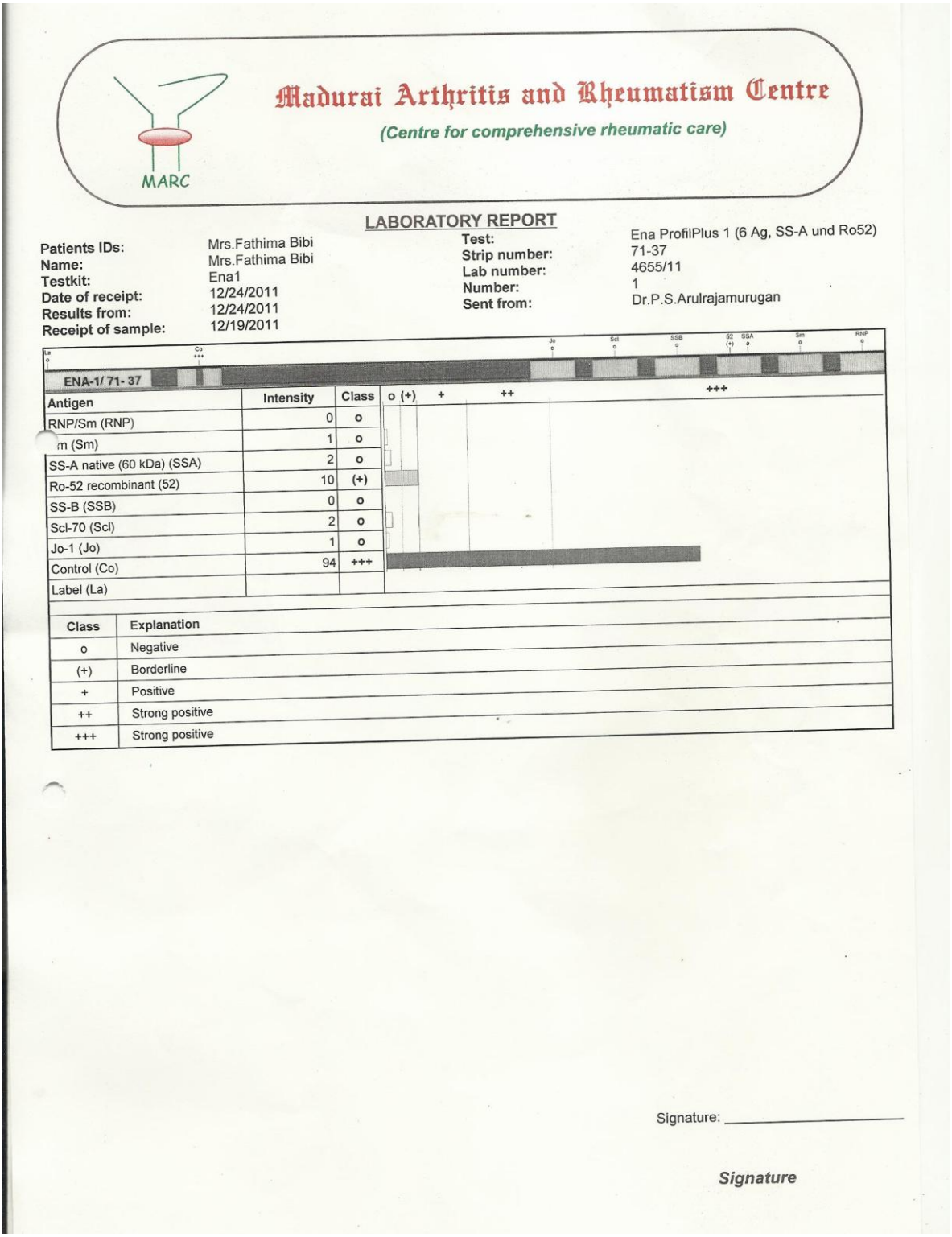
Class	Explanation
o	Negative
(+)	Borderline
+	Positive
++	Strong positive
+++	Strong positive

Signature: _____

Signature

ENA REPORT OF PATIENT SHOWING STRONG POSITIVITY FOR

SS-A & Ro - 52



Madurai Arthritis and Rheumatism Centre

(Centre for comprehensive rheumatic care)

MARC

LABORATORY REPORT

Patients IDs:	Mrs.Fathima Bibi	**Test:**	Ena ProfilPlus 1 (6 Ag, SS-A und Ro52)
Name:	Mrs.Fathima Bibi	**Strip number:**	71-37
Testkit:	Ena1	**Lab number:**	4655/11
Date of receipt:	12/24/2011	**Number:**	1
Results from:	12/24/2011	**Sent from:**	Dr.P.S.Arulrajamurugan
Receipt of sample:	12/19/2011		

ENA-1/ 71- 37

Antigen	Intensity	Class
RNP/Sm (RNP)	0	o
m (Sm)	1	o
SS-A native (60 kDa) (SSA)	2	o
Ro-52 recombinant (52)	10	(+)
SS-B (SSB)	0	o
Scl-70 (Scl)	2	o
Jo-1 (Jo)	1	o
Control (Co)	94	+++
Label (La)		

Class	Explanation
o	Negative
(+)	Borderline
+	Positive
++	Strong positive
+++	Strong positive

Signature: _____

Signature

ENA REPORT OF PATIENT SHOWING BORDERLINE POSITIVITY FOR Ro - 52

STATISTICS :

Data analysis was done using epidemiological information statistical software. Using the software, the frequencies, mean, standard deviation and 'p' values were calculated. Chi square test and one way ANOVA were applied to the quantitative variables. 'p' value < 0.05 was taken as significant.

RESULTS

Baseline demographics and clinical characteristics:

The study was conducted from December 2010 to November 2011 recruiting subjects from the rheumatology outpatient clinic of Government Rajaji Hospital, Madurai. A total of 40 RA patients were enrolled during this study period. Women outnumbered men in the study population with 32 women and 8 men. In our study, the age of the participants varied from 17 to 60 years.

Table - 1

AGE DISTRIBUTION:

Age in years	No.of males	No.of Females	Total
15 – 25	0	0	0
26 - 35	12	2	10
36 – 45	9	3	6
46 – 55	13	1	12
> 55	6	2	4
Total	40	8	32

In our study, the age of the participants varied from 25 to 60 years. Age greater than 60 years was an exclusion criterion.

AGE DISTRIBUTION

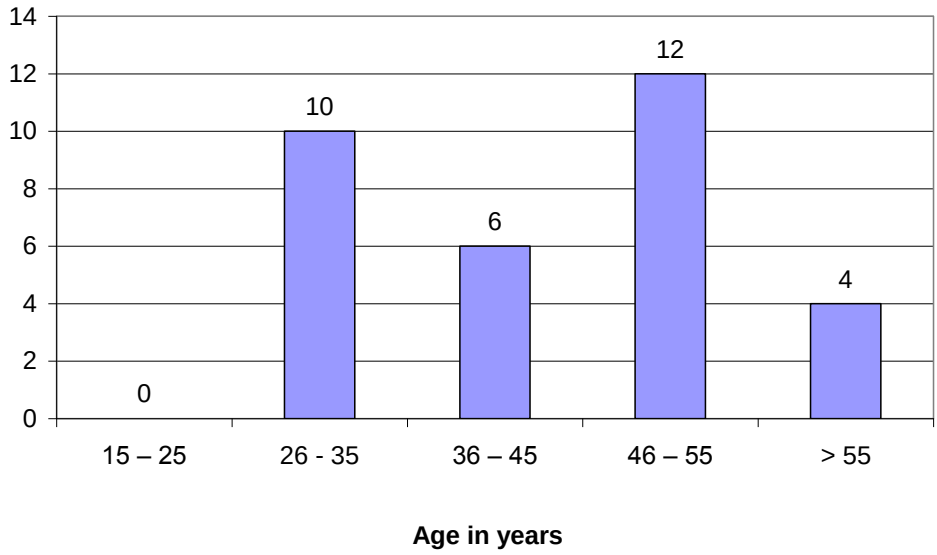


Table - 2

SEX DISTRIBUTION

Sex	No.of cases
Male	8
Female	32

Of the total 40 RA patients, 32 were women and 8 were men in a ratio of 4:1

SEX DISTRIBUTION

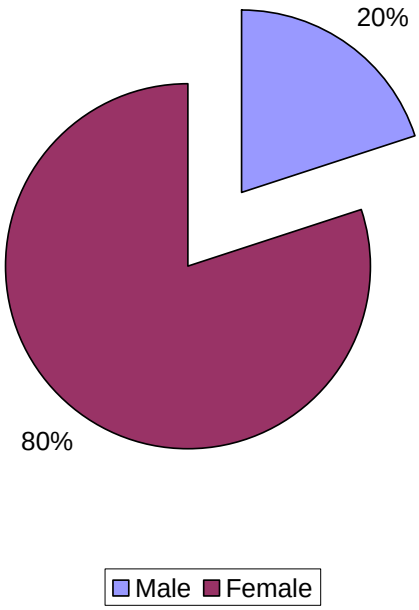


Table – 3

Duration of Illness

Duration	No.of cases
< 1 year	6
1 – 10 years	29
11 – 20 years	4
> 20 years	1
Total	40

In our study, the duration of illness ranged from as short as 2 months to as long as 22 years. The maximum number of patients were found to have an illness duration of 1- 10 years.

DURATION OF ILLNESS

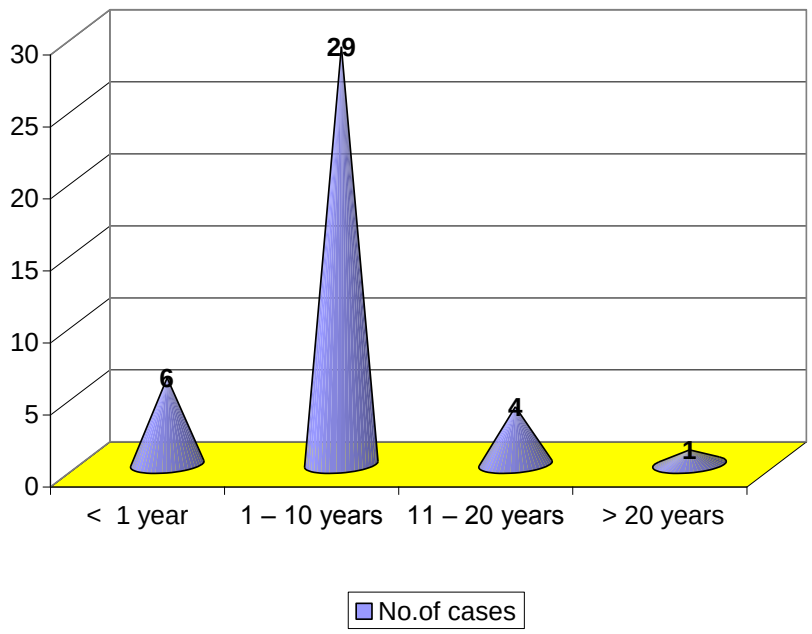


Table - 4

PREVALENCE OF SICCA SYMPTOMS

Sicca Symptoms	No.of cases
Dry Eye only	25
Dry mouth only	7
Both Dry eye and Dry mouth	7

Of the 40 patients, 25 patients had only symptoms of dry eye with a prevalence of 62.5 %. 7 patients (17.5%) had only symptoms of dry mouth and 7(17.5%) patients had symptoms of both dry eyes and dry mouth.

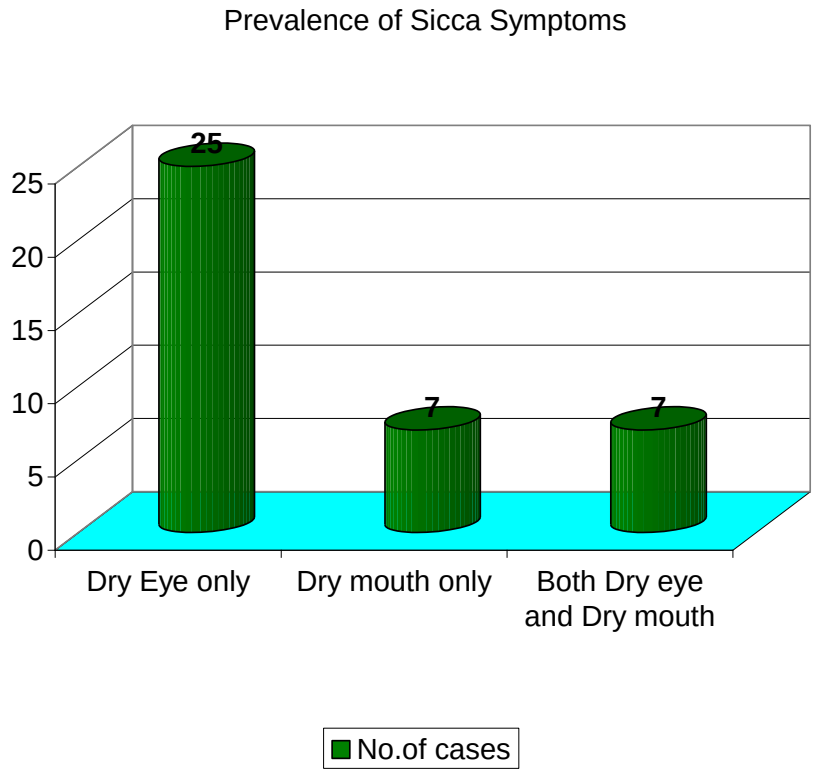

Prevalence of Sicca Symptoms
25
20
15
10
5
0
25
7
7
Dry Eye only
Dry mouth only
Both Dry eye and Dry mouth
No.of cases

Table – 5

PREVALENCE OF OBJECTIVE EVIDENCE OF DECREASED TEAR PRODUCTION (POSITIVE SCHIRMER'S TEST)

Schirmer's Test	No.of cases	Both Eyes < 5mm	One eye < 5mm
< 5mm	13 (32.5%)	8	5
> 5 mm	27 (67.5%)		

Of the 40 patients studied, 13(32.5%) patients had a positive Schirmer's test. Of these 8 patients were positive in both eyes and 5 were positive in one eye.

Table – 6

CORRELATION BETWEEN DRY EYE AND DISEASE DURATION:

Duration	No.of cases	Dry Eye Yes	Dry Eye No
< 1 year	6	2	4
1 – 10 years	29	19	10
11 – 20 years	4	3	1
> 20 years	1	1	0
Total	40	25	15

There was no correlation between duration of illness and the occurrence of dry eye symptoms with a ‘p’ value of 0.271.

CORRELATION BETWEEN DRY EYE AND DISEASE DURATION

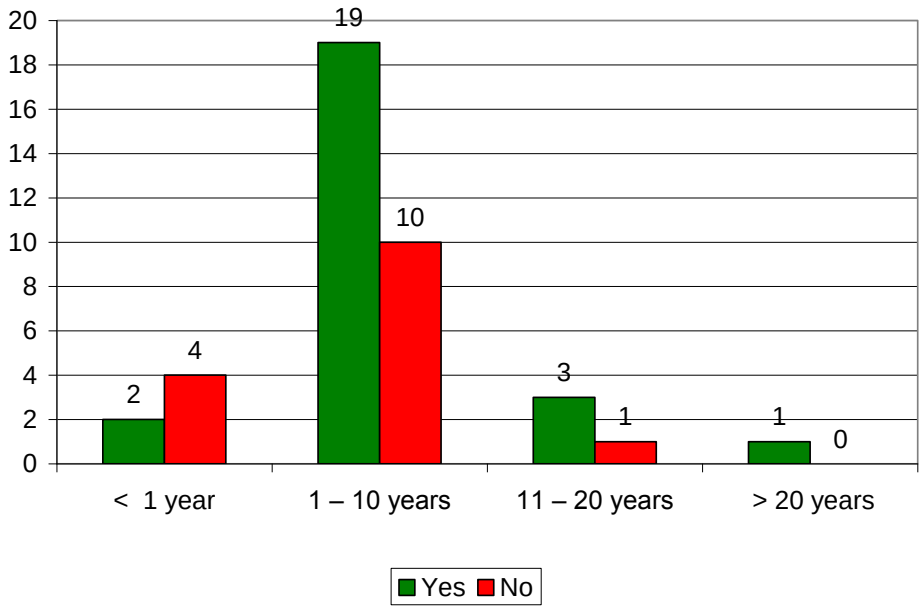


Table – 7

CORRELATION BETWEEN DRY EYE AND DAS 28

DAS 28	Total cases	Dry Eye Yes	Dry Eye No
< 3.2	2	1	1
3.2 – 5.1	24	16	8
> 5.1	14	8	6
Total	40	25	15

There was no correlation between disease severity assessed by DAS 28 and occurrence of dry eye symptoms with a ‘p’ value of 0.271.

CORRELATION BETWEEN DRY EYE AND DAS 28:

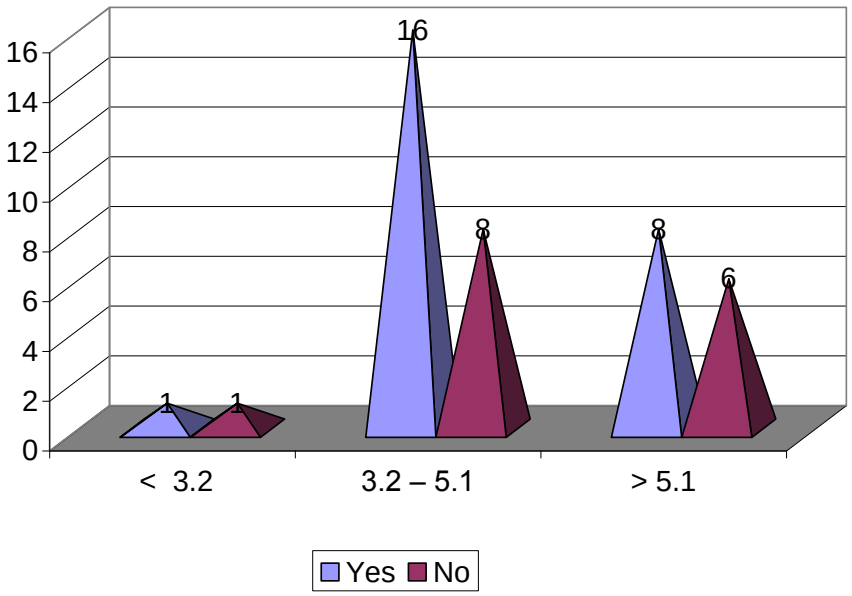


Table – 8

CORRELATION BETWEEN DRY MOUTH AND DISEASE DURATION

Duration of illness	Total cases	Dry Mouth Yes	Dry Mouth No
< 1 year	6	0	6
1 – 10 years	29	3	26
11 – 20 years	4	3	1
> 20 years	1	1	0
Total	40	7	33

There was no correlation between duration of disease and the occurrence of dry mouth symptoms with a 'p' value of 0.4

Table - 9

CORRELATION BETWEEN DRY MOUTH AND DAS 28:

DAS 28	Total cases	Dry Mouth Yes	Dry Mouth No
< 3.2	2	1	1
3.2 – 5.1	24	5	19
> 5.1	14	2	12
Total	40	8	32

There was a positive correlation between disease severity assessed by DAS 28 and the occurrence of dry mouth symptoms with a 'p' value of 0.03.

Only 2 of the 40 patients studied, satisfied the revised AEC criteria for the diagnosis of primary sicca syndrome by testing positive for either SS- A or SS- B yielding a prevalence rate of 5 %.

DISCUSSION

The prevalence of Sjogren' s syndrome in association with autoimmune disease is not well established. This results from the lack of uniform criteria for the diagnosis of this syndrome, differences in diagnostic techniques for evaluating keratoconjunctivitis sicca and xerostomia, and the absence of prospective studies on the true prevalence of the syndrome in association with other diseases.

Sjogren's syndrome can be diagnosed when any two of the following three clinical features are present : dry eyes, dry mouth and arthritis. Typical lesions in the eyes and mouth, however, are not always present at the same time nor at the same stage of development ; also, spontaneous clinical remission may occur.

Demographics and clinical characteristics :

This was a cross- sectional study carried out on 40 RA patients of whom 32 were women and 8 were men. Duration of illness ranged from less than a year to as long as 22 years.The age of the patients ranged from 25 – 60 years with an age > 60 years being an exclusion criterion for the study.

Prevalence of sicca symptoms and objective evidence of decreased tear production:

In our study , 62.5% of the 40 patients responded positively to questions on dry eye symptoms, 17.5% had symptoms of dry mouth, 17.5% had symptoms of both dry eye and dry mouth. In a similar study done by T Uhlig et al[26] , ocular sicca symptoms were reported in 38%, oral sicca symptoms in 50% and a combination of both in 27 %. Reduced tear production as evidenced by a positive Schirmer's test was present in 29%. Of the 40 patients studied, 13 patients had a positive Schirmer's test with a prevalence of 32.5% closely paralleling the findings of the above mentioned study. Previous studies examining the sicca symptoms in RA patients are sparse. Andonopoulos et al[27] examined 111 RA patients and found sicca symptoms from eyes in 38% , from mouth in 6%. In another minor study[28], Schirmer's test was reduced in 30% of RA patients mirroring the findings of our study. Such different results may be partly explained by different approaches in the assessment of sicca symptoms

Correlation of sicca symptoms with disease activity and duration:

Our study showed a lack of correlation between dry eye symptoms and disease duration. Likewise there was also no correlation between

symptoms of dry eye and disease activity as assessed by DAS 28. In our study however, a positive correlation was found between symptoms of dry mouth and disease activity whereas no correlation could be made out between dry mouth symptoms and disease duration. These findings are similar to those of the study conducted by T Uhlig et al[26] in which no correlation could be found between ocular and oral dryness and disease activity and duration.

Prevalence of sicca syndrome in RA patients:

The prevalence of sicca syndrome in our study as evidenced by patients satisfying the revised AEC criteria was 5%. In a study by Fujita et al[29] of 72 Japanese patients, just 10% of them had secondary Sjogren's syndrome. The presence of sicca syndrome in RA has been found to be higher in other studies. Cimmino et al[30] found it in 17.5% of Italian RA patients and Martinez Castro et al[31] in 55% of Spanish RA population. This high variability from study to study may be due to the genetic background of the studied population and methods chosen to evaluate glandular dysfunction.

According to the findings of our study and the above mentioned studies,rheumatologists and ophthalmologists should be aware of high indices of sicca symptoms in RA & seek for sicca syndrome independently of the activity and duration of rheumatoid arthritis.

CONCLUSION

In conclusion, the prevalence of ocular sicca symptoms in RA patients attending the rheumatology outpatient clinic in Government Rajaji hospital was 62.5% and that of oral symptoms alone was 17.5%. A combination of both ocular and oral dryness was present in 17.5%.

There was no significant correlation between disease duration and symptoms of dry eye in our study group. There was no statistically significant correlation between dry eye symptomatology and disease activity. Though no correlation could be found out between disease duration and dry mouth, there was a statistically significant correlation between dry mouth symptoms and disease activity.

The patients who completely satisfied the AEC criteria for the diagnosis of primary sicca syndrome in our study population were 2 in number yielding a prevalence of primary sicca syndrome of 5% .

This study highlights the need for close and continual follow up of all patients with rheumatoid arthritis with a thorough clinical history and examination supplemented by screening tests for ocular and oral dryness. If patients test positive in screening tests, more advanced and invasive tests like minor salivary gland biopsy and auto antibody assay can be done to establish a diagnosis of Sjogren’s syndrome. Such patients should

be closely observed by physicians for the development of lymphomas which are highly likely to occur in this subset of patients of RA with the sicca syndrome.

SUMMARY

The study " Prevalence of sicca syndrome in patients with rheumatoid arthritis" is a cross- sectional study conducted on patients visiting the outpatient department of rheumatology, Government Rajaji hospital,Madurai.Forty patients with rheumatoid arthritis fulfilling the American Rheumatologists association criteria(1987) were included in the study.Inclusion and exclusion criteria were strictly followed. Selected patients underwent clinical and laboratory evaluation to assess the severity and activity of disease including Schirmer's test for ocular dryness .DAS 28 score was calculated as an indicator of disease severity. Statistical analysis showed no correlation between disease activity , disease duration and the occurrence of sicca syndrome which was found to be present in 5% of our study patients reiterating the findings of other similar studies.

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PROFORMA

A STUDY ON THE PREVALENCE OF SICCA SYNDROME IN PATIENTS WITH RHEUMATOID ARTHRITIS

Name :

Age : Sex :

Address : Ph :

CLINICAL FEATURES

Duration of illness –

Disease Activity –

Sicca symptoms –

Ocular symptoms –

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?

2. Do you have a recurrent sensation of sand or gravel in the eyes?

3. Do you use tear substitutes more than three times a day?

Oral symptoms –

1. Have you had a daily feeling of dry mouth for more than 3 months?

2. Have you had recurrent or persistently swollen salivary glands as an adult?

3. Do you frequently drink liquids to aid in swallowing dry foods?

Negative history - History of head and neck irradiation, usage of anticholinergics/TCA, Jaundice

EXAMINATION –

Oral cavity examination –

Examination of eye – scleritis/ episcleritis

Schirmer's test - <5mm >5mm

Examination of salivary glands –

Lymphadenopathy –

Examination of joints for swelling and tenderness

LABORATORY INVESTIGATIONS –

Renal function test

Liver function test

Hb

TC

ESR

Anti HCV

HIV

Rheumatoid factor

ENA profile –

SSA SSB Rho 52

No	Name	Age	Sex	DOI	EMS	Hypertension	Diabetes	DAS 28	s/o dry eye	s/o dry mouth	Blood urea	Creat	RBS	Hb
1	Thirumalaiselvi	40	f	3 months	1/2 hr	No	No	5.06	No	No	22.3 mg%	0.78 mg%	110 mg%	9.3
2	Kaleeswari	28	f	2 years	No	No	No	5.54	Yes	No	24.6 mg%	0.92 mg%	115 mg%	9.6
3	Krishnaveni	58	f	2 years	No	Yes	No	4.89	Yes	Yes	26.2 mg%	0.89 mg%	77 mg%	6.9
4	Arumugam	32	m	1 year	No	No	No	4.12	No	No	18.6 mg%	0.63 mg%	160 mg%	11.9
5	Surendiran	58	m	3 years	No	No	No	3.95	No	No	19.0 mg%	1.2 mg%	86 mg%	12
6	Murugan	33	m	2 years	1/4 hr	No	No	4.43	Yes	No	27 mg%	0.8 mg%	68 mg%	11
7	Pushpam	56	f	1 year	1/2 hr	Yes	No	4.99	Yes	Yes	18 mg%	0.8 mg%	90 mg%	10
8	Ramalakshmi	32	f	4 years	1/4 hr	No	No	3.38	Yes	Yes	24 mg%	0.89 mg%	157 mg%	11.7
9	Dhanalakshmi	52	f	15 years	1/4 hr	No	No	5.96	Yes	Yes	24.2 mg%	0.88 mg%	113 mg%	10.4
10	Thilagam	53	f	2 years	1/4 hr	Yes	No	6.78	No	No	24.3 mg%	0.81 mg%	105 mg%	11.6
11	Anarkali	58	f	10 years	1/4 hr	No	No	6.46	No	No	24 mg%	0.89 mg%	187 mg%	9.4
12	Arokiammal	54	f	17 years	1/4 hr	No	No	4.47	No	No	20 mg%	0.7 mg %	123 mg%	10

13	Manimala	48	f	3 years	1/4 hr	No	No	5.28	No	No	21.1 mg%	0.7 mg %	114 mg%	12.7
14	Ajanta	49	f	1 year	1/4 hr	Yes	No	2.94	No	No	20 mg%	1.0 mg%	102 mg%	11.8
15	Manimegalai	50	f	1 year	1/4 hr	No	No	4.9	No	No	26.4 mg%	0.82 mg%	122 mg%	10.2
16	Amudha	36	f	5 years	1 hr	No	No	4.09	No	No	26.7 mg%	0.92 mg%	114 mg%	10.2
17	Gunasekaran	58	m	5 years	1 hr	No	No	5.35	No	No	27.2 mg%	0.96 mg%	148 mg%	9.2
18	Lalitha Ganesan	39	f	10 years	1/2 hr	No	No	6.18	No	No	16 mg%	0.71 mg%	77 mg%	11
19	Vasantha	50	f	2 years	1/4 hr	Yes	No	4.87	Yes	No	24 mg%	0.6 mg%	117 mg%	12
20	Chandra	47	f	20 years	1/2 hr	No	No	3.28	Yes	Yes	29 mg%	0.8 mg%	107 mg%	10.6
21	Veerammal	47	f	3 years	1/2 hr	No	No	5.87	No	No	29.7 mg%	0.7 mg%	135 mg%	9.8
22	Chellammal	50	f	2 years	No	No	No	4.68	Yes	No	20.3 mg%	0.7 mg%	114 mg%	12
23	Rajeswari	25	f	2 months	1/4 hr	No	No	4.78	No	No	19.8 mg%	0.6 mg%	105 mg%	11
24	Jasmine	31	f	1 year	No	No	No	5.09	Yes	No	23 mg%	0.8 mg%	95 mg %	11.1
25	Jothi	45	m	2 months	No	No	No	4.11	No	No	24.5 mg%	0.76 mg%	108 mg%	10
26	Saraswathy	38	f	1 year	1/4 hr	No	No	2.89	No	No	29 mg%	0.7 mg%	99 mg%	12
27	Gomathy	54	f	10 years	1 hr	No	No	6.7	No	No	27.3 mg%	0.86 mg%	132 mg%	10.2
28	Bakeeral Begum	56	f	22 years	1/2 hr	Yes	Yes	4.3	Yes	Yes	29 mg%	1.4 mg%	150 mg%	10.2

29	Uma Maheswari	36	f	5 months	No	No	No	5.15	No	No	14.42 mg%	1.04 mg%	72 mg%	12
30	Vazhivittan	47	m	8 months	No	No	No	4.51	Yes	No	26.2 mg%	0.86 mg%	134 mg%	9.7
31	Fathima Beevi	45	f	12 years	No	No	Yes	5.13	Yes	Yes	27.3 mg%	0.92 mg%	124 mg%	10.7
32	Jareena Begum	48	f	2.5 years	No	No	Yes	5.8	Yes	No	24 mg%	0.9 mg%	130 mg%	9.2
33	Mariappan	38	m	7 years	1/4 hr	No	No	4.26	No	No	25 mg%	1.0 mg%	123 mg%	9.8
34	Latha	34	f	3 years	1/4 hr	No	No	5.48	No	No	30 mg%	0.6 mg%	118 mg%	10.7
35	Kaliammal	27	f	2 years	1/2 hr	No	No	4.21	Yes	No	29 mg%	0.8 mg%	143 mg%	12
36	Chandran	43	m	10 years	No	No	No	5.07	No	No	34 mg%	1.2 mg%	118 mg%	10.8
37	Durga	27	f	8 months	1/2 hr	No	No	4.56	Yes	No	32 mg%	0.9 mg%	104 mg%	12.4
38	Chitra	32	f	5 years	1/4 hr	No	No	4.37	Yes	No	24 mg%	0.6 mg%	97 mg%	9.4
39	Chinnammal	28	f	3.5 years	1 hr	No	No	3.84	No	No	28 mg%	0.6 mg%	130 mg%	11.2
40	Pothumponnu	35	f	2 years	1/2 hr	No	No	5.85	Yes	No	19 mg%	0.9 mg%	124 mg%	9.7

TC	ESR	ST - R	ST - L	SS-A	SS-B	Ro-52
8000	62	24 mm	20 mm	-	-	-
6400	50	< 5mm	<5 mm	Positive	Negative	Positive
8300	60	9 mm	12 mm	-	-	-
8500	15	< 5 mm	7 mm	Negative	Negative	Negative
9500	8	15 mm	15 mm	-	-	-
11400	15	25 mm	20 mm	-	-	-
9800	20	< 5mm	< 5 mm	Negative	Negative	Negative
14500	10	15 mm	20 mm	-	-	-
8500	55	< 5 mm	< 5 mm	Negative	Negative	Negative
9800	20	21 mm	17 mm	-	-	-
11800	70	< 5 mm	7 mm	Negative	Negative	Negative
8700	10	15 mm	15 mm	-	-	-
8900	8	< 5 mm	< 5 mm	Negative	Negative	Negative
6700	8	10 mm	12 mm	-	-	-
9200	55	20 mm	15 mm	-	-	-
10200	45	20 mm	20 mm	-	-	-

8800	55	< 5 mm	< 5 mm	Negative	Negative	Negative
7200	55	30 mm	28 mm	-	-	-
5600	30	< 5 mm	< 5 mm	Negative	Negative	Negative
4700	20	10 mm	15 mm	-	-	-
7000	45	20 mm	25 mm	-	-	-
8300	25	< 5 mm	9 mm	Negative	Negative	Negative
15700	47	18 mm	25 mm	-	-	-
6700	39	12 mm	12 mm	-	-	-
9500	60	14 mm	12 mm	-	-	-
7000	12	15 mm	12 mm	-	-	-
10000	47	14 mm	12 mm	-	-	-
14400	25	<5 mm	< 5 mm	Negative	Negative	Negative
7400	30	15 mm	20 mm	-	-	-
6700	40	10 mm	12 mm	-	-	-
6900	75	< 5 mm	< 5 mm	Negative	Negative	Positive
11100	40	10 mm	8 mm	-	-	-
9800	26	< 5 mm	8 mm	Negative	Negative	Negative
10300	38	8 mm	10 mm	-	-	-
12000	30	20 mm	16 mm	-	-	-
8000	35	10 mm	12 mm	-	-	-
6700	27	15 mm	14 mm	-	-	-
4500	30	< 5 mm	10 mm	Negative	Negative	Negative
8600	15	14 mm	12 mm	-	-	-
13000	45	18 mm	20 mm	-	-	-