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ROLE OF LABORATORY IN DECODING THE PREVALENCE OF COMMONEST AUTOIMMUNE CONNECTIVE TISSUE DISORDERS SYSTEMIC LUPUS ERYTHROMATOSUS, RHEMATOID ARTHRITIS AND ITS RARE COMBINATION IN A TERTIARY CARE HOSPITAL

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Abstract

Background: Autoimmune Connective Tissue Disorders are increasing our country day by day reported among our country. Our encounter with these cases shows that the disease are not rare after all. The objective of this study was to report the prevalence, clinical presentations, laboratory and serological characteristics of patients presenting with autoimmune connective tissue disorders in our tertiary care hospital. **Method:** This was a retrospective study of patients presenting with autoimmune disorder attending the Rheumatology OPD in Medical College, Kolkata, over a period of five and half year. A review of the case records of all patients diagnosed and treated for autoimmune connective tissue disorders was utilized using the American College of Rheumatology Criteria for Systemic Lupus Erythematosus, and Rheumatoid Arthritis mainly. **Results:** Our study indicates that out of 104112 Rheumatology/Dermatology cases seen, 3748 were autoimmune connective disorders indicating a frequency of 3.6%. Out of this 3.6%, Systemic lupus erythematosus (SLE) constituted about 95% and rheumatoid arthritis 5%. The age range of the subjects was between 15-65years with a mean age of 33.7years, indicating the universal young age at presentation. Females constituted 95.3% of the patients with a female to male ratio of 20.3:1. The duration of disease ranged from (3mont-17 years) with a mean of 13.7years. The most clinical presentation of systemic lupus was discoid rash constituting about 92.2%, while that from rheumatoid arthritis was deformities of the proximal interphalangeal and distal interphalangeal joints. Rheumatoid factor was positive in 93.3% of the tested subjects. The prevalence of both in a same patient has been estimated to be 0.25% which has a different clinical entity known as Rhupus. **Conclusion:** Hence, the outcome of this study has shown that the prevalence of rheumatoid arthritis found in this study was 6.7% and Rhupus syndrome has been estimated to be 0.25% of all rheumatologic diseases in our area.

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Keywords: Prevalence, Autoimmune Connective Tissue Disorders, Systemic Lupus Erythromatosus, Rhematoid arthritis, Rhupus.

1. INTRODUCTION

Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are connective tissue autoimmune disorder with various clinical and serological features affecting different organs and systems. Although SLE can affect the skin, lungs, and kidneys, it can also affect the joints in 90% cases.

Another term “Rhupus”, which is used to describe patients with coexistence of RA with SLE and there is evidence to support the presence of rhupus as a true overlap syndrome.[1] It has been defined as a deforming and erosive symmetric polyarthritis accompanied by symptoms of SLE and the presence of antibodies such as anti-double stranded DNA (anti-dsDNA), anti-Smith, and rheumatoid factor (RF) with or without anti-cyclic citrullinated peptides (anti-CCP) antibody.[2,3] The syndrome is a rare clinical entity which has an estimated prevalence rate of 0.01 to 2%.[2,4]

Rheumatoid arthritis has a worldwide prevalence of near about in 0.5–1.0% of adult population and SLE prevalent in 6.5–27.7/100,000.[5,6] In India, incidence of SLE varies from 0.1% to 9.7% whereas that of RA is 0.92%.While these hospital-based statistics do indicate the existence of a fair number of SLE and RA patients in worldwide or country based but no exact figure is available on the prevalence of the disease in the our community. Moreover, the heterogeneity of SLE manifestations is due to an interplay of genetic, environmental, and hormonal influences. [7] The role of environmental influence is indicated by different manifestations in patients belonging to the same ethnicity and genetic ancestry but residing at different geographical locations. [8,9]

So, in the present study, large population survey was conducted to find out the prevalence of and to describe the diagnostic and clinical features of the most common ACTDs in Kolkata, West Bengal, India.

2. MATERIAL AND METHODS

2.1 Study Area

This hospital based open, single-centre, open-label cross-sectional retrospective study was conducted in the Rheumatology OPD with the collaboration of Department of Biochemistry of Medical College, Kolkata, West Bengal, India.

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2.2 Ethics Statement

The study was approved and permitted by the institutional ethics committee for patient care and use of laboratory and started after obtaining the written consent from the concerned ethics committee.

2.3 Study population

The present study was conducted between March 2018 and November 2023. Sample size was calculated at 95% confidence interval, with a power of 80%. [10]

As shown in Figure 1, the 914 study population consisted of patients who had been diagnosed with having Systemic Lupus Erythematosus and 108 were with Rheumatoid Arthritis, fulfilling the American Rheumatology Criteria (ARA)[10,11] as in Tables 1 and 2. Patients with active tuberculosis, hepatitis C or B virus, HIV, history of lympho-proliferative syndrome, history of malignant tumor, congestive heart failure (New York Heart Association class III or IV) and patients who had history of central nervous impairment were excluded from the study. Patients with connective tissue disease who have co-existing infectious diseases or carcinomas not included in present study. After 3 month, when they came to the OPD from check up retesting was performed. It was found that 2 patients that were previously SLE positive and one patient who were previously remaining RA positive develop features of Rhupus.

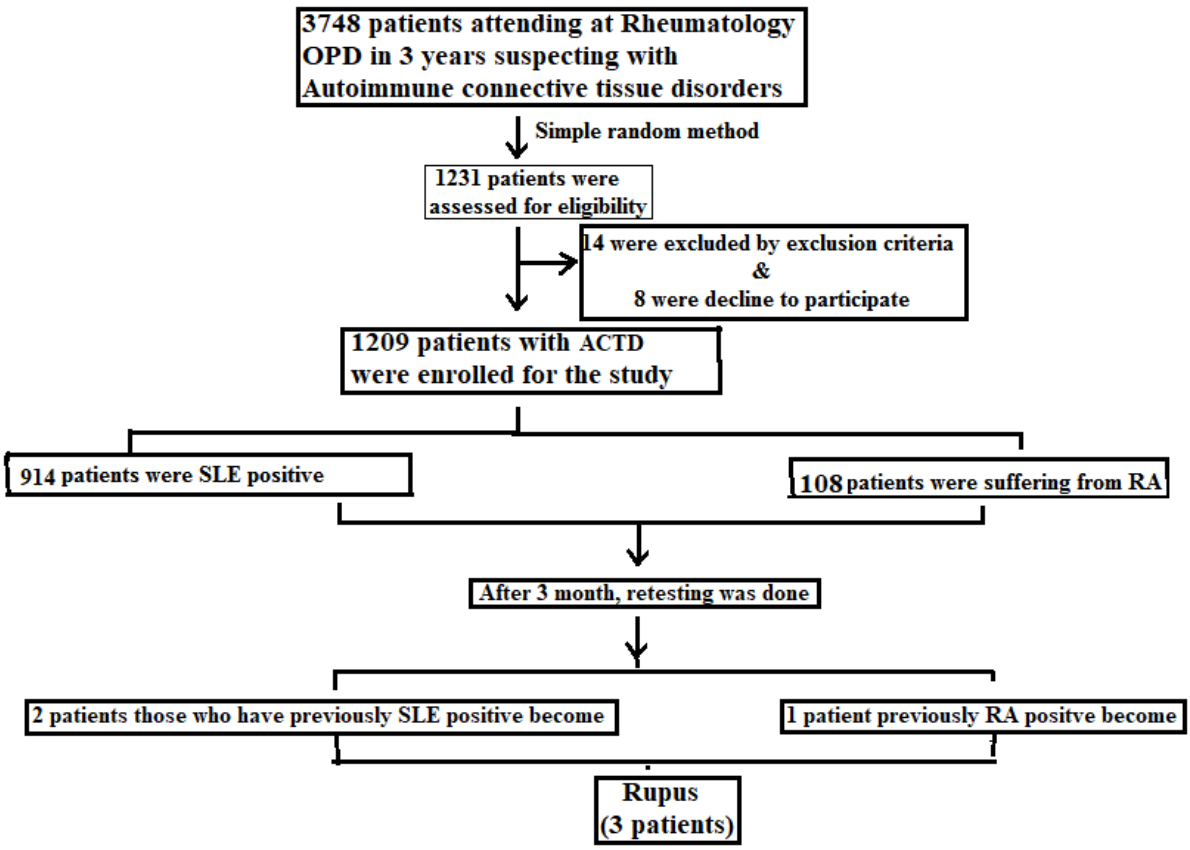

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Figure 1: Study design of the present study

2.4 Diagnostic criteria of SLE

Table 1: ARA Criteria for the diagnoses of SLE

Features	Description	Sensitivity	Specificity
Malar rash	Rash on cheek	57%	97%
Discoid rash	Scaly rash	18%	99%
Serositis	Pleurisy/pericarditis	56%	86%
Oral ulcers	Ulcers on mouth	27%	96%
Arthritis	Non-erosive	86%	37%
Immunologic	Anti-sm, Anti ds DNA, serology, syphilis test	85%	93%
Photosensitive		43%	96%
ANA test		99%	49%
CNS disorders	Seizures/psychosis	20%	98%
Renal	>0.5gm/day protein	51%	94%
Haematological	Hb <10mg/dl, lymphopenia < 1500/µl thrombocytopenia < 100000/ul, leucopenia < 4000/µl in absence of offending drugs	59%	89%

*CNS stands for Central nervous system; ANA is Antineutrophilic antibody; sm means Smith; ds is double stranded; DNA for Deoxyribonucleic acid; Hb symbol for haemoglobin; To make a diagnosis, the patient should fulfill 4 out of the 11 clinical features.

2.5 Diagnostic criteria of RA

Table 2: American College of Rheumatology Criteria for Rheumatoid Arthritis.

Early morning stiffness greater than one hour
Arthritis of 3 or more joints of the following; right or left proximal interphalangeal joints, elbows, Metarcarpophalangeal joints, wrist, knee, ankle and metartarsophalangeal joints.
Symmetric involvement of joints
Rheumatoid nodules on bony prominences or extensor surfaces or in juxta-articular regions
Positive serum rheumatoid factor
Radiographic changes including erosions or bony decalcifications localized in or adjacent to the involved joint
Arthritis of wrist, proximal interohalangeal ioint or metarcarpophalangeal joint

Four of the following must be present in a minimum of six weeks

2.6 Criteria for diagnosis of Rhupus syndrome

It has been defined as a deforming and erosive symmetric polyarthritis accompanied by symptoms of SLE and the presence of antibodies such as anti-double stranded DNA (anti-dsDNA), anti-Smith, and rheumatoid factor (RF) with or without anti-cyclic citrullinated peptides (anti-CCP) antibody.[2,3] Typical arthritis associated with SLE is rarely erosive and differs from RA.[3,12] Unlike SLE patients, Rhupus patients have significantly less kidney

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involvement, while no differences have been observed between neuropsychiatric, cutaneous, and hematological involvement or serositis. [12]

2.7 Collection of samples

Peripheral venous blood was drawn under aseptic precautions from all participants. Sera were analyzed for anti-CCP2 antibodies by ELISA (Inova Diagnostics, San Diego, CA, USA) with a cutoff value of 60 U/ml. Fine antinuclear reactivities (ELISA; Inova Diagnostics), RF (nephelometry), ANA (indirect immunofluorescence on HEp-2 slides), and anti-dsDNA (indirect immunofluorescence on Crithidia luciliae substrate) antibodies were also determined.

ANA was detected by indirect immunofluorescence using Hep-2 as substrate, anti-dsDNA by antigen strips coated with dsDNA isolated from salmon testes, and anti-Smith (antiSm), and anti-U1-ribonucleoprotein (U1-RNP) by affinity chromatography using bovine and rabbit thymus.

All serum samples were stored at (-70^0C) and kept under these conditions until chemical analysis was performed. All parameter assays should be done as soon as possible.

3. RESULT

3.1 Personal profile and clinical details of study population -

Out of the 1209 autoimmune connective tissue disorder patients 914 (75.6%) had SLE and 108 patients suffering from RA (8.93%). The personal profile and clinical details is shown in Table 1. The study group of SLE comprised 871 females (95.3%) and 43 males (4.7%) with a female: male ratio of 20.3:1 and in case RA, 97 was females (89.8%) and 11 were male with ratio of 8.8:1. The patients' age range was 15-65 years with a mean age at presentation being 33.7 years. The most common age group was the third decade (55%). The age of onset was 13-56 years (mean age of onset 24.6 years) (Table 3). The youngest patient was a 16-year-old female who developed the disease at 13 years.

Table 3: Personal profile and clinical details of study population

SLE (n = 914)		RA (n = 108)	
Characteristics	**n (%)**	**Characteristics**	**n (%)**
Gender		Gender	
Male	871 (95.3)	Male	97 (89.8)
Female	43 (4.7)	Female	11 (10.2)
Age in year		Age in year	
<20	256 (28)	<20	22 (20)
20-30	503 (55)	20-30	52 (56)
31-40	82 (9)	31-40	6 (5)
>40	73 (8)	>40	28 (19)

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3.2 Positivity of serological markers among SLE and RA cases –

Among the patients 91% cases were RA positive. The rate of positivity of ANA was 69.8%. 85.7% patients were had elevated ESR.

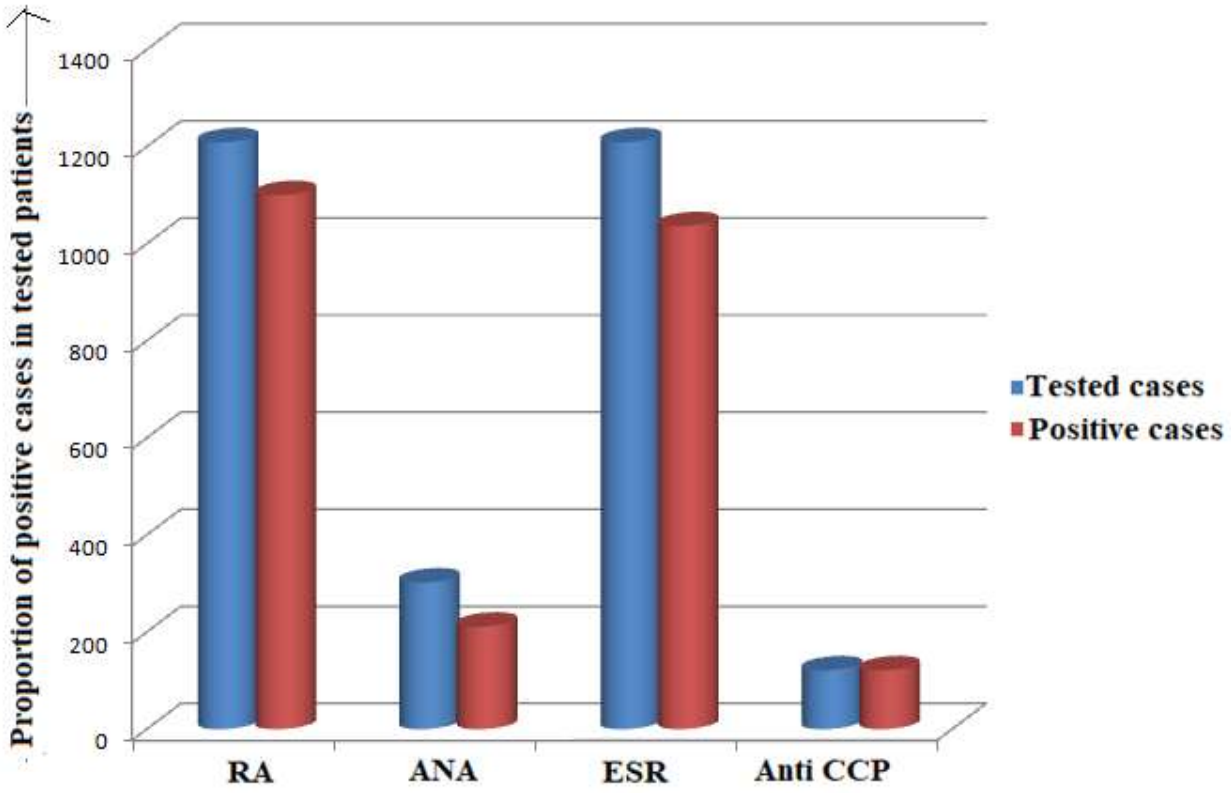

Figure 2: Positivity of serological markers among SLE and RA cases

3.3 Clinical presentation of SLE & RA

Different clinical features were shown in Figure 2 & 3 of study population of the present study.

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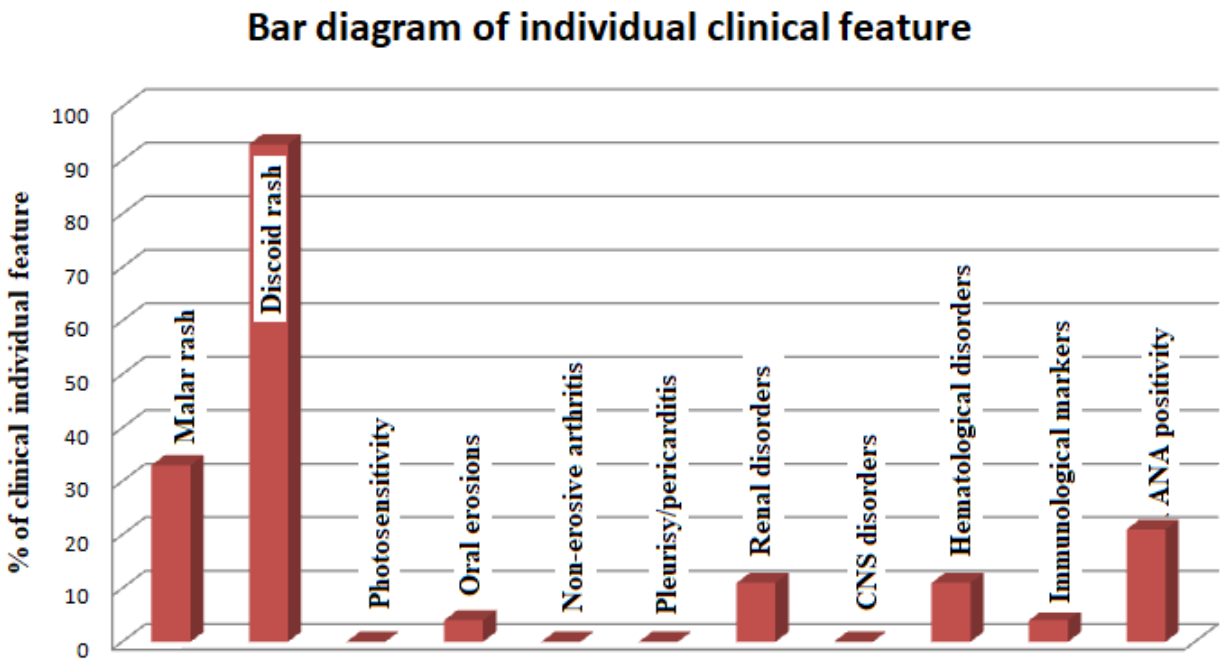

Figure 3: Clinical presentation of SLE

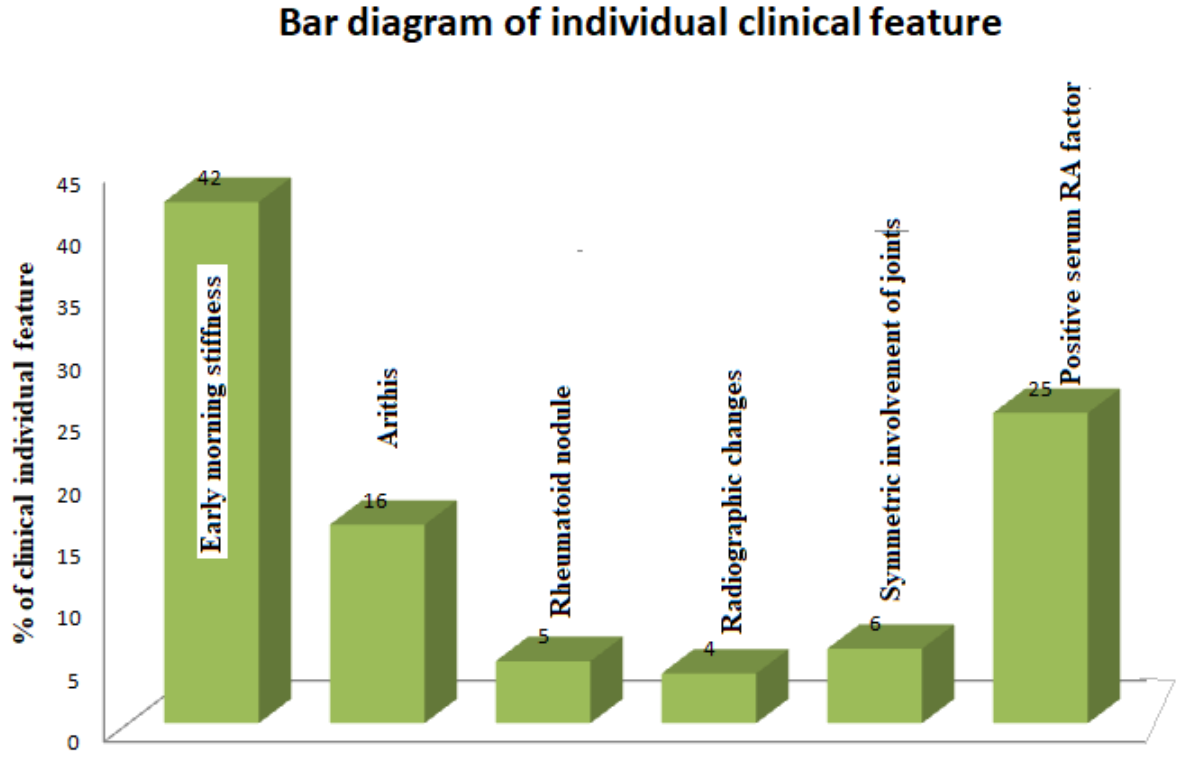

Figure 4: Clinical presentation of RA

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3.4 Generalized biochemical profiles of SLE & RA patients –

Biochemical parameters of clinically suspected SLE such as ANA profile and anti-dsDNA are shown in the Table 4 and ANA Hep2 pattern in figure 4.

Table 4: Generalized biochemical profiles of SLE patients (n = 914)

ANA Hep2 (IIFT)	ANA profile	ANTI-dsDNA (IU/ml)
4+ Homogenous	RNP/Sm +++ RO 52 +++ SSA +++	Reference limit:100 Positive: >100 Range:300-2400
3+ Coarse speckled	RO 52 +++	

RNP - Ribonucleoprotein; ANA - Antinuclear antibody; Sm-Smith; Anti-CCP - Anti-Cyclic Citrullinated Peptide; RA Factor - Rheumatoid arthritis Factor Ro52/SSA - Sjogren Syndrome related antigen A

Biochemical parameters of clinically suspected RA such as ANA Hep2, ANA profile and anti-dsDNA are shown in the Table 5 and ANA Hep2 pattern in figure 4.

Table 5: Generalized biochemical profiles of RA patients (n = 108)

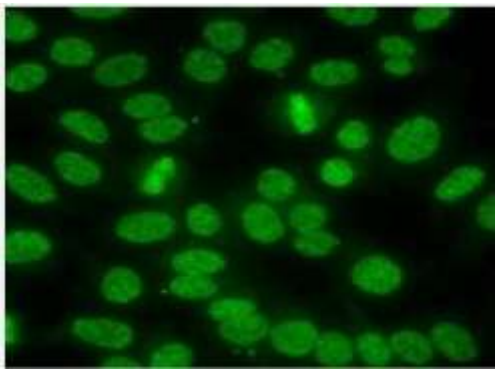
ANA Hep2 (IIFT)	ANA profile	ANTI-CCP (IU/ml)	RA factor (IU/ml)
3+ Anti-golgi	HI ++	Reference limit:5 Positive:>5 Range:25-850	Reference limit:20 Positive:>20 Range:35-125

Abbreviation-

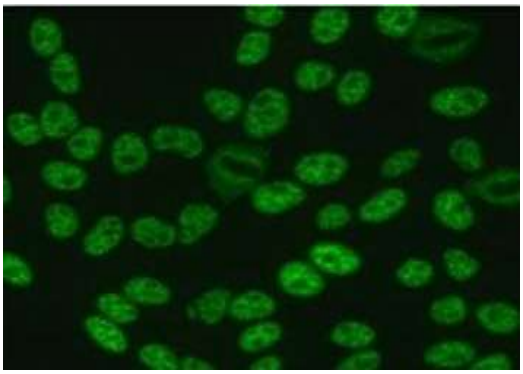
RNP - Ribonucleoprotein; ANA - Antinuclear antibody; Sm-Smith; Anti-CCP - Anti- Cyclic Citrullinated Peptide

Ro52/SSA - Sjogren Syndrome related antigen A RA Factor - Rheumatoid arthritis Factor

SLE (IIFT)



HOMOGENOUS PATTERN



COARSE SPECKLED PATTERN

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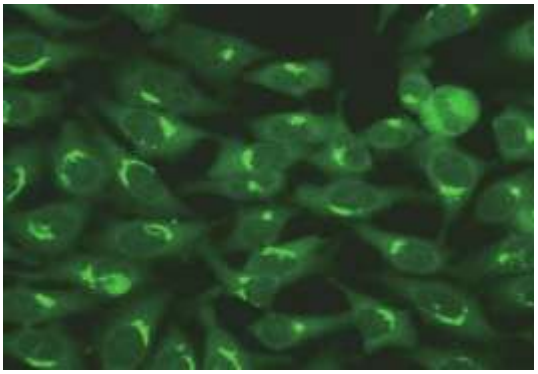
RA IIFT



ANTI-GOLGI PATTERN

IIFT: INDIRECT IMMUNOFLUORESCENCE TEST

Figure 5: ANA Hep2 patterns of SLE and RA performed by IIFT -

Biochemical parameters of clinically suspected Rhupus syndrome such as ANA profile and anti-dsDNA are shown in the Table 6 and ANA Hep2 pattern in figure 5.

Table 6: Generalized biochemical profiles of (n=3) patients

ANA Hep2(IIFT)	ANA profile	Anti-dsDNA (IU/ml)	Anti-CCP (IU/ml) Reference limit:200	RA factor (IU/ml) Reference limit: 20
4+ Homogenous with cytoplasm homogenous	RNP/Sm +++ Ro52/SSA +++	1367 (previous = 1035)	456 (previous = 56)	62 (previous = <10)
3+ Coarse speckled with cytoplasm homogenous	Ro52/SSA +++	1402 (previous = 1150)	698 (previous = 64)	78 (previous = <10)

RNP - Ribonucleoprotein; ANA - Antinuclear antibody; Sm-Smith; Anti-CCP - Anti- Cyclic Citrullinated Peptide

Ro52/SSA - Sjogren Syndrome related antigen A RA Factor - Rheumatoid arthritis Factor

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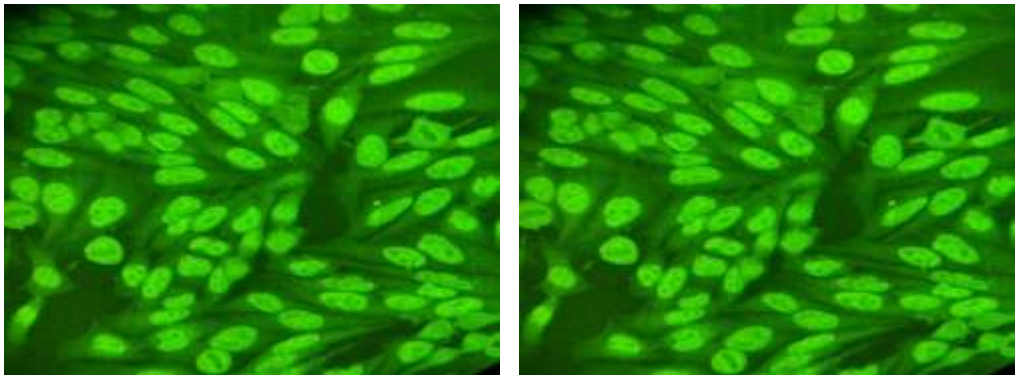
RHUPUS IIFT



HOMOGENOUS PATTERN COARSE SPECKLED PATTERN

Figure 6: ANA Hep2 patterns of Rupus performed by IIFT ANA HEP2 PATTERN (IIFT)

4.DISCUSSION

Autoimmune rheumatology diseases are a major cause of death among young and middle aged women.[13] The reported prevalence varies markedly worldwide depending on case definition and population studied. So prevalence of common ACTD in our area tries to calculate.

In this profile study, we found out that autoimmune connective disorders have been under diagnosed previously in our environment. Systemic lupus erythematosus (SLE) constituted about 95% and rheumatoid arthritis 5%. The age range was between 15-65years with a mean age of 33.7years, indicating the universal young age at presentation, although 3 of the patients were elderly rhupus at ages above 50.

Most of the patients 95.3% were mostly females with a ratio of 20.3:1 while the duration of the disease in present study ranged from 3month to 17years with a mean of 7years. The finding of our study is similar to the worldwide prevalence of females being more affected with the age range of between 15-50 years.[14]

SLE was the most common (91%) autoimmune connective tissue disorder diagnosed in this study. This finding is well corroborated to a retrospective study in Ghana which recorded 11cases of SLE out of 25 rheumatology cases.[15] Though the study by Adelowo et al in Lagos Nigeria revealed that SLE accounted for 5.28% of the 1,250 rheumatology cases,[16] the difference may be explained by the smaller study size and shorter duration of our study. The observed high prevalence in present study may be due to the increasing awareness among physicians and availability of better diagnostic facilities nowadays. In addition the fact that this study was a tertiary hospital survey may suggest that true prevalence of this condition may even be higher as many patients may be misdiagnosed and not referred. So, the study therefore concludes that SLE is significantly prevalent in our environment.

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The most common presentation of SLE was discoid and malar rash which is found in our study about 91.7% and 32.8% respectively. This finding was similar to the work done in kenyetta hospital in which malar rash actually constituted one of the major features.[17] Interestingly, most of the patients that had discoid and malar rash did not have any other clinical sign on examination but had additional laboratory investigations which made up the 4 out of the 11 criteria for diagnosis. No patient had a mixed type of autoimmune connective tissue disorder. In addition to this, most patients presented with non-specific malaise and low grade fever across the 3 types of autoimmune disorder. Only one case of a male presenting with SLE was seen. The male patient also had malar rash and discoid rash in addition to and oral lesions on examination, with a positive ANA. The high female predominance seen in this study in line with findings from other studies[16,18-20] and has been attributed to the presence of the female hormone oestrogen.[21]

The mean year of symptom duration seen in SLE patients was about five years. This duration of disease before presentation demonstrates the chronic course of SLE. Though Adelowo et al showed a prevalence of 2.6 years in a report of the pattern of SLE among Nigerians, the difference in the mean year of symptom duration may be explained by the fact that the above cited study was done in a private specialist rheumatology clinic with the possibility of earlier referrals to this centre.[16]

The high positivity rates for both rheumatoid factor and erythrocyte sedimentation rate seen in this study indicate the importance of these two laboratory findings in patients with autoimmune connective tissue disorders. This same trend has been established in other studies.[22,23] The high positivity rates for ANA in patients diagnosed with SLE in this study also mirrors the established trend and makes it a useful tool in SLE diagnosis.[23-26]

The prevalence of rheumatoid arthritis found in this study was 6.7% of all rheumatologic diseases. The subjects were all females; who had all the six criteria of American College of Rheumatology criteria in addition to positive tests for anti-citrullated peptide and features of erosive arthritis of the knee on x-ray. Our findings on Rheumatoid Arthritis which indicate a delayed presentation with the presence of destructive changes is similar to what Adelow et al and Wadee et al found.[16,27]

The prevalence of Rhupus syndrome has been estimated to be 0.25% that is similar with prevalence rate of previous studies around 0.01% to 2% of patients with rheumatic diseases.[2,28] Rhupus syndrome has been defined as a deforming and erosive symmetric polyarthritis accompanied by symptoms of SLE and the presence of antibodies such as anti-double stranded DNA (anti-dsDNA), anti-Smith, and rheumatoid factor (RF) with or without anti-cyclic citrullinated peptides (anti-CCP) antibody.[2,3] Typical arthritis associated with SLE is rarely erosive and differs from RA.[2,12] Unlike SLE patients, Rhupus patients have

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significantly less kidney involvement, while no differences have been observed between neuropsychiatric, cutaneous, and hematological involvement or serositis.[29] As It is a rare finding need to be confirmed both clinically and with other more sophisticated biochemical tests and probable genetic analysis.

5. Conclusion

Hence, the outcome of this study has shown that the prevalence of rheumatoid arthritis found in this study was 6.7% and Rhupus syndrome has been estimated to be 0.25% of all rheumatologic diseases in our area.

6.Authors' contributions

Dr (Prof) Subhramay Chatterjee participated in the conception and design of the experiments, in the acquisition, analysis and interpretation of data, and was involved in drafting the manuscript. Suparna Datta performed the immunoassays. Subinay Datta participated in the analysis and interpretation of data and performed the statistical analysis. Subinay Datta participated in the analysis and interpretation of data. Sangita Biswas participated in the recruitment of patients and the acquisition of data. Jayeeta Pandey and Neha karar participated in the interpretation of data, revising the manuscript for intellectual content and giving the final approval of the version to be published. All authors read and approved the final manuscript.

7. Financial support and sponsorship

Nil.

8. Conflicts of interest

There are no conflicts of interest.

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