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Pattern of Autoimmune Connective Tissue Diseases Among Patients Attending Al-Thawra Teaching General Hospital, Sana'a-Yemen

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ABSTRACT

Background: Connective tissue is also called connectivum. Many autoimmune diseases affect the connective tissue and blood vessels, are often referred to as connective tissue disorders. Autoimmune diseases currently are estimated to affect 2-5% of the population in the developed countries.

Aim: The aim of this study was to determine the pattern of autoimmune inflammatory connective tissue diseases among patients attending Al-Thawra teaching general hospital, Sana'a-Yemen.

Method: This study is observational prospective study conducted at Al-Thawra hospital, Sana'a-Yemen, department of internal medicine, duration of the study was 12 months. Sample size was 137.

Results: The results showed that systemic lupus erythematosus, antiphospholipid syndrome and rheumatoid arthritis have the highest prevalence. The main clinical presentations are arthritis, leg swelling and dyspnea. The main drugs used are corticosteroids, low molecular weight heparin, and rituximab. The proportion of females to males is 3.55 to 1. The age range 20 – 30 years is the highest representing 47% of the total patients. Patients from Sana'a, Taiz, and Ibb being the most common. Illiterates represent 63%, housewives represent 72% of the total patients.

Conclusion: We conclude that autoimmune connective tissue diseases affect 8% of the total patients admitted to the internal medicine department. SLE is the most common autoimmune connective tissue disease encountered and represents 43% of total cases. Arthritis and leg swelling are the most common clinical presentations encountered; both represents 48% of the total presentations. Corticosteroids are the most common prescribed drugs, 45%. The aetiology of autoimmune connective tissue diseases is still not fully known. Immuno-modulators are needed to regulate the immune system. Physiotherapy is recommended beside medical therapy.

CONTENTS

1. Introduction:

Connective tissue is also called connectivum (Yusuf, 2011). The main classes of connective tissue are connective tissue proper which includes fat and fibrous tissue of ligaments, cartilage, bone tissue and blood. Its major functions are binding and support, protection, insulation, and as blood,

transportation of substances within the body. The common characteristics of connective tissue are their common origin: the mesenchyme, their degrees of vascularity, cartilage is avascular; dense connective tissue is poorly vascularized and the other types of connective tissue have a rich supply of blood vessels. And the third characteristic of connective tissue is its extracellular matrix which enable it to bear weight, withstand great tension and endure abuses, such as physical trauma and abrasion, that no other tissue would be able to tolerate (Elaine, 2007, Payvand, 2023, **,** K Gelse , 2023, Elena, 2023).

Autoimmune rheumatic diseases are characterised by an autoimmune inflammatory response to antigens of synovial tissue, muscles, and other organs (Patrick, 2022). They affect principally the connective tissue and blood vessels. Therefore, these diseases are often referred to as collagen vascular or connective tissue disorders. Autoimmune diseases currently are estimated to affect 2-5% of the population in developed countries. Autoimmune connective tissue diseases (AICTD) include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), SjÖgren syndrome, systemic sclerosis (SS), mixed connective tissue disease, inflammatory myopathies: polymyositis, dermatomyositis and inclusion body myositis, in addition autoimmune connective tissue diseases include non-infectious necrotizing vasculitis differentiate these conditions from those attributable to direct vessel infection. Non-infectious necrotizing vasculitis comprise giant cell (temporal) arteritis, Takayasu arteritis, polyarteritis nodosa, Kawasaki disease, microscopic polyangitis, Wegener's granulomatosis, Churg-Stauss syndrome, thromboangitis obliterans (Buerger disease), antiphospholipid syndrome and Henoch-Schonlein purpura (HSP) **(**Vinay, 2013, Kardas, 2022, Pepmueller, 2016, Fotini, 2022).

Disorders of the musculoskeletal system affect all ages and ethnic groups. In the UK, about 25% of new consultations in general practice are for musculoskeletal symptoms. Musculoskeletal diseases may arise from processes affecting bones, joints, muscles or connective tissues such as skin and tendon. The principal manifestations are pain and impairment of locomotor function. Diseases of the musculoskeletal system tend to be more common in women and most increase in frequency with increasing age. The prevalence of connective tissue diseases (mainly lupus) is 0.2%, while that of rheumatoid arthritis alone is 1% (Stuart, 2018).

Women are healthier and live longer than men. They are less susceptible to infectious diseases (Vom, 2016), but on the other hand 80% of individuals with autoimmune diseases are women. These diseases affect 5–10% of the population, are often chronic, and represent a considerable burden on healthcare budgets (Rose, 2022, Invernizzi, 2009, Ozcelik, 2008).

Systemic lupus erythematosus (SLE), systemic sclerosis (SS), Sjögren's syndrome, inflammatory muscle diseases and overlap-syndromes are grouped together as connective tissue disorders (Pepmueller, 2016, Kimberly, 2001, Dina, 2022).

The reported prevalence and incidence of connective tissue disorders are quite variable, depending on differences in study methodology. Most important differences are the study duration, the classification criteria used for diagnosis and the country in which the study was undertaken. Sjögren's syndrome has the highest prevalence ranging between 0.5 and 3% of a given population. The prevalence of systemic lupus erythematosus (SLE) is estimated between 15 and 50 per 100 000 individuals, with a female: male ratio of 6–10:1 in the age group between 15 and 40 yrs. The prevalence of systemic sclerosis is lower, however, varying significantly between different studies and countries. The prevalence of overlap syndromes, especially mixed connective tissue disease, is unknown, and polymyositis and dermatomyositis are regarded as very rare rheumatic diseases (Ragnar, 2011, Gaubitz, 2006).

In Togo, West Africa, a retrospective and descriptive study was conducted from January 1, 1993 to December 30, 2012, The study aimed to highlight the epidemiological, clinical,

therapeutic and evolutionary profile of connective tissue diseases in the hospitals setting in Lomé focused on the medical records of patients with connective tissue diseases hospitalized in five Departments of Dermatology and Rheumatology at the Hospitals in Lomé. The study identified 231 cases of connective tissue diseases in the five study centers, corresponding to a frequency of 0.19% of consultations. The average age of patients was 36,96±15 years, the sex-ratio was 0,2. Major connective tissue diseases included lupus disease (50.22%), sclerodermas (21,64%) and rheumatoid polyarthritis (20.35%). Clinically, the main clinical manifestations of connective tissue diseases included discoid lupus lesions (87.50%) and photosensitivity (82.50%) in patients with systemic lupus erythematosus, skin sclerosis (90.48%) in patients with systemic scleroderma and distal joint involvement (100%) in patients with rheumatoid arthritis. Treatment in patients with systemic lupus erythematosus (92.5%) and rheumatoid arthritis (73.47%) was based on systemic corticosteroids. Connective tissue diseases are rare in people living in Lomé, with a predominance of lupus disease. They are more frequent in young women. Treatment is based on systemic corticosteroids (Teclessou, 2018).

The aim of our work is to study the pattern of autoimmune inflammatory connective tissue diseases among patients attending Al-Thawra teaching general hospital, Sana'a-Yemen.

2. Method

This work was an observational prospective study, at Al-Thawra hospital, Sana'a-Yemen, department of internal medicine. Duration of the study was 12 months. Sample size was calculated by using the following equation:

Sample size = $8 * (r (100 – r) + s (100 – s))/ (r - s)^2$, (Norman, 2013)

r = Expected incidence in our study = 10%

s = Incidence in similar study = 2% (Vinay, 2013)

8 = 80%, the power of the study

$= 8 * (10 (100 – 10) + 2 (100 – 2)/ (10 – 2)^2$

= 137

Inclusion criteria: all patients of all ages and both genders with evidence of diagnosed autoimmune inflammatory connective tissue diseases.

Exclusion criteria: all patients of both genders with no evidence of diagnosed autoimmune and inflammatory connective tissue diseases.

Medical history was taken from the patients including the socioeconomic and behavioral information. Patients' privacy, feelings, concerns and dignity were highly considered.

3. Ethical consideration

This study was approved from the ethical committee in the faculty of medicine and health sciences, Sana'a university, Yemen.

4. Statistical analysis

All collected data were entered in computer using the statistical package of the excel program, for the purpose of categorization, manipulation, description and comparison of proportions and percentages.

As summarized in the following figures.

5. Results and Discussion

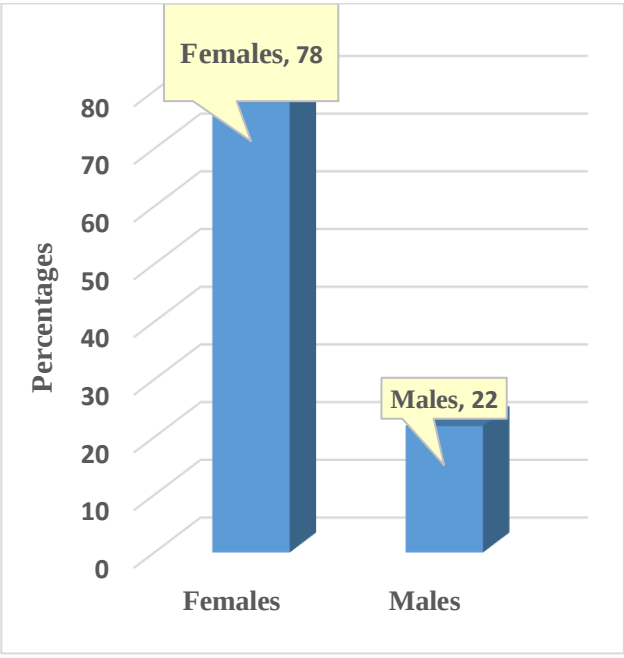

Figure 1: Percentages of gender distribution among patients with autoimmune connective tissue diseases attending Al-Thawra Hospital

Figure 1 shows the proportion of females to males with autoimmune connective tissue diseases is 3.55 to 1. The global proportion is higher than this ratio, almost 4 to 1, and in the Togo's study it was 5 to 1, the reason may be that the access of females to medical care in Yemen is less than that of males due to local culture of habits and customs.

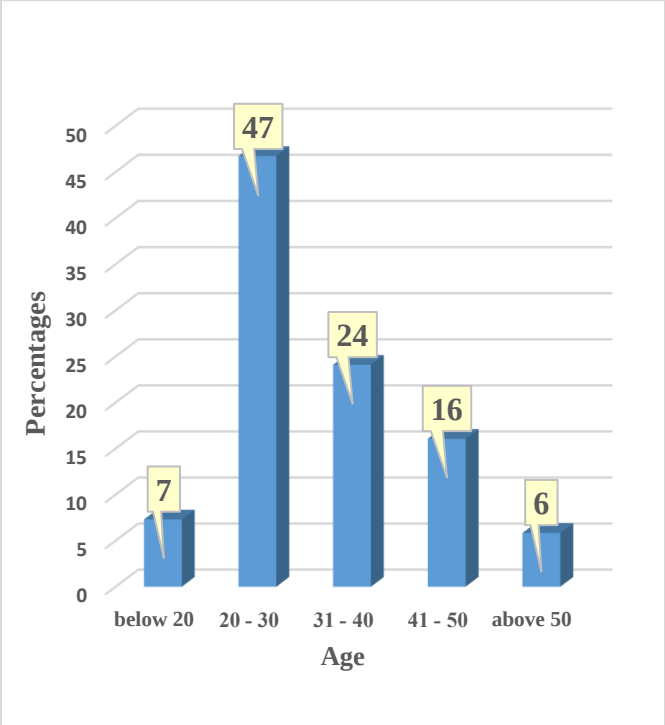

Figure 2: Percentages of age range among patients with autoimmune connective tissue diseases attending Al-Thawra hospital

Figure 2 shows that the age range 20-30 years are the highest range with autoimmune connective tissue diseases and this match with the international statistics. The relatively high percentages of patients with age range 30- 40 years with autoimmune connective tissue diseases may reflect delayed diagnosis. The average age in our study is 33, the average age in the Togo's study was 37. This can be explained that in Togo the clinical presentation of autoimmune connective diseases is mainly dermatological while in Yemen the clinical presentation is more serious e.g. visual disturbances which necessitate admission.

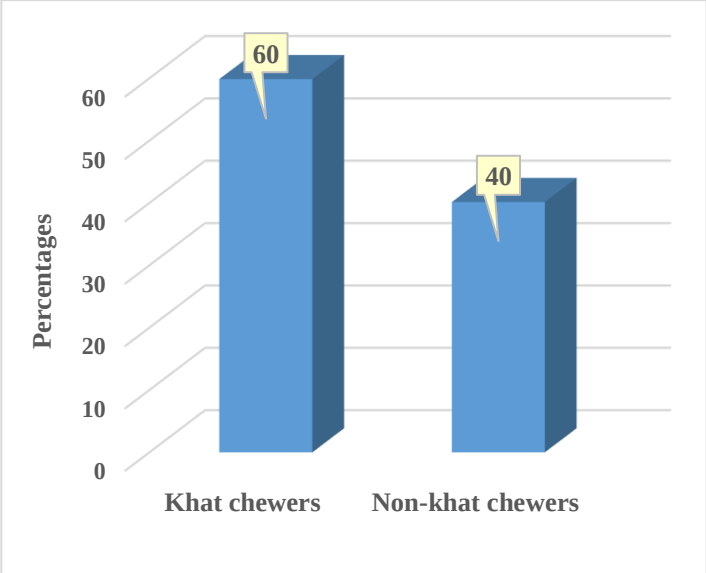

Figure 3: Percentages of khat chewers in patients with autoimmune connective tissue diseases attending Al-Thawra hospital

Figure 3 shows the percentage of khat chewers in patients with autoimmune connective tissue diseases is 60%, this is less than the research figures; approximately 60–90% of male and 35% of female Yemenis chew khat daily (Ochiba, 2015, Balint, 2009), this can be explained by that most of our patients are young females who are mainly non-khat chewers.

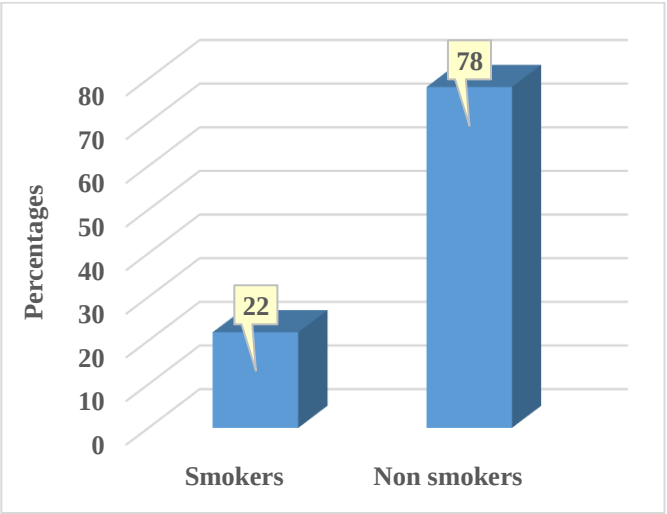

Figure 4: Percentages of smokers in patients with autoimmune connective tissue diseases attending Al-Thawra hospital

Figure 4 shows the percentage of smokers in patients with autoimmune connective tissue diseases is 22%, this is less than the researches figures; 36.3% for men and 28% for women (Abdulsalam, 2020), this can be explained again by that most of our patients are young females who are mainly non-smokers.

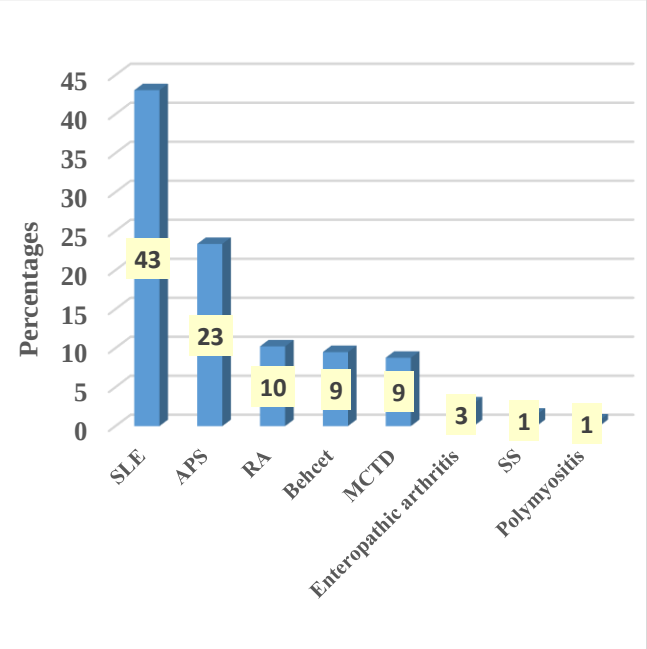

Figure 5: Percentages of autoimmune connective tissue diseases among patients attending Al-Thawra Hospital

Figure 5 shows the percentage of the types of autoimmune connective tissue diseases; SLE, APS, RA, Behcet, and MCTD have the highest prevalence, 43%, 23%, 10% and 9% for each of the last two respectively. Enteropathic arthritis, systemic sclerosis and polymyositis have the lowest prevalence; 3% and 1% for each of the last two respectively. Globally Sjogren's syndrome has the highest prevalence (Paolo, 2016, Gaubitz, 2006). But since this disease is a slowly progressive, inflammatory autoimmune disease affecting primarily the exocrine glands and the hallmarks are diminished tear production and xerostomia, they do not necessitate early admission.

Moreover, Yemen is an Asian country very close to the African continent especially the horn of Africa so it is not surprise to find SLE as the most common autoimmune connective tissue disease, representing 43% of the whole admitted cases of autoimmune connective tissue disease. This result match with the Teclessou JN study which showed SLE as the most common autoimmune connective tissue disease in Togo representing 50% of the whole admitted cases.

Globally the prevalence of rheumatoid arthritis alone is 1%, placing it as the most common autoimmune connective tissue disease, and the cardinal presenting features are arthritis and morning stiffness which do not necessitate early admission.

Antiphospholipid syndrome is the second most common autoimmune connective tissue disease in our study, and most of the patients are females presenting with leg swelling and a history of recurrent fetal loss.

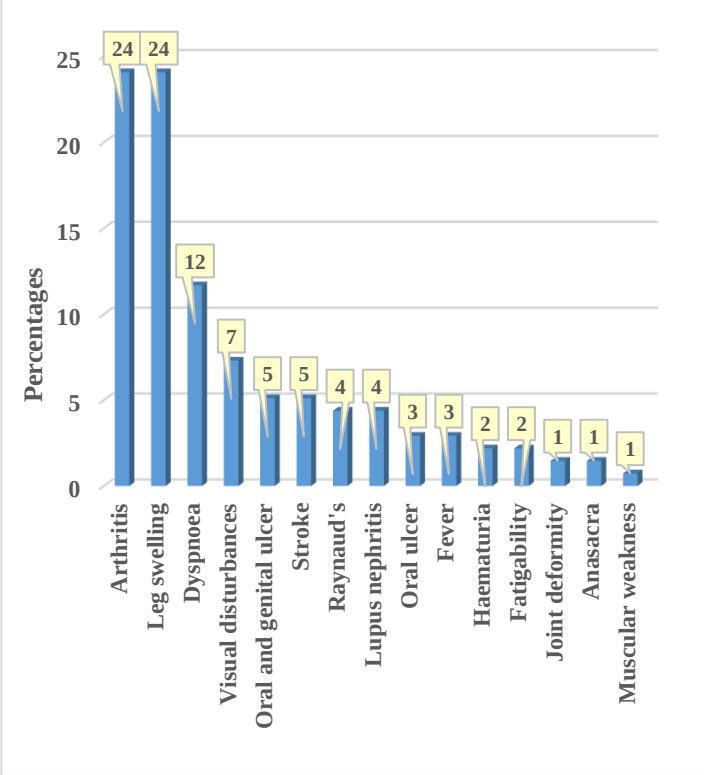

Figure 6: Percentages of the main clinical presentations for patients with autoimmune connective tissue diseases attending Al-Thawra Hospital

Figure 6 shows the percentages of the main clinical presentations in patients with autoimmune connective tissue diseases; arthritis, leg swelling dyspnea, visual disturbances, oral and genital ulcers and stroke being the most common; 24%, 24%, 12%, 7%, 5% and 5% respectively.

Since our study is concerned with rheumatology, it is not surprising for arthritis to be the most common presentation. Leg swelling is the second most common presentation associated with antiphospholipid syndrome, the second most common autoimmune connective tissue disease in our study.

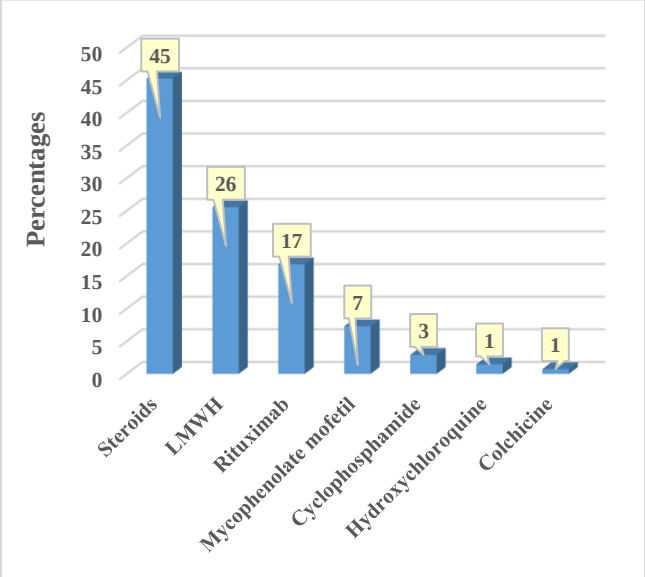

Figure 7: Percentages of the main drugs used for patients with autoimmune connective tissue diseases attending Al-Thawra hospital

Figure 7 shows the percentages of the main drugs used for patients with autoimmune connective tissue diseases; corticosteroids, LMWH, rituximab, mycophenolate mofetil and cyclophosphamide being the most common, 45%, 26%, 17%, 7% and 3% respectively.

Since we are dealing with autoimmune diseases so it is not surprised to find corticosteroids as the most common prescribed drugs (45%); prednisolone being the first and methylprednisolone the second. The latter is usually prescribed with cyclophosphamide as pulse therapy in flare cases.

Low molecular weight heparin (LMWH) is the second most common prescribed drug in our study. It is the first choice in antiphospholipid syndrome.

Rituximab is the third most common prescribed drug. It is usually reserved for resistant cases to save lives and to prevent organs damage and to halt further severe joint deformity.

Mycophenolate mofetil (MMF) is the fourth most common prescribed drug, it is frequently used in systemic lupus erythematosus especially lupus nephritis, moreover neutropenia is a rare side effect which would be advantageous in SLE patients complicated with autoimmune neutropenia.

Cyclophosphamide alone represents 3% of the prescribed drugs, this is a strong alkylating anticancer and immunosuppressant drug and usually produces a dramatic improvement in symptoms, however infertility and haemorrhagic cystitis are drawbacks that limit its widespread use.

Hydroxychloroquine is also prescribed in our study either alone (1%) or with other drugs. It is usually prescribed for arthralgia and arthritis not associated with internal organ involvement.

Finally, colchicine is prescribed alone usually as first line to relief oral and genital ulcers of Behcet's syndrome.

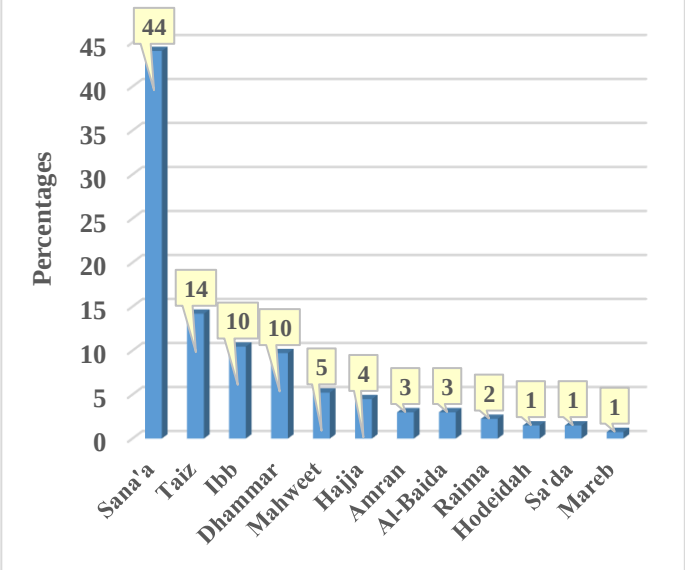

Figure 8: Percentages of patients with autoimmune connective tissue diseases attending Al-Thawra Hospital, according to their governorates

Figure 8 shows the percentages of patients with autoimmune connective tissue diseases attending Al-Thawra Hospital, according to their governorates; Sana'a, Taiz, Ibb, Dhammar Mahweet and Hajja being the most common, 44%, 14%, 10%, 10%, 5% and 4% respectively.

Of course, the geographic proximity and the population density are responsible for this order.

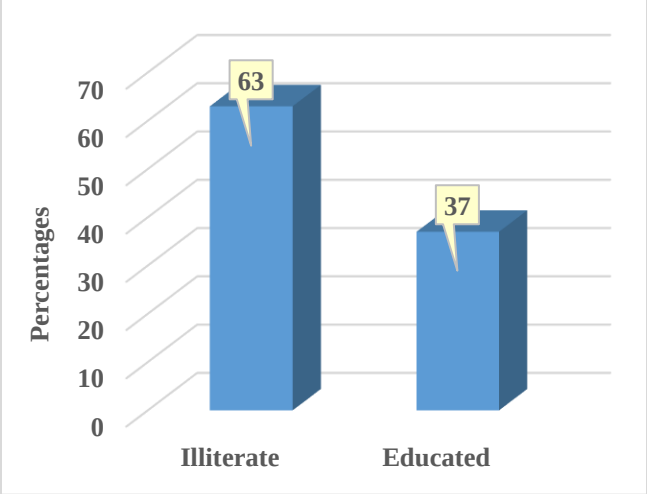

Figure 9: Percentages of patients with autoimmune connective tissue diseases attending Al-Thawra Hospital, according to their educational state

Figure 9 shows the percentages of patients with autoimmune connective tissue diseases attending Al-Thawra Hospital, according to their educational state; The illiterate and the patients with primary education represent 63% of the total patients.

Since autoimmune connective tissue disease affect mostly young females and the illiteracy in Yemen is common in females, so it is not surprising to find the illiterates and the patients with primary education represent most of the patients.

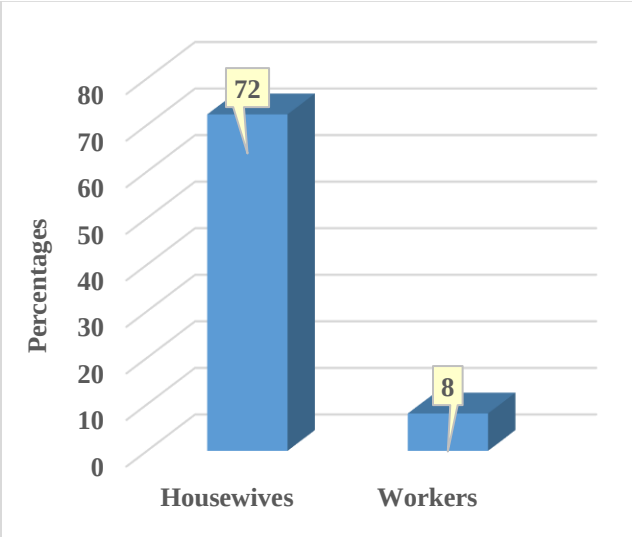

Figure 10: Percentages of patients with autoimmune connective tissue diseases attending Al-Thawra Hospital, according to their jobs

Figure 10 shows the percentages of patients with autoimmune connective tissue diseases attending Al-Thawra Hospital, according to their jobs; housewives represent 72% of the total patients.

This result reflects the early marriage of young females in Yemen, so it is not surprising to find that most of patients with autoimmune connective tissue diseases are housewives.

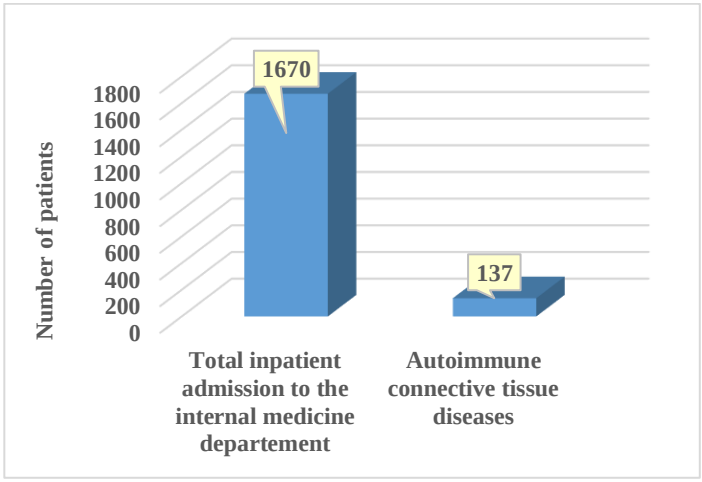

Figure 11: Number of inpatients with autoimmune connective tissue diseases attending Al-Thawra Hospital, in 2021

Figure 11 shows the number of inpatients with autoimmune connective tissue diseases attending the department of internal medicine in Al-Thawra hospital, in 2021; 137 out of 1670 the total number of patients.

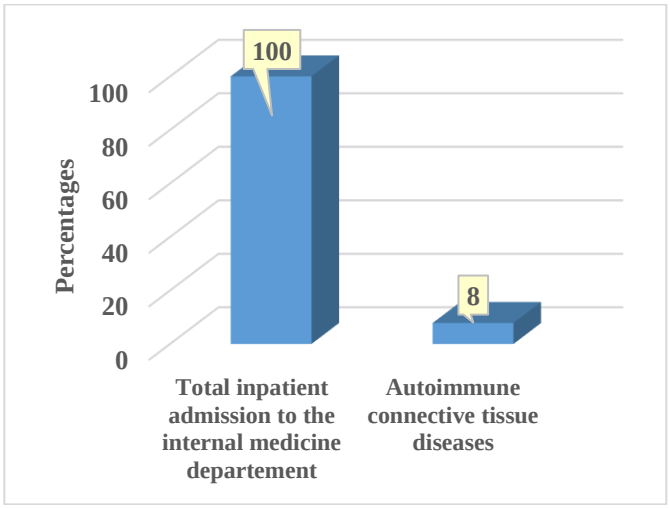

Figure 12: Percentage of inpatients with autoimmune connective tissue diseases attending Al-Thawra Hospital, in 2021

Figure 12 shows the percentage of inpatients with autoimmune connective tissue diseases attending the department of internal medicine in Al-Thawra hospital, in 2021; it was 8%.

Al-Thawra hospital is the largest reference hospital in Yemen and serves almost all the population of Yemen and receives the most difficult and complicated medical problems and houses the most famous physicians in different specializations, we can consider the admitted number of patients represents the total population of Yemen.

Figure 13: Severe hands deformity in a patient with rheumatoid arthritis

In the Togo's study the main clinical presentations are discoid lupus lesions (87.50%) and photosensitivity (82.50%) in patients with systemic lupus erythematosus. Dark skin is known to protect against skin cancers but may be more susceptible to allergic reactions. However, we found only one case of SLE with discoid lupus lesions.

Dyspnea is the third most common presentation and may result from pulmonary fibrosis, a known complication of systemic lupus erythematosus and rheumatoid arthritis.

Visual disturbances may result from uveitis associated with Behcet disease and keratoconjunctivitis, episcleritis, scleritis and keratitis are associated with rheumatoid arthritis.

Oral and genital ulcer is the fifth most common presentation, and with uveitis they are pathognomonic and compose the triad of Behcet syndrome.

Stroke is among the presentations encountered in my study, and may result as a complication of antiphospholipid syndrome and Behcet's syndrome.

Raynaud's syndrome is secondary to systemic sclerosis (90%), mixed connective tissue disease (85%), rheumatoid arthritis and systemic lupus erythematosus.

Lupus nephritis is a known clinical presentation of systemic lupus erythematosus and is one of the main determinants of prognosis (with low C4 and pancytopenia), the typical renal lesion is diffuse proliferative glomerulonephritis characterized by heavy hematuria, proteinuria and cast on urine microscopy.

Oral ulcer represents 3% of the presentations and it is one the 11 criteria used for the diagnosis of systemic lupus erythematosus.

Fever (3%) and fatigability (2%) are nonspecific clinical features of many autoimmune connective tissue diseases.

Joint deformity also encountered in our study (1%), it is a late complication of rheumatoid arthritis, and most of them are treated with rituximab to prevent further deterioration.

Anasarca represents only 1% of the presentations and it is caused by massive proteinuria, usually associated with lupus nephritis.

The least common presentation in our study is symmetrical proximal muscular weakness

encountered in one patient diagnosed with polymyositis.

6. Conclusion

AICTD affect 8% of the total patients admitted to the internal medicine department in the hospital. SLE is the most common. Arthritis and leg swelling are the most common clinical presentations. Corticosteroids are the most common prescribed drugs. The proportion of females to males with AICTD is 3.55 to 1. The age range 20 – 30 years is the highest.
Illiterates represent 63% of the total patients. Housewives represent 72% of the total patients. Patients residing in the capital and the governorate Sana'a represent 44% of the total patients.

Recommendations

We recommend studies of the outcome of long-term treatment of patients with AICTD. Moreover, we recommend studies of the aetiology of these studies.

Authors contributions

Dr. Asma Alwan is the co-ordinator of this work, professor Yahya El-Izzi is the head of Dept., of internal medicine and with professor Ahmed Qayed played a pivotal role in the diagnosis of patients, finally professor Adnan al-Adhal has the major role in contacting the patients and reviewing their history, physical examination and investigations, in addition is the correspondent of this work.

Acknowledgment

We like to thank our God for his help, our patients for their cooperation and we like to thank the directory of Al-Thawra hospital for their kind treatment.

Conflict of interest statement

The authors declare no conflict of interest.

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