Profile of Autoimmune Connective Tissue Disorders in the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria.

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ABSTRACT

BACKGROUND

Autoimmune Connective Tissue Disorders have rarely been reported among African blacks and even in Nigeria, in contrast with African-Americans. Our encounter with these cases shows that the disease may not be 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 the University of Port-Harcourt Teaching hospital.

METHOD

This was a retrospective study of patients presenting with autoimmune disorder attending the Rheumatology and Dermatology clinic in University of Port Harcourt Teaching Hospital, Port Harcourt, located in Rivers state, South-South, Nigeria, over a period of one year (2012-2013). 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, Systemic Sclerosis and Rheumatoid Arthritis.

RESULTS

Our study indicates that out of 931 Rheumatology/Dermatology cases seen, 30 were autoimmune connective disorders indicating a frequency of 3.2%. Out of this 3.2%, Systemic lupus erythematosus (SLE) constituted about 91%, rheumatoid arthritis 6% and systemic sclerosis constituted about 3%. The age range of the subjects was between 14-59years with a mean age of 34years, indicating the universal young age at presentation. Females constituted females 93.3% of the patients with a female to male ratio of 14:1. The duration of disease ranged from (0.1-15 years) with a mean of 5years. The most clinical presentation of systemic lupus was discoid rash constituting about 93%, while that from rheumatoid arthritis was deformities of the proximal interphalangeal and distal interphalangeal joints. The major causes of mortality for the SLE patients were lupus nephritis, congestive cardiac failure and pulmonary hypertension, while death from systemic sclerosis was mostly linked to the renal crises. Rheumatoid factor was positive in 28 (93.3%), while Anti Neutrophilic Antibody was positive in 8 (26.6%) of the tested subjects.

CONCLUSION

Autoimmune disorders may not be uncommon in Port-Harcourt, Nigeria, contrary to previous reports, as both the prevalence and incidence are rising probably due to increasing awareness and better diagnostics. Age, gender and ethnicity may also account for the risk factors. This is the first study to report prevalence of autoimmune connective disorders in Port-Harcourt, Rivers State.

KEYWORDS

Profile; Autoimmune connective tissue disorders; Nigeria.

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INTRODUCTION

Connective tissue diseases are a group of rheumatologic diseases which are autoimmune in nature and include Rheumatoid Arthritis, Systemic Lupus Erythematosus, Scleroderma, Mixed connective tissue disease, Dermatomyositis, Polymyositis and Sjogrens amongst others [1].

Connective tissues are the structural portions of the body that essentially hold the cells of the body together. These tissues form a framework, or matrix, for the body and are composed of two major structural protein molecules, collagen and elastin.

Autoimmunity has been considered to represent disorders associated with reaction of the patient's own immune system against self-antigens or body systems. These diseases feature abnormal immune system activity with inflammation in tissues as a result of an immune system that is directed against one's own body tissues (autoimmunity) and are also referred to as systemic autoimmune diseases [2].

In many of these disorders, the tissues involved show lesions or morphology indicating destructive inflammatory or reactive features clearly produced by or associated with cell-mediated or antibody-driven reactions of the patient against his own tissues.[1]

Systemic lupus erythematosus (SLE) is recognized more often in African blacks who have a younger age of onset and a confirmed genetic association with HLA DR4[3]. Features such as photosensitivity and serositis are less common in blacks while renal disease which is more common makes the early screening for renal disease important[3].

The reported prevalence of systemic lupus erythematosus (SLE) in the world population is 20 to 150 cases per 100,000[4]. The prevalence is known to be higher in women with varying rates from 164/100,000 in whites to 406/100,000 in African Americans[4].

The prevalence of SLE is higher among Asians, Afro-Americans, Afro-Caribbeansand Hispanic Americans compared with Americans of European descent in the United States, and among Asian Indians compared with Caucasians in Great Britain [5].

Due to improved detection of mild disease, the incidence nearly tripled in the last 40 years of the 20th century[4], consequently the disease appears to be more common in urban than rural areas.

Although data on the prevalence of SLE among Africans and Asians living in the tropics are limited, SLE is more severe in people of African and Asian extraction compared to Europeans[5].The high prevalence of SLE in recent migrants from West Africa also suggests that the disease is not rare in West Africa, and that there is a genetic basis for the high risk of SLE in people of West African descent compared with other groups[6].

In Ghana, a retrospective study over a 6 year period in a tertiary hospital recorded 11cases of SLE out of 25 Rheumatology cases with the majority of the cases being females[7].

Frasier et al, in Cote d Ivoire, reviewed a total of 9 cases seen over an 11 year period in a tertiary hospital using a retrospective analysis. All patients seen were females, aged between 20 – 40 years[7].

In Zimbabwe, a prospective analysis in a hospital survey by Malembaet al[8] over a 13 year period showed 18 patients with SLE out of 141 (13%) rheumatology cases seen with females making up the majority of the subjects. Malemba et al thus suggested that SLE was not rare in Africa[8].In Kinshasa Congo, a retrospective hospital study of connective tissue disease done by Malemba et al in 2008 reported that SLE constituted up to 5.2% of the 12.1% rheumatology cases[9].

In the same vein and with similar outcomes to the study by Malemba et al; a study done by Adelowo et al at the Athrimed hospital Lagos

revealed that SLE accounted for 5.28% of the 1,250 rheumatology cases seen over the study period of 6 years (2000-2006). Females constituted 95.5% of the 66 cases seen. The subjects were aged 17–55 with a mean of 33 years at presentation and had the symptoms for a mean of 2.6 years [10].

In the same way, Rheumatoid arthritis (RA) once a rarity in Africa, has now been reported in Africa.[2]

The prevalence of rheumatoid arthritis (RA) is relatively constant in many populations, at 0.5–1.0%[2,3].Although epidemiological surveys have shown that the prevalence in urban populations of Africa is similar to that in western communities, it is less common in rural areas[2]. Further epidemiological studies are needed to confirm these findings and identify factors contributing to this difference in order to provide a better understanding for the emergence of RA in Africa. Especially as studies in rural African populations, both in South Africa and in Nigeria, have failed to find any cases of RA in studies of 500 and 2000 adults, respectively.[2]

Studies in populations from Southeast Asia, including China and Japan, have similarly shown very low occurrences (0.2–0.3%) for RA. In terms of gender, a similar pattern is seen worldwide, affecting females three times more commonly than men[11]. The cases of rheumatoid arthritis are more common among persons aged between 40 and 65 years [11].

A study from Nigeria by Adelowo[12] showed a prevalence of 12.3% out of the 1,623 patients attending a private rheumatology clinic in Lagos over a period of 7 years (2001-2008). Females were more affected in the ratio 2.4:1, with a mean age of 46.9 years. The duration of symptoms ranged from 4-264 months with the proximal interphalangeal joint as the mostly affected site[12].

Systemic scleroderma on the other hand, usually develops between the ages of 35 and 55[12]. Localized scleroderma is more common in children than adults, but is extremely rare even in the young age group. It occurs in between 0.2 and 0.4 per 100,000 people. Systemic scleroderma in children is even rarer[14].

The infrequent occurrence of systemic sclerosis worldwide has also been noted, although the localized type occurring with the absence of anti-centromere antibodies in blacks was noted in a recent large series in the western world[3], in our environment not much work has been done on this. But the outcome of this disease is still very poor which may be attributed to a lot of factors such as lack of awareness of the disease, poor access to health facilities, illiteracy and poverty[3].

Worldwide, the incidence of scleroderma is three to eight times higher in women than in men. Of possible importance was a 2002 study reporting that the disease tended to be less severe in women who developed it in middle age after being pregnant.[8]

A retrospective study by Adelowo[9] also showed scleroderma prevalence of 1.1% out of 1,250 rheumatology cases over a 5-year period (2001-2006) with a total of 14 cases. The majority (12) 85.7% of the patients were females compared to males(2)14.3%. The age range of the cases was between 26-69 years with a mean of 40.3years[9].

The outcome of the studies on connective tissue diseases in Africa and Nigeria as reviewed above show's that Autoimmune Connective Tissue Diseases are not as rare as previously thought in Nigeria. In spite of this situation, there are few studies which have documented the National epidemiology and trend of these diseases. Reports on the epidemiology and profile on these conditions in Port Harcourt are also a rarity. It is on this background that this study aims to determine the profile and pattern of Autoimmune Connective Tissue Disorder in University of Port Harcourt Teaching over a one year period from January 2012- January 2013.

METHODOLOGY

Study Site

The study was carried out in the department of internal medicine of the University of Port-Harcourt Teaching Hospital. The hospital serves as the main tertiary centre for Rivers State and the neighbouring South-South States of the Niger Delta. Rivers State has a heterogenous population of about 5.1million, (according to the national population census 2006) consisting of several tribes as well as foreigners involved in the various economic activities in the area with many engaged in the oil and gas sector.

In this study, we investigated the prevalence of Autoimmune Connective Tissue Disorders for a period of one year from 2012 -2013. First, we assessed whether there was any gender or age predilection. Next, we assessed the serological markers, clinical features, mean disease duration and overall clinical outcome

Study Design and Population

This was a cross-sectional retrospective study. The study population consisted of patients who had been diagnosed with having Systemic Lupus Erythematosus, Rheumatoid Arthritis and Scleroderma, fulfilling the American Rheumatology Criteria[15,16,17](as in Tables 1, 2 and 3 respectively) attending the Medical Out Patient Clinics and on admission in the medical wards of UPTH and also referred from other out-patient clinics. The data of patients who fulfilled the criteria of the American College of Rheumatology[15,16,17]for Systemic lupus, Rheumatoid Arthritis and Systemic Sclerosis were included in the study. Ethical approval was obtained from the ethical committee of the UPTH for the study.

RESULTS

A total of 931 Dermatology/ Rheumatology cases were seen, out of which 30(3.2%) cases of Autoimmune Connective Tissue Disorders treated in the hospital were reviewed.

Out of the 30 patients, 27(91%) of these patients fulfilled the American Criteria for Rheumatology for Systemic Lupus Erythematosus, 2(6%) fulfilled the American College of Rheumatology for Rheumatoid Arthritis and 1(3%) fulfilled the American College for Rheumatology for Sclerodermasee (Table 4). There was a significance difference in sex, age, clinical features and laboratory markers reviewed in these patients see (Table 5).

Table 1: ARA Criteria for the diagnoses of SLE[15]

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	>0.5g//day protein	51%	94%
Haematologic	HB<10mg/dl, lymphopenia< 1500/ul thrombocytopenia< 1oo,ooo/ul, leukopenia<4000/ul, in the absence of offending drug	59%	89%

*CNS(Central nervous system); ANA(Antineutrophilic antibody); sm(Smith); ds(double stranded); DNA(Deoxyribonucleic acid); Hb(haemoglobin)}. To make a diagnosis, the patient should fulfil 4 out of the 11 clinical features.

Table 2 - American College of Rheumatology Criteria For Rheumatoid Arthritis.[15]
Four of the following must be present in a minimum of six weeks

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 juxtaarticular regions
Positive serum rheumatoid factor
Radiographic changes including erosions or bony decalcifications localized in or adjacent to the involved joint
Arthritis of wrist, proximal interphalangeal joint or metarcarpophalangeal joint

Table 3 - Criteria For Diagnosing Scleroderma -1980 Criteria for the Classification of Systemic Sclerosis.

The American College of Rheumatology (former American Rheumatism Association - ARA) has defined criteria, that are 97% sensitive and 98% specific for systemic sclerosis (SSc) as follows [17]:

Major criterion:	Minor criteria:
Proximal diffuse (truncal) sclerosis (skin tightness, thickening, non-pitting induration)	• Sclerodactyly (only fingers and/or toes). • Digital pitting scars or loss of substance of the digital finger pads (pulp loss) • Bilateral basilar pulmonary fibrosis

The patient should fulfil the major criterion or two of the three minor criteria. Raynaud's phenomenon is observed in 90-98% of SSc patients.

Table 4 - Profile of Autoimmune Connective Tissue Disease Over a 1 Year (2012-2013)

AUTOIMMUNE DISORDER	NUMBER OF CASES	PERCENTAGE %
Systemic Lupus	27	91
Rheumatoid Arthritis	2	6
Scleroderma	1	3
Total number of cases	30	100

Discoid rash, malar rash and ANA positivity were the commonest clinical presentations of SLE. 93% had discoid rash, 33% malar rash and 21% with ANA positivity. No patient had photosensitivity, non-erosive arthritis, serositis or central nervous system disorders.

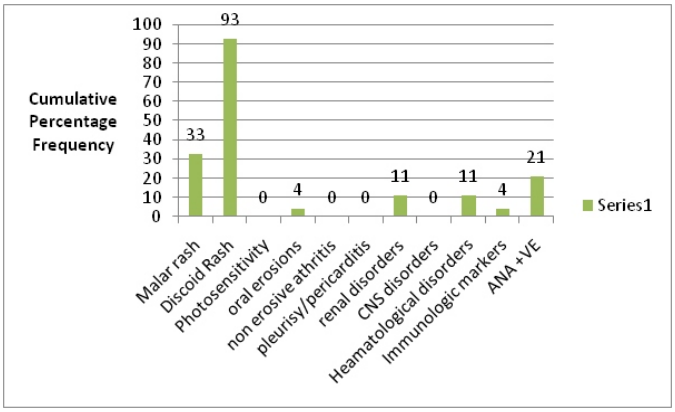

Figure 1: Showing clinical presentation of SLE.

Twenty eight (93%) of the 30 patient tested for rheumatoid factor were reactive. The rate of positive ANA test among the 8 patients tested was 6(75%). Twenty three (77%) of the patients had elevated ESR, while the two patients who had Anti- CCP tests were positive.

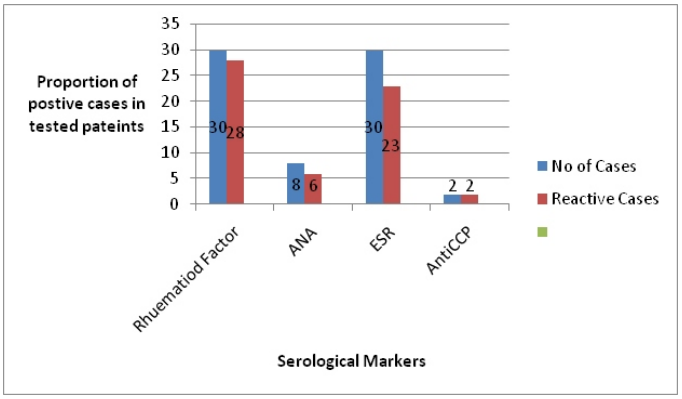

Fig. 2 Showing positivity of serological markers.

The female to male ratio was 14:1, age range at onset was 14 to 59years with a mean of 34.Disease duration ranged from 0.1- 15 years with a mean of 5years.On follow up of the patients3(10%) had died, 25(83.3%) were still attending clinic while 2(6.7%) were lost to follow up.

Table 5: Showing demographic data of patients.

Total Number of Patients	30
Female:Male Ratio	14:1
Mean Age at Onset in years(Range)	34 ± SD (14 – 59)
Mean disease duration in years (range)	5 ± SD (0.1 – 15)
Lost to Follow Up	2 (6.6%)
Dead	3 (10%)
Continuing to attend clinic	25 (83.3%)
Lost to Follow up	2 (6.7%)
Standard deviation for ages	122+/-26
Standard deviation for disease	21+/-15

DISCUSSION

Auto-immune rheumatology diseases are a major cause of death among young and middle-aged women.[20]The reported prevalence varies markedly worldwide depending on case definitions and population studied. The prevalence rate ranged from 0.08 to 0.013% in 1995 to 2000, and rose to 0.13 to 0.16% in 2005 to 2010. Prevalence rate for females aged > 50 years rose from 0.25% in 1995 to 2000 to 0.36% in 2005 to 2010.[20] overall, females are more affected in 85% of cases with age range between 15-50 years.[21]

In this profile study however, we found out that autoimmune connective disorders have been under diagnosed previously in our environment. Systemic lupus erythematosus (SLE) constituted about 91%, rheumatoid arthritis 6% and systemic sclerosis constituted about 3%. The age range was between 14-59years with a mean age of 34years, indicating the universal young age at presentation, although 3 of the patients were elderly lupus at ages above 50.

Most of the patients 93.3% were mostly females with a ratio of 14:1 while the disease duration in this study ranged from (0.1-15) with a mean of 5years. 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[21].

SLE was the most common (91%) autoimmune connective tissue disorder diagnosed in this study. This finding is similar to a retrospective study in Ghana which recorded 11cases of SLE out of 25 Rheumatology cases[7]. Though the study by Adelowo et al in Lagos Nigeria revealed that SLE accounted for 5.28% of the 1,250 rheumatology cases[11], the difference may be explained by the smaller study size and shorter duration of our study. The observed high prevalence in this study may also be due to the increasing awareness among physicians and availability of better diagnostic facilities. 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. We therefore conclude that there is enough evidence that SLE is significantly prevalent in our environment.

The most common presentation of SLE was discoid and malar rash constituting about 93% and 33% respectively. This was also similar to the work done in kenyetta hospital in which malar rash actually constituted one of the major features[22]. 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[3,4,10,11] and has been attributed to the presence of the female hormone oestrogen.[23]

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[11] 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 by Adelowo et al[11] was done in a private specialist rheumatology clinic with the possibility of earlier referrals to this centre.

The positive 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.[24,25] The high positive 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.[25-28]

Most of the SLE patients were on treatment with prednisolone, azathioprine and hydroxychloroquine, in addition to drugs for the treatment of other comorbidities like hypertension. A study by Marie et al in Douala Cameroon also showed that SLE patients benefitted from using steroids, immunosuppressives and antimalarias.[29] This is also in line with the European League Against Rheumatism (EULAR) for the treatment of SLE as patients without major

organ involvement will benefit from taking steroids and antimalarials but immunosuppressives should be taken in refractory cases and patients with major organ involvement[30]. It should however be noted that in patients with retinitis antimalarial should be avoided. One of the patients in this study, who had retinitis, was exempted from taking hydroxychloroquine.

Only one case of scleroderma in a female was seen in this study. This prevalence of 3.3% of all rheumatologic conditions seen in this study made scleroderma the rarest of the rheumatologic disorders. This finding is similar to the study in western Nigeria done by Adelowo et al[16] that reported scleroderma as a rare disease in Nigerians.

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 Adelowo[16] et al and Wadee et al [31] found.

The results of this study indicate that connective tissue diseases are more prevalent than previously thought in our environment. However, the limitation of this study is that, it covered only a 12month study period, which may be inadequate to investigate the profile of these disorders. The short period of review may also be responsible for the small number of patients seen within this period. The small sample size may have also resulted in an underestimation of the true burden of these diseases.

The outcome of this study has shown that it is important to study the profile of these disorders in order to determine the current prevalence of these disorders, rather than relying on outdated estimations. The results of recent prevalence evaluation from studies like this will also be useful in evaluating any associated risks in this environment as compared to other regions within the country as well as other countries.

There is need for higher index of suspicion and early referrals to improve probable underdiagnoses and late presentation. More public and physician education is recommended in order to promote early diagnosis and early referrals in addition to changing perceptions on these diseases as incurable diseases which defy medical care and treatment.

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