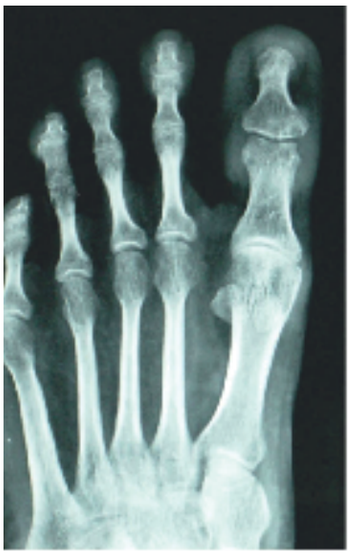

African Journal of Rheumatology

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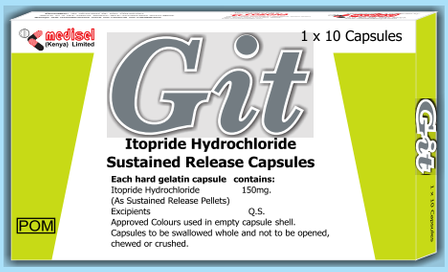

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NIC PHARMA

ACR San Diego 2017: Part Sponsorship for African Trainees

Dear All

This is to inform you that the ACR has been gracious enough to once again provide sponsorships for deserving African trainees to attend the ACR meeting in San Diego in November this year. The first offer was last year and it is hoped this will continue in the future.

The sponsorships are meant as much as possible for rheumatology trainees. It will consist of;

1. Complimentary Registration

2. Hotel accommodation which will either be shared or single occupation

3. Complimentary pre programme course of your choice

As it was last year, you are encouraged to apply to me giving your country of residence, whether you are in a training programme, your year of training and your corresponding email addresses.

Preference will be given to those trainees whose abstracts have been accepted.

You may wish to apply latest July ending. You are also advised to ask for letter of recommendation from other rheumatologists in your country.

Only those successful applicants will be informed.

Prof. Femi Adelowo FRCP, MACR

President, AFLAR

Editorial comment

Asgar Ali Kalla
Editor-in-Chief
Professor of Rheumatology
University of Cape Town
South Africa
Email: kallaa@iafrica.com

The June issue of the *African Journal of Rheumatology* (AJR) is an example of the extent to which rheumatology is growing on the African continent. The spectrum of research being reported reflects the broad spectrum of rheumatological diseases elsewhere in the world and confirms that Africans are affected by musculoskeletal disorders which present a burden on society. We need to encourage more research projects and consider review articles to improve the impact of our journal in the world of rheumatology.

The report on rheumatoid arthritis at a teaching hospital in Nigeria by Ohagwu *et al*[1] from the Lagos State University Teaching Hospital Ikeja reports that more than 1,200 patients with musculoskeletal diseases were treated over a four year period. This emphasises the need for a rheumatology service among the general medical outpatient services of teaching hospitals. These should evolve into arthritis clinics run by rheumatologists, as is happening in Nigeria. They found 10% of their patients had rheumatoid arthritis. While the general features with respect to seropositivity, distribution of joint involvement, elevation of acute phase proteins and response to Disease Modifying Anti-Rheumatic Drugs (DMARDs) is similar to reports from other parts of the world, there were some interesting differences. None of the patients in this retrospective cohort were smokers. The ratio of females to males was much higher at 6:1 and the age at onset was younger at a mean age of 41.4 years. Patients had active disease and radiological changes, suggestive of delayed diagnosis and emphasising the need for strategies aimed at early diagnosis.

The case report of late onset Pompes disease by Mativo[2] of the Department of Medicine at Aga Khan University Hospital, Nairobi, Kenya describes a new genetic variant causing glycogen storage disease, resulting in severe respiratory muscle weakness. Muscle biopsy was negative and the only test suggestive of Pompes disease was a low level of glucosidase. The cause was found to be a gene mutation resulting in the substitution of proline for arginine at codon 451. The patient presented at the age of 54 years with respiratory symptoms and the differential diagnosis is reviewed. Unfortunately, the patient did not have access to the state of the art treatment with myozyme due to costs and the prognosis is poor.

The study from Libya on the effect of adalimumab in a variety of rheumatic diseases confirms that the use of biologic therapy is a reality in Africa. This study by Basma *et al*[3] of the Rheumatology Department, Tripoli Medical Center, Tripoli, Libya reviews the use of adalimumab in patients witrh rheumatoid arhtritis, ankylosing spondylitis, psoriatic arthritis and Adult Onset Still's Disease (AOSD). As expected, adalimumab was effective in all the 31 patients, who tolerated it well. No significant adverse events were reported and there were no reports of the development of Tuberculosis (TB).

The study by Umar *et al*[4] from Nairobi describes the prevalence of fibromyalgia syndrome in diabetic patients suffering from chronic pain. They identified 219 patients with chronic pain within the diabetic clinic of 1280 at Kenyatta National Hospital, giving a prevalence of 27.9%. The mean tender count was 13.7 and majority of the patients had moderate disease with a FIQR score of 51.9. Females predominated and those with FMS were significantly older. They found type 2 diabetes in 91.6% and most of them were on oral agents. The mechanism for this association between diabetes and FMS is unknown. The authors highlight the importance of making the diagnosis and suggest appropriate treatment of FMS to improve the quality of life for these individuals.

Oguntona *et al*[5] of the Department of Medicine, Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria studied the cardio-pulmonary manifestations of Rheumatoid Arthritis (RA) among rheumatology patients in a teaching hospital in Nigeria. They identified a cohort of 21 patients who fulfilled the 1987 ACR criteria for RA, 38% (8 patients) manifesting cardio-pulmonary involvement. The commonest feature was pleural effusion, seen in all 8 patients. Interstitial lung disease was present in 3 patients while the cardiac features consisted of pericardial effusion, arrhythmias and cardiac failure. The most significant finding was a mortality

of 50% over 3 years in the patients with cardio-pulmonary manifestations. The authors highlight the importance of chest X-ray in detecting the pleural effusions and compare their results with other reported studies. Several other extra-articular manifestations were encountered but these are not reported in any detail. The importance of this report is that it highlights the young age at death and the variable disease duration at time of death.

The article on the prevalence of abnormal liver function tests in rheumatoid arthritis by Olago-Rakuomi *et al*[6] from the Department of Clinical Medicine and Therapeutics and the Department of Pharmacy, College of Health Sciences, University of Nairobi, Kenya is very important, since methotrexate is well established in the treatment of RA. Interestingly, of the 107 patients studied, at least 57% had at least one abnormal liver function test. Surprisingly, the commonest abnormality was elevated bilirubin and alkaline phosphatase, rather than AST and ALT abnormalities. The authors introduce the concept of "rheumatoid liver" as a specific entity, but do not expand the idea in their study. Liver function tests remain an important aspect of monitoring liver toxicity, especially with methotrexate. The findings of this study were encouraging in that they found a protective effect related to use of DMARDs, including methotrexate. Additionally, AST and ALT were generally within normal limits in most patients. However, this study highlights the concept of liver disease as an extra-articular manifestation of RA and this concept may require further study.

This June issue is packed with interesting research from Kenya and Nigeria and confirms that rheumatology is alive and well on the African continent. There is clearly more work to be done in our region but the reports in this issue are encouraging. The Editorial Board is grateful to the authors for their interesting and valuable research studies and would like to encourage Rheumatologists from around the continent to contribute to the material. The Editorial Board will also be considering the publication of review articles on interesting aspects of rheumatology. Hope you enjoy reading the various studies in the AFLAR journal.

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Research article

Pattern of rheumatoid arthritis in Nigeria; Study of patients from a Teaching Hospital

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Abstract

Introduction: Rheumatoid Arthritis (RA) is an autoimmune inflammatory polyarthritis with numerous extra-articular manifestations. It is said to be rare among black Africans, however there has been a report from a private clinic in Nigeria. We hereby present the clinical and laboratory patterns of presentation of rheumatoid arthritis in a tertiary hospital in Nigeria.

Methods: This was a four year retrospective study of patients that presented to the Rheumatology unit of Lagos State University Teaching Hospital (LASUTH). The diagnosis was based on either the American College of Rheumatology (ACR) criteria or the ACR/ European League of Associations Against Rheumatism (EULAR) 2010 classification criteria for RA.

Results: A total of one thousand two hundred and fifteen patients with rheumatological disorders were seen at the rheumatology unit of LASUTH during the four year period. Of these, 128 (10.6%) patients fulfilled classification criteria for RA. Female to male ratio was 6.1:1. Mean age of the patients was 41.4 years.The proximal interphalangeal joint was mostly affected. ESR and CRP were mostly elevated. Test for Rheumatoid Factor (RF) was positive in 78 (72.2%). Anti-CCP was positive in 54 (61.1%). Radiographs of the hands predominantly showed erosions and periarticular osteopenia. Treatment was with Disease – Modifying Anti-Rheumatic Drugs (DMARDs) and prednisolone.

Conclusion: Rheumatoid arthritis could be a significant medical condition among Nigerians. Nigerians who suffer RA have predominantly high titres of RF and anti-CCP. ESR and to a less extent CRP are usually elevated.

Key words: Rheumatoid arthritis, Clinical and laboratory parameters, Treatment, Nigerians

Introduction

Rheumatoid Arthritis (RA) is a systemic autoimmune inflammatory polyarthritis with articular and extra-articular manifestations[1]. It is regarded as the most common inflammatory arthritis and has a prevalence of 0.5 – 1% in industrialized nations[2,3]. Its prevalence in Africa is estimated at 0.2 – 0.3%[4]. RA has a female to male preponderance of about 3:1. It is usually associated with increased morbidity, mortality and cardiovascular events[5–7]. Hitherto, RA has been regarded as a rare disease among black Africans[8,9].

A report from a private rheumatology clinic in Lagos, Nigeria however showed that RA accounted for 12.3% of patients seen over an eight year period[1]. Report from Democratic Republic of Congo showed that 8.5% of patients that attended a rheumatology clinic over a three year period had RA[10]. RA manifests clinically with joint pain and swelling, significant joint stiffness, constitutional symptoms and impaired quality of life. It is associated with numerous extra – articular manifestations including anaemia, subcutaneous nodules and sicca symptoms[4]. Commercially available serologic markers of the disease include tests for rheumatoid factor and anti – Cyclic Citrullinated Peptide (anti-CCP). The diagnosis of RA is currently based on the 2010 ACR/EULAR classification criteria which requires the presence of synovitis (joint swelling) and a score of at least 6 in four domains; joint affectation, symptom duration, acute phase reactant and serology for rheumatoid factor and/ or anti-CCP)[11]. The American College of Rheumatology 1987 criteria had also been used to make a diagnosis of RA. The treatment of RA is aimed at limiting disease progression, pain relief, improving quality of life and management of co-morbidities. Disease Modifying anti-Rheumatic Drugs (DMARDS) are the mainstay of treatment[4,12]. We hereby present the cases of rheumatoid arthritis seen in a tertiary hospital in Nigeria.

Materials and Methods

This was a four year cross - sectional retrospective study of patients that presented to the Rheumatology unit of Lagos State University Teaching Hospital

(LASUTH), Lagos, Nigeria. Study duration was from July 2011 to June 2015. The diagnosis of RA was made using either the American College of Rheumatology criteria[13] during the first year of study and thereafter using the 2010 ACR/EULAR classification criteria for RA[11]. Smoking history of the patients was documented. Abdominal, as well as cardiovascular and respiratory systems examinations were carried out. The first recorded results of haemoglobin concentration, white blood cell and platelet counts, Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) were documented. Results of rheumatoid factor by latex agglutination and anti-CCP by ELISA were also documented. Radiographs of the hands and feet as reported by radiologists were also documented. Disease activity using the Clinical Disease Activity Index (CDAI) was documented. Medications such as DMARDs, glucocorticoid use and Non Steroidal Anti-Inflammatory Drugs (NSAID) were also documented.

Results

A total of one thousand two hundred and fifteen patients were seen at the rheumatology unit of LASUTH during the four year study period. Of these, 128 (10.6%) patients fulfilled either the American College of Rheumatology classification criteria of RA or the ACR/EULAR 2010 classification for RA. One hundred and ten (85.9%) were females while 18 (14.1%) were males with a female:male ratio of 6.1:1. Age of patients was between 23 – 67 years (mean – 41.4 years). Duration of symptoms before presentation ranged from 2 – 300 months (median- 41 months). There was no patient with history of cigarette smoking. Ten (7.8%) patients gave history of alcohol consumption. None of the patients smoked cigarette. Recurrent fever was present in 43(33.6%) of the patients. Polyarticular pattern of presentation was mostly seen (87.5%). The Proximal Interphalangeal Joint (PIP) was most frequently involved followed by the wrist, knee, elbow and the Metacarpo-Phalangeal Joints (MCP) respectively (Table 1a).

Table 1a: The pattern and frequency of joint involvement

Joint affectation	No.	(%)
Proximal interphalangeal	114	89.0
Wrist	98	76.6
Knee	94	73.4
Elbow	84	65.6
Metacarpophalangeal	82	64.1
Shoulder	74	57.8
Ankle	70	54.7
Metatarsophalangeal	28	21.9

Non – haematologic extra – articular features are shown in Table 1b. The results of haematology and radiology investigations are as shown in Tables 2a and 2b respectively. One hundred and eight (84.4%) patients had Erythrocyte Sedimentation Rate (ESR) done while only 62(48.4%) had C-Reactive Protein (CRP) tested. The ESR was raised in 98/108 (90.7%) and CRP was elevated in 32/62 (51.6%) patients.

Table 1b: Frequency of extra-articular features

Feature	No.	(%)
None	99	77.3
Subcutaneous nodule	23	18.0
Pulmonary	1	0.8
Uveitis	4	3.1
Sicca	1	0.8

Table 2a: Haematologic investigations

Investigation		No.	(%)
Haemoglobin conc. (g/dl) (N=97)	≤10.0	30	30.9
	>10.0	67	69.1
Leucocyte count (per litre) (N=97)	<4	5	5.2
	4-11	81	83.5
	>11	11	11.3
Platelet count (per litre) (N=94)	<150	4	4.2
	150-450	78	83.0
	>450	12	12.8

Table 2b: Radiologic features

Finding	Frequency (N=32)	(%)
Normal	10	31.3
Erosions	8	25
Osteopenia	5	15.6
Erosion and osteopenia	2	6.2
Subchondral sclerosis	2	6.2
Joint space narrowing, osteopenia, subchondral sclerosis	3	9.5
Joint deformities, narrowed joint space periarticular osteopenia	2	6.2

Table 3: Serology determination in patients with RA

Serology			No.	(%)
RF (N=108)	Positive		78	72.2
		<3x ULN	12	11.1
		≥3x ULN	66	61.1
		≥10x ULN	24	22.2
	Negative		30	27.8
Anti-CCP (N=88)	Positive		54	61.1
		<3x ULN	4	4.6
		≥3x ULN	50	56.8
		≥100x ULN	26	29.1
	Negative		34	38.6

ULN = Upper Limit of Normal

Table 4: DMARDs prescription in patients with RA

DMARDs	No.	(%)
MTX	28	21.8
HCQ	16	12.5
MTX + HCQ	62	48.4
SSZ + HCQ	2	1.6
MTX+HCQ+SSZ + RTX	2	1.6
MTX+SSZ+HCQ	6	4.7
LEF	6	4.7

Test for Rheumatoid Factor (RF) was done in 108 (84.4%) patients and anti-CCP in 88 (68.8%). RF was positive in 78/108 (72.2%) and anti-CCP was positive in 54/88 (61.1%). Twenty six (29.5%) patients were negative for both RF and anti-CCP and were classified as seronegative RA. Titres of RF and anti – CCP were high in most of the patients (Table 3).

The Clinical Disease Activity Index (CDAI) was obtained in 76 (29.69%) patients at presentation and of these, 8 (10.5%), 19 (25%) and 49 (64.5%) had low, moderate and high disease activities respectively.

Short term Non – Steroidal Anti – Inflammatory Drugs (NSAIDs) were given to most of the patients for immediate pain relief. All patients received low dose oral prednisolone (15mg or less) which was tapered off to the minimum possible dose over six months. In addition to prednisolone, 28 (21.9%) received only methotrexate (MTX), 17 (13.3%) received only hydroxychloroquine (HCQ),67(52.3%) received a combination of MTX and HCQ. Two (1.6%) patients received triple therapy with HCQ, MTX, SSZ and later received the biologic rituximab (RTX) due to poor disease control. Two (1.6%) could not tolerate other DMARDS and were treated with leflunomide as the only Disease Modifying Anti-Rheumatic Drug (DMARD). Overall, MTX was included in the regimen for 102 (79.7%) patients while HCQ was included in 98 (76.6%) patients (Table 4).

Discussion

In this study, 128 RA patients were seen over four years representing 10.6% of all rheumatology patients seen in the clinic. This gives an average of 32 new cases per year. This ratio is similar to findings of 12.3% found in an earlier study by Adelowo *et al*[1]. This supports the notion that RA and probably other systemic autoimmune diseases may not be so rare in black Africans as previously assumed[14]. The proportion of patients seen in the rheumatology clinic with RA is higher than that reported from Zambia (4.7%)[15] and Democratic Republic of Congo (8.5%)[10] but significantly less than those reported from South Africa (52%)[16] and Kenya (37.3%)[17]. The female:male ratio in this study is higher than that previously reported by Adelowo *et al*[1] but similar to that reported by Muia *et al*[18] from Kenya and Mendiratta *et al*[19] from India. Smoking is known to be the strongest environmental risk factor for seropositive RA[20–22]. None of our patients however had history of active cigarette smoking. This finding is similar to the finding by Malemba *et al*[10] where only 2 out of 114 patients with RA smoked cigarretes. It is generally assumed that black Africans smoke less than their Caucasian counterparts.

This study also showed that RA affects mostly women which is similar to findings in other populations[10,18,23]. Most of the patients had high disease activity at presentation which should necessitate aggressive treatment to reduce progressive joint damage, disability, and overall morbidity and mortality. The high disease activity may be due to delay in presentation. Few patients had radiography of the affected joints done. This is due to the prevailing poverty in the region which therefore leads to prioritization of funds for effective healthcare delivery as previously documented[24]. Anaemia is an important extra – articular manifestation of RA contributing to impaired quality of life. The frequency of anaemia among RA patients in this study is similar to that found in Kenya[18] and Congo[10].

Rheumatoid arthritis from this study is mainly seropositive in nature with only 29.5% having seronegative RA. This finding is similar to the finding in Caucasians. It is also similar to finding in South Africa where 85% of RA patients were found to be RF positive[16]. The percentage of patients seropositive for RF is also similar to that found in Libya by Basma *et al*[23]. The patients seropositive for RF was higher than what has been obtained in Nigeria previously by Adelowo *et al*[1]. Also, this finding is higher than what was obtained in Congo where only 48.6% of patients were seropositive (47.2% for anti-CCP, 34.7% for RF)[10]. However, the study had fewer patients with serology results and this might explain the higher seropositive cases in this present study. The percentage of patients positive for anti-CCP is also comparable to studies outside Africa. No previous study exists in Nigeria regarding RA and anti-CCP positivity. Of note is the fact that most of the patients had high titres of RF and anti-CCP and acute phase reactants were mostly elevated. High titres of RF, anti-CCP and raised acute phase reactants, in addition to female sex and high disease activity at presentation, may be poor prognostic indicators that are prevalent among these patients in this resource poor setting[25].

The treatment of RA from this study showed that MTX is the most prescribed agent, both as monotherapy and in combination with other DMARDs. This is in accordance with the EULAR guidelines for RA management[26]. It is similar to what is practiced in other parts of the world[19,21,27]. Reports from South Africa, Kenya and Libya also showed that MTX is the most prescribed DMARD[12,18,23]. However, some patients may not tolerate MTX or other DMARDs or may have them

contraindicated. Pregnant women and those desirable of pregnancy may have MTX withheld as is seen in patients that were treated with HCQ monotherapy. Biologic agents have been shown to improve disease control and outcome even in patients with poor disease control while on a combination of DMARDS. Oyoo *et al*[28] in Kenya demonstrated significant improvements in simplified disease activity index and overall functional status in patients receiving rituximab after their disease was not controlled while on triple therapy. Two of our patients had to be placed on rituximab following uncontrolled disease while on combination therapy. Regrettably, biologic use in the setting of high disease activity and other poor prognostic factors is low due to prohibitive costs especially since most patients pay out of pocket.

Conclusion

Rheumatoid arthritis is a significant medical condition in Nigeria. It affects predominantly females. Nigerians who suffer RA have predominantly high titres of RF and anti-CCP. ESR and to a less extent CRP are usually elevated and disease activity is usually high at presentation. Poor prognostic indicators are usually high among these patients. Treatment is with combination of DMARDs with MTX and HCQ being the most prescribed agents. Unfortunately, only few patients can afford biologic therapy due to its prohibitive cost and the fact that most of our patients pay out of the pocket.

Acknowledgement

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Research article

Adalimumab effect in a cohort of Libyan patients with rheumatic diseases

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Abstract

Background: Adalimumab is a recombinant human IgG1 monoclonal antibody. It is a tumour necrosis factor-inhibiting, anti-inflammatory, biologic medication. It binds to tumour necrosis factor alpha (TNF), which normally binds to TNF receptor, leading to the inflammatory response of autoimmune disease. By binding to TNF, adalimumab reduces this inflammatory response.

Objective: The study was done to monitor the effects and side effects of adalimumab in our Libyan patients with rheumatic diseases.

Methods: The inclusion criteria for the study were all patients with rheumatic diseases who were treated with adalimumab in the period from April 2013 to April 2016 in the Rheumatology Department, Tripoli Medical Center, Tripoli, Libya. There were 31 patients, 10 of them had RA, 16 patients had Ankylosing Spondylitis (AS), 4 patients had Psoriatic Arthropathy (PsA) and 1 patient had Adult Onset Still's Disease (AOSD). Adalimumab 40mg subcutaneous was given every 2 weeks. Demographic details such as age and sex were recorded. Clinical characteristics as rheumatoid factor in RA patients, disease duration, duration of taking adalimumab and drugs used before starting adalimumab were noted. Assessment of disease activity was measured by DAS28 for RA patients, by BASDAI for AS patients and by DAPsA for PsA patients. For all patients, complete blood count, erythrocyte sedimentation rate, liver function test, hepatitis screen, urine routine examination and tuberculin test before adalimumab were requested to monitor its side effects during follow up.

Results: All patients with rheumatic diseases who took adalimumab in the period between April 2013 and April 2016 were included in the study. Ten patients had rheumatoid arthritis, their mean age was 39.1 years, 10% were male and 90% were female. Rheumatoid factor was positive in 60%, negative in 30% and unknown in 10%. Sixteen patients were ankylosing spondylitis; their mean age was 39 years, 81.25% were male and 18.75% were female. Four patients had psoriatic arthritis, mean age was 40 years, two were females and two were males. One patient had AOSD; she was a female aged 58 years. All RA patients were on prednisolone and/or one or two DMARD before starting adalimumab and failed to show a response. Fourteen AS patients were on one or two NSAIDs and/or salazopyrine and failed to show a response before starting adalimumab and two patients were on infliximab which was not responding to it. Two psoriatic arthritis patients were on methotrexate (MTX) alone, two patients were on leflunomide alone. The AOSD patient was on MTX and prednisolone. The mean of DAS28 before starting adalimumab for RA patients was 4.06 and the mean of DAS28 at the last dose was 2.7 (P-value =0.0135). The mean of BASDAI before using adalimumab was 5.13 and the mean of BASDAI at the last dose was 1.656 (P-value <0.0001). PsA patients had moderate disease activity (mean of DAPsA=20$\pm$SD1.6) and became (mean of DAPsA=6$\pm$SD1.2) which means low disease activity (P-value <0.02). The AOSD patient showed significant improvement clinically and ESR dropped from 53 at the start to 12 at the last dose.

Conclusion: During three years of follow up of our rheumatic diseased patients on adalimumab, we noticed a significant improvement in disease activity scores with minimal side effects.

Introduction

Adalimumab is a recombinant human IgG1 monoclonal antibody. It is a tumour necrosis factor- inhibiting, anti-inflammatory, biologic medication. It binds to tumour necrosis factor alpha (TNF), which normally binds to TNF receptor, leading to the inflammatory response of autoimmune disease. By binding to TNF, adalimumab reduces this

inflammatory response. Adalimumab is administered by subcutaneous injection. For most indications, the maintenance treatment is an injection every other week.

In Rheumatoid Arthritis (RA), it has been approved for use alone or with methotrexate or similar medicines, in the U.S since 2002[1,2]. Adalimumab in RA has a response rate similar to methotrexate, and in combination, it nearly doubles the response rate of methotrexate alone[3].

In ankylosing spondylitis, adalimumab is indicated for reducing signs and symptoms in adult patients with active disease. Adalimumab is also indicated for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in adult patients with psoriatic arthritis. Other indications of adalimumab are juvenile idiopathic arthritis, adult Crohn's disease, paediatric Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa and uveitis.

Materials and Methods

The inclusion criteria for the study were all patients with rheumatic diseases who were treated with adalimumab in the period from April 2013 to April 2016 in Rheumatology department, Tripoli Medical Center, Tripoli, Libya. There were 31 patients, 10 of them had RA, 16 patients had AS, 4 patients had PsA and 1 patient had Adult Onset Still's Disease (AOSD). All patients consented to participate in the study. The study was done after receiving consent from the Tripoli Medical Center ethical and research committee. Adalimumab 40mg subcutaneous was given every 2 weeks.

Demographic details such as age and sex were recorded. Clinical characteristics such as rheumatoid factor in RA patients, disease duration, duration of taking adalimumab and drugs used before starting adalimumab were noted. Assessment of disease activity was measured by DAS28 for RA patients, by BASDAI for AS patients and by DAPSA for PsA patients.

Disease activity scores were measured at the start of adalimumab and every month thereafter. For all patients, complete blood count, erythrocyte sedimentation rate, liver function test, hepatitis screen, urine routine examination and tuberculin test before starting adalimumab were requested to monitor its side effects during follow up. Data was analysed using SPSS computer software package. The mean and standard deviations of the age, disease duration and duration of taking adalimumab were calculated. P-value to measure if there was significant difference between the means of DAS28, BASDAI or DAPSA (according to the patient either RA, AS or PsA) at the start of adalimumab and at the last follow up were calculated using t-test.

Results

All patients with rheumatic diseases who took adalimumab in the period between April 2013 and April 2016 were included in the study. Ten patients had rheumatoid arthritis, their mean age was 39.1±SD8.6 years, 10% were male and 90% were female. Rheumatoid factor was positive in 60%, negative in 30% and unknown in 10%. Sixteen patients were ankylosing spondylitis; their mean age was 39±SD9.95 years, 81.25% were male and 18.75% were female. Four patients had psoriatic arthritis, mean age was 40±SD4.3 years, two were females and two were males. One patient had AOSD; she was a female aged 58 years. The mean duration of rheumatic diseases and the mean duration of taking adalimumab are shown in Table 1. All RA patients were on prednisolone and/or one or two DMARD before starting adalimumab and failed to show a response.

Table 1: The mean duration of rheumatic diseases and the mean duration of taking adalimumab

No. of patients (n=31)	Mean of disease duration (years)	Mean duration of taking adalimumab (months)
RA (10)	6+SD3.0	9.77+SD5.3
AS (16)	6.13+SD7.08	17.5+SD14.8
PsA (4)	11.5+SD9.8	10.5+SD6.4
AOSD (1)	Duration = 4 years	Duration = 3 months

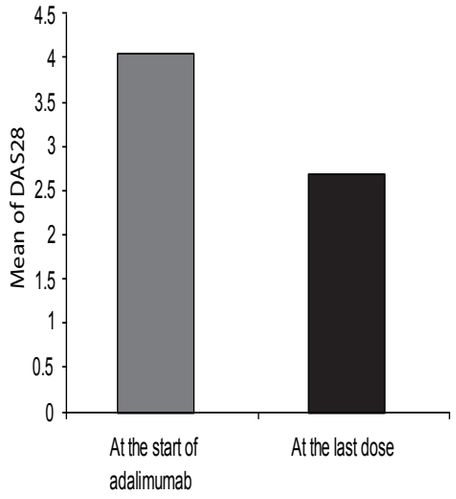
Fourteen AS patients were on one or two NSAIDs and/or salazopyrine and failed to show a response before starting adalimumab and two patients were on infliximab which was not responding to it. Two psoriatic arthritis patients were on methotrexate (MTX) alone, two patients were on leflunomide alone. The AOSD patient was on MTX and prednisolone. Table 2 shows different rheumatic diseases and different drug regimens used for them.

Table 2: Different rheumatic diseases and different drug regimens used for them

Drug regimen	No. of patients
Rheumatoid arthritis patients	(n=10)
Methotrexate (MTX) alone	4
MTX+ Hydroxychloroquine (HCQ)	1
Prednisolone + MTX+ HCQ	2
Leflunomide alone	2
Prednisolone + Leflunomide	1
Ankylosing spondylitis	Total n=16
NSAID	9
Salazopyrine	2
Prednisolone + Salazopyrine	1
MTX	1
Infliximab	2
NSAID + Salazopyrine	1
Psoriatic arthritis patients	Total n=4
Leflunomide alone	2
MTX alone	2
AOSD patient	1
Prednisolone + MTX	1

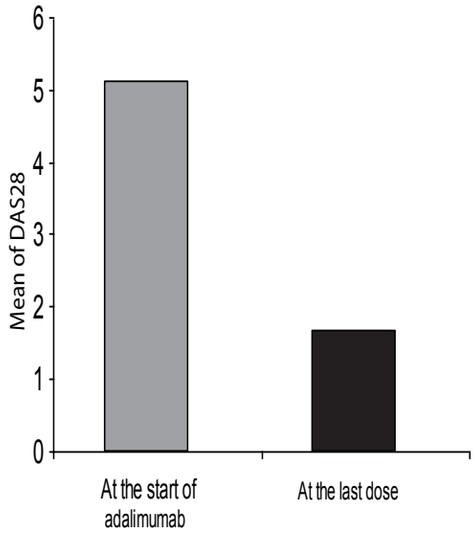
The mean of DAS28 before starting adalimumab for RA patients was 4.06±SD1.18 and the mean of DAS28 at the last dose was 2.7±SD0.81. P-value=0.0135, this difference was considered to be statistically significant (Figure 1).

Figure 1: The difference between DAS28 at the start and at the last dose of adalimumab (P-value=0.0135)



The mean of BASDAI before using adalimumab was 5.13±SD1.63 and the mean of BASDAI at the last dose was 1.656±SD1.49. P value<0.0001, this difference is considered to be extremely statistically significant (Figure 2).

Figure 2: The difference between BASDAI at the start and at the last dose of adalimumab. (P-value=0.0001)



PsA patients had moderate disease activity (mean of DAPsA=20±SD1.6) and became (mean of DAPsA=6±SD1.2) which means low disease activity (P value <0.02). AOSD patients showed significant improvement clinically and ESR dropped from 53 at the start to 12 at the last dose. Regarding side effects of adalimumab, one female RA patient developed hypersensitivity reaction at the first dose of adalimumab and one male AS patient had hypersensitivity reaction 9 months after starting it.

Discussion

Adalimumab is effective and well-tolerated in RA patients who had previously been treated with infliximab and/or etanercept[4]. All measures of the disease activity indicated that patients who had been intolerant of prior TNF-antagonist therapy achieved response rates similar to TNF- antagonist-naïve patients. Clinically meaningful improvement in patients with no response to prior TNF-antagonist treatment were demonstrated during adalimumab treatment, with 59% of patients who had no response to infliximab and in 41% of patients who had no response to etanercept achieving an ACR20 response at week 12[4].

In our study, we started adalimumab for two AS patients, after failure of response to infliximab. Both of them showed a good response to adalimumab which measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). BASDAI consists of six questions measuring the severity of fatigue, spinal pain, peripheral joint pain, tenderness, and stiffness on a visual analogue scale (VAS) (0-10). More than 50% improvement in BASDAI is considered clinically relevant[5]. The Assessment in Ankylosing Spondylitis international working group criteria or ASAS20 response criteria are now used more often[6]. An ASAS20 responder is defined as a patient experiencing improvement of at least 20% and an absolute improvement of at least 1 unit (on a 0-10 scale) compared with the baseline in at least three of the following four domains: patient's global assessment of disease activity as assessed by a VAS; patient assessment of pain represented by a total back pain score as assessed by VAS; patient function as assessed by Bath Ankylosing Spondylitis Function Index (BASFI) score (VAS)[7]; and inflammation, represented by the mean of the severity and duration of the morning stiffness as assessed by questions five and six of the BASDAI score (VAS).

Adalimumab has been used successfully in some patients with AOSD[8]. Adalimumab was effective in treating a patient with AOSD who failed to respond to etanercept[9]. It was also prescribed after infliximab to a patient with AOSD to treat chronic arthritis without further out come details[10]. In this study, adalimumab was given to one patient with AOSD and showed a good response clinically and her inflammatory markers decreased to normal. Regarding side effects in our patients, apart from hypersensitivity reactions, no other side effects were recorded.

Conclusion

During the three years of follow up of our rheumatic diseased patients on adalimumab, we noticed a significant improvement in disease activity scores with minimal side effects.

Acknowledgement

To Amna Elhabbash, statistical analyzer, Faculty of Science, Tripoli University.

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Research article

Prevalence of fibromyalgia syndrome in diabetics with chronic pain at the Kenyatta National Hospital

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Abstract

Background: Fibromyalgia Syndrome (FMS), an increasingly recognized disorder with heightened response to pressure, characterized by Chronic Widespread Pain (CWP), for which no other cause can be identified. Diabetes Mellitus (DM) is the most common metabolic endocrinopathy. It is estimated that more than 50% of diabetic patients will suffer from chronic disability. Musculoskeletal complications of diabetes may be as a consequence of DM complications or direct associations e.g. FMS.

Objectives: To determine the prevalence of FMS in diabetics with chronic pain and to determine the severity of FMS related symptoms using the revised FMS questionnaire (FIQR) tool.

Design: Descriptive cross-sectional study.

Setting: The Diabetic Out-patient Clinic (DOPC), Kenyatta National Hospital (KNH).

Subjects: Two hundred and nineteen patients with chronic musculoskeletal pain.

Results: The prevalence of fibromyalgia in this group of patients was 61 (27.9%) (95% CI 21.9-34.2). Mean age for patients with FMS was 59.9 years, significantly older than patients without FMS (55.6%) (P=0.034). There was a higher female preponderance at 49 (80%). Majority of our study population were on follow-up for Type 2 DM (94.1%). The mean tender-point count for patients with FMS was estimated at 13.7 (SD 2.1). The mean FIQR score was 51.9 (SD 18.4) (moderate disease). Patients with FMS had a higher HBA1c value compared to those without (9.6% vs. 9.3%) (P=0.565). Other factors such as marital status, nature of employment, activities of daily living and type of medications used were not found to be statistically significant. (P>0.05).

Conclusion: FMS is a prevalent disease in the diabetic population. There is increased need of awareness by the clinicians of this disease entity and a multidisciplinary approach required to manage patients presenting with CWP in DM.

Introduction

FMS is a common disorder with cardinal symptoms of diffuse chronic pain associated with muscle stifness and tenderness of specific points on examination. This disease has strong biologic underpinnings and the aetiopathogenesis is variable. Trigger factors may be environmental or psychosocial. This condition affects mainly women, and its estimated prevalence in various populations varies between 0.2% and 4.4%. The American College of Rheumatology Criteria (ACR) 1990 requires CWP for at least 3 months and presence of >11/18 pre-specified Tender Points (TP) on examination[1].

A newer diagnostic criteria published in 2010-2011, no longer requires performing a tender point count to make the diagnoses and instead entails asking about the constellation of non-pain somatic symptoms that are typically present in addition to the widespread pain[2]. DM affects connective tissue in multiple ways and this may be as a result of micro or macrovascular complications, a consequence of metabolic derangements inherent to DM, and notable associations, FMS being a key presentation[3]. Over the past few years, the most important predictor that predisposed to development of musculoskeletal complications is blood glucose control. The HUNT study[4] outlined the association between DM and chronic musculoskeletal complaints in 64,785 patients and noted a high prevalence of FMS and a positive correlation with HbA1c levels. Attar[5], revealed that up to 17.9% of diabetics suffer from chronic musculoskeletal manifestations, fibromyalgia being one of them. Yunus[6], in his review article, in 2011, noted that Central Sensitization Syndromes (CSS) have an increased prevalence in patients with diabetes mellitus. Of particular interest, a study

done by Tishler *et al*[7], the prevalence of FMS in diabetes mellitus was at 17% and this was associated with elevated levels of HbA1c in patients with FMS than those without (9.2 ± 1.1%) vs. (6.4 ± 1.5%). Current prevalence of DM in Kenya is estimated at 3.3% and is projected to rise to 4.5% by 2025[8], according to the Kenya National Diabetes Strategy. The ageing cohort and better health care facilities for all does not improve the prevalence of chronic musculoskeletal complaints, as age is a common predisposing factor for development of pain related disorders in the diabetic subset. This is the first study on the continent aiming to evaluate the prevalence of FMS in DM. The study aimed to sensitize the clinicians on the disease condition and create awareness regarding the CSS related conditions.

Materials and Methods

Our research question was to study the magnitude of FMS in DM with chronic musculoskeletal pain at the DOPC, KNH. The broad objective was to determine the burden of FMS in DM with chronic pain at the DOPC, KNH. Our specific objective was to determine the prevalence of FMS in diabetics with chronic pain and to determine the severity of FMS related symptoms using the FIQR tool. The secondary objective was to correlate FMS with sociodemographic characteristics and metabolic control of patients attending the DOPC presenting with chronic musculoskeletal pain.

This was a cross sectional descriptive study carried out at the DOPC, KNH. The DOPC, KNH is arguably the busiest clinic facility with more than 6000 registered patients attending[9]. It serves as a point of care for referral from minor facilities around the nation. It runs on a daily basis, with a major clinic every Friday where up to 120 patients are reviewed on a day. Consultant physicians/ endocrinologists, senior house officers and DM educators run this facility. This study included all patients with a file diagnoses of DM ≥18 years with chronic pain lasting more than 3 months. Patients were requested to give an informed written consent prior to participation. This study excluded all patients with significant neurologic impairments who were unable to give a proper description of symptoms. Consecutive sampling was used.

Sample size: The minimum study sample population using the Fischers 1998 formula was calculated at n=217 patients. The margin of error was set at 5%. Patient confidentiality was maintained throughout the process. Duplication was avoided by using serial numbers on the questionnaires.

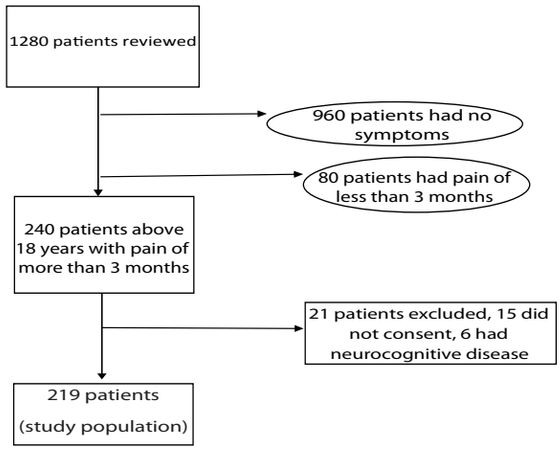
Data collection tools and methods: Consecutive sampling was used for recruitment of study population. This was followed by interviewer administered study proforma. All patients were subjected to an HBA1c test to check on glucose control. A clinical examination to check for tender points was performed and patients who satisfied the ACR 1990[1] criteria for FMS (i.e. pain >3 months and ≥11/18 TP) were subjected to the FIQR. Data was collected and recorded on the study proforma by the PI and research assistants. SPSS version 21.0 was used to process the available information.

Study variables: The independent variable included demographic, clinical characteristics and the HBA1c level. Levels of pain, energy, stiffness, quality of sleep, anxiety or depression, memory, balance and increased sensitivity to environment (cold, noise, odors), each scored out of ten, were all listed as independent variables. The 10 point scoring was on the basis of the FIQR. The prevalence of FMS was listed as a dependent variable and calculated with a 95% CI.

Results

A total of 1280 patients were interviewed between April 2016 and June 2016. Of these 960 reported to having no pain symptoms and a further 80 patients had pain less than 3 months. Twenty one patients were further excluded (fifteen did not consent and 6 patients had neurocognitive disease) and the study population reached to 219 patients. This information is presented on Table 1.

Table 1: Patient flow chart



Demographic and clinical characteristics of study population: The mean age was at 56.8 years (SD13.6). Females predominated at 70.8% giving a male to female ratio of 1:2.4. About 114 (52.1%) patients reported to be involved in non-manual form of ADL. A vast majority were on follow up for Type 2 DM (n=206, 94.1%). One hundred eighty two patients (82.6%) were on Oral Glucose Lowering Agents (OGLA) either as monotherapy or in combination with insulin. Biguanides therapy with metformin and sulfonylureas were drugs of choice. Mixtard insulin 30/70 was used by 17.4% of all the study population. This is shown on Table 2.

Table 2: Sociodemographic and clinical characteristics of study population

Variable	Frequency (%)	Variable	Frequency (%)
Mean age (SD)	56.8 (13.6)	Type of diabetes	
		Type I	13 (5.9)
		Type II	206 (94.1)
Gender		Medications used	
Male	64 (29.2)	Insulin based regime	38 (17.4)
Female	155 (70.8)	OGLA	104 (47.0)
		Combination	78 (35.6)
Marital status		OGLA (n=182)	
Single	13 (5.9)	Sulfonylureas	99 (45.2)
Married	148 (67.6)	Biguanides	146 (80.2)
Separated	13 (5.9)	DPP 4 inhibitors	7 (3.8)
Widowed	45 (20.5)	Glitazones	2 (1.1)
Daily activities			
Manual labour	64 (29.2)	Insulin	38 (100.0)
Office job	41 (18.7)	Pre mixed	
Non manual	114 (52.1)		
Occupation			
Employed	77 (35.2)		
Unemployed	90 (41.1)		
Retired	52 (23.7)		

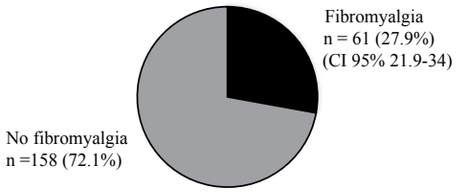
The mean HBA1c levels for the study population was at 9.4% (SD 2.6). Very good control was only seen in 16.6% (n=37). Conversely, 35.2% had an HBA1c level of ≥10% (Table 3).

Table 3: Mean HBA1c levels for study population

Variable	Frequency
Mean HBA1c (SD)	9.4% (2.6)
Range of HBA1c	n (%)
≤7	37(16.9)
7.0-7.99	39(17.8)
8.0-8.99	35(16.0)
9.0-9.99	28(12.8)
≥10	77(35.2)
Missing	3(1.4)

Prevalence of FMS in DM with chronic pain: Of the 219 patients, 61 patients satisfied the ACR 1990[1] criteria for FMS. This gives a prevalence of 27.9% (95% CI 21.9-34.2) (Figure 1).

Figure 1: Prevalence of FMS



Frequency and severity of FMS related symptoms: The 3rd domain of the revised FM questionnaire was used to assess this information. Each patient was asked to rate the degree of impact the disease had on their symptoms. One hundred percent had pain over the past 7 days, 100% reported reduced levels of energy, 100% had stiffness experienced, 98% reported disturbances in sleep patterns, depression was present in 95%, memory problems in 93%, anxiety was reported in 91%. One hundred percent reported to have tenderness to touch, balance problems were present in 98% and increased sensitivity to loud noises was reported in 98%. This is depicted on Table 4.

Table 4: Frequency and severity of FMS related symptoms

Symptoms	Severity of symptoms (n=61)			
	0(%)	1-3 (%)	4-6 (%)	7-10 (%)
Pain	0	13 (21.3)	18 (29.5)	30 (49.2)
Energy	0	12 (19.7)	21 (34.4)	28 (45.9)
Stiffness	0	10 (16.4)	21 (34.4)	30 (49.2)
Sleep quality	1 (1.6)	8 (13.1)	12 (19.7)	40 (65.6)
Depression	3 (4.9)	16 (26.2)	28 (45.9)	14 (23.0)
Memory	4 (6.6)	17 (27.9)	29 (47.5)	11 (18.0)
Anxiety	5 (8.2)	19 (31.1)	26 (42.6)	11 (18.0)
Tenderness	0	15 (24.6)	29 (47.5)	17 (27.9)
Balance	1 (1.6)	23 (37.7)	21 (34.4)	16 (26.2)
Sensitivity	1 (1.6)	9 (14.8)	17 (27.9)	34 (55.7)

FIQR domain scores: The FIQR scores were rated as follows: 0-39, 40-59 and more than 60, classified as having mild, moderate and severe disease respectively. The mean FIQR score for the study population, (n = 61) was 51.9 (SD 18.4). This denotes them as having moderate disease. From our study, 24.6% had mild disease, 42.6% moderate disease and 32.8% had severe disease (Table 5).

Table 5: The FIQR domain scores

Variable	Frequency(%)(SD)	95% CI
FMS n(%)		
Yes	61(27.9)	21.9-34.2
No	158(72.1)	65.8-78.2
FIQR Score (n=61)		
Mean (SD)	51.9(18.4)	
Severity		
Mild	15(24.6)	13.1-36.1
Moderate	26(42.6)	29.5-54.1
Severe	20(32.8)	21.3-45.9

Discussion

Fibromyalgia Syndrome is a clinical syndrome having a common group of symptoms. No single aetiologic factor is present though environmental and psychosocial factors do play an important role in the trigger. Certain non-rheumatic conditions such as depression and hypothyroidism closely mimic FMS[11]. Although FMS and DM are very common, no association had been reported in this region. The factors associated include gender and age. Gender though not statistically significant (P=0.053), showed a trend in which female preponderance was present. The OR was calculated at 2.0(95% CI 1.0-4.1) Tishler *et al*[7], Malombe *et al*[12], Dokwe *et al*[13] and Yanmaz *et al*[14] in their studies previously showed that the female gender was more prone to developing CWP. From the findings, the study also concluded that DM patients with FMS were significantly older than their counterparts without FMS (P=0.034). The study did not find statistically significant association between FMS and medication use, type of diabetes, ADL or the marital status (P>0.05).

In this study, FMS was detected in 61 (27.9%) of the DM patients presenting with chronic pain (total n=219). The detection of FMS in patients with DM is important since muscle aches and stiffness are inadvertently managed as cases of diabetic polyneuropathy by physicians. Nevertheless, clinical findings of specific TP on examination and symptom evaluation using the revised FIQR noted without doubt that FMS is an independent disease entity in this group of DM patients. Pain, sleep disturbances, anxiety, depressive illness, heightened sensitivity to environmental stimuli all support the diagnoses of FMS in our study. These patients are subjected to a poor quality of life, warranting frequent visits to the health facilities for frequent analgesics or sedatives.

Pain is central to the diagnoses of FMS and the FIQR. We noted that 100% of patients presented with pain over the past seven days. The concept of hyperalgesia and allodynia is worth a mention as entities present in central sensitization syndromes, FMS being one of them. Other components of the revised FM questionnaire (FIQR) noted loss of balance, mood disorders and sleep disturbances being highly prevalent. This negatively impacts on the quality of life of patients having both diseases i.e FMS and DM.

Conclusion

FMS in DM is a pertinent and prevalent disease and worth looking for in all diabetic patients presenting with chronic pain. The intransigent nature of FMS makes it very difficult for the patients as well as the healthcare professionals to take care of. It is our hope that from this study, part of diabetes care will be to look for chronic pain syndromes in diabetics. Timely diagnoses and appropriate referral to specialized care would greatly improve the quality of life of patients already condemned to a chronic debilitating disease such as diabetes**.**

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Research article

Cardio-pulmonary manifestations of rheumatoid arthritis among rheumatology patients of a tertiary hospital

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Abstract

Background: Rheumatoid arthritis is a chronic systemic inflammatory disease, characterized by polyarthritis and extra-articular manifestations. The cardio-pulmonary manifestations of rheumatoid arthritis were studied retrospectively in a cohort of rheumatoid arthritis patients.

Methods: This was a retrospective study of all cases of rheumatoid arthritis seen during the period of January 2011 to December 2013. Case notes of patients that fulfilled the 1987 American College of Rheumatology Criteria for rheumatoid arthritis were retrieved. Data was retrieved from the case notes and analyzed. The case records of patients with pulmonary and cardiac manifestations of rheumatoid arthritis were further studied.

Results: Four hundred and seventy two rheumatology cases were seen; twenty one fulfilled the 1987 American College of Rheumatology Criteria for rheumatoid arthritis. Out of the twenty one cases of rheumatoid arthritis identified, eight cases developed cardio-pulmonary manifestations of rheumatoid arthritis, predominantly serositis. The onset of cardio-pulmonary features was independent of the disease stage. Among patients with cardio-pulmonary manifestations of rheumatoid arthritis, three people died of heart disease while one died of pulmonary complication, representing 50% mortality.

Conclusion: Pulmonary manifestation as represented by pleural effusion was the leading cardio-pulmonary manifestation among the patients studied. Cardiac disease was however the leading cause of mortality. We therefore conclude that cardio-pulmonary manifestation is associated with increased mortality among rheumatoid arthritis patients.

Key words: Cardiopulmonary, Involvement, Hospital, Rheumatoid disease

Introduction

Rheumatoid arthritis is a chronic inflammatory, multisystemic disease with extra-articular involvement. It has a prevalence of about 1% in most populations[1]. The extra-articular manifestations include rheumatoid nodule, cardio-pulmonary disease, neuropathy, ophthalmic manifestations, vasculitis, Felty's syndrome, and amyloidosis[2]. Extra-articular manifestations of rheumatoid arthritis are associated with increased morbidity and mortality. It occurs in 19.8-40.9% of rheumatoid arthritis patients and about 1.5-21.6% of them present as severe forms[3]. The extra-articular manifestations of rheumatoid arthritis can develop at any time during the course of the disease, even in the early stages[3]. Factors that have been associated with the development of extra-articular features include, significant positive rheumatoid factor, long-standing severe disease, and smoking[3].

Cardio-pulmonary manifestation has been associated with patients with rheumatoid nodule, especially in those patients that develop rheumatoid nodule within two years from the diagnosis of rheumatoid arthritis[4].

Lung disease is a major contributor to morbidity and mortality. In some cases, respiratory symptoms may precede articular symptoms. Lung involvement could be a direct complication of rheumatoid arthritis or from the immune modulation therapy. The pulmonary manifestations include interstitial lung disease, pleural thickening and effusion, vasculitis and pulmonary hypertension[5]. Prognosis varies depending on the type and severity of involvement[5]. Interstitial lung disease is second only to cardiac disease as a cause of mortality in rheumatoid arthritis[6].

Based on a review of mortality by Olson *et al*[7] in the USA from 1988 to 2004, it was found that interstitial lung disease contributed to death in 6.8% of females and 9.8% of males with rheumatoid arthritis. The mean survival for rheumatoid arthritis interstitial lung

disease has been estimated at 2.6 years from time of diagnosis[8].

Cardiac manifestations of rheumatoid arthritis include pericarditis, cardiomyopathy, myocarditis, coronary vasculitis, arrhythmias and congestive cardiac failure. Majority of rheumatoid arthritis mortality originate from cardiovascular disease[9]. A recent meta-analysis indicated that the risk of cardiovascular disease-associated death could be as much as 50% higher among patients with rheumatoid arthritis compared to controls[10]. Several recent studies however suggest a lower frequency of cardio-pulmonary involvement probably due to a better control of disease activity[11,12].

Diagnosis of cardio-pulmonary manifestations of rheumatoid arthritis is a challenge, given its variable presentations, the diagnosis is based on clinical recognition and exclusion of other causes of such signs and symptoms [13-15].

There was no prior study of extra-articular manifestations of rheumatoid arthritis in the country. This study therefore aimed to retrospectively examine the clinical presentations of cardio-pulmonary involvement among the patients with rheumatoid arthritis in our tertiary hospital rheumatology clinic.

Materials and Methods

Cases were the patients seen at the Olabisi Onabanjo University Teaching Hospital, Ogun State, South West of Nigeria. The medical outpatient records and the in-patients records were studied to determine patients that were diagnosed and treated for rheumatoid arthritis. The case notes of such patients were retrieved from the medical records and studied. Patients with cardio-pulmonary involvement were further studied.

The study was carried out over a three year period from January 2011 to December 2013. Excluded from the study were patients with inconclusive diagnosis, juvenile idiopathic arthritis and unclassified arthritis. Those patients that fulfilled the 1987 American College of Rheumatology Criteria for rheumatoid arthritis were therefore included in the study. The duration of rheumatoid arthritis before the onset of cardiopulmonary manifestation was noted for each patient. Other extra-articular manifestations of rheumatoid arthritis were noted. Simple statistical analysis was used to calculate the percentages.

The affected patients were offered the standard treatment for rheumatoid arthritis at the point of contact in the teaching hospital. They were all placed on the triple therapy consisting of methotrexate, hydroxychloroquine and sulphasalazine, and where necessary, non-steroidal anti-inflammatory agents. Those with cardio-pulmonary complications were offered further therapies as indicated.

The socio-demographic characteristics of the patients were documented (age, sex, marital status and the occupation). The identity of the patients was concealed. Ethical clearance was obtained for this retrospective study from the ethical committee of the hospital.

Case definition

Rheumatoid Arthritis (RA): RA was defined according to the classification criteria of the American College of Rheumatology 1987. A person is said to have RA if he/she has four out of the seven criteria, and the symptoms have been persistent for at least six weeks[16]. The classification criteria are:

(i) Early morning joint stiffness duration longer than one hour
(ii) Polyarthritis – arthritis affecting three or more joints simultaneously
(iii) Arthritis affecting joints of the hands (proximal inter-phallangeal joint, metacarpo-phallangeal joint, wrist)
(iv) Symmetrical arthritis
(v) Subcutaneous nodules
(vi) Positive rheumatoid factor
(vii) Radiological changes of peri-articular osteopenia or erosion.

Criteria for inclusion in the cardio-pulmonary manifestations

Fulfillment of the 1987 American College of Rheumatology Criteria for rheumatoid arthritis and any of the following;

(i) *Pericarditis:* Clinical suspicion and detection of effusion by echocardiogram.
(ii) *Arrhythmia*: Clinically detected and confirmation by electrocardiogram.
(iii) *Congestive cardiac failure*: Clinically detected and supported by chest radiograph and echocardiograph.
(iv) *Pleural effusion*: Clinical suspicion and detection by chest-X-ray
(v) *Pulmonary nodule*: Detection by plain chest-X-ray
(vi) *Pulmonary fibrosis:* Clinical suspicion and detection by plain chest radiograph.

Laboratory and radiological investigations

All the patients had rheumatoid factor, erythrocyte sedimentation rate and full blood count done. Plain radiograph of the hands and feet were done where necessary. Electrocardiography and echocardiography were carried out as necessitated by the clinical condition. Chest –X- ray was done in all patients with symptoms referable to the lung and the heart. Pulmonary function was ordered when necessary.

Results

Twenty eight cases were identified but seven were excluded as the diagnosis was polyarticular inflammatory

disease without a conclusive diagnosis of rheumatoid arthritis. Twenty one patients fulfilled the 1987 American College of Rheumatology Criteria for rheumatoid arthritis over the study period.

Eight (38%) patients fulfilled the inclusion criteria for cardio-pulmonary manifestations of rheumatoid arthritis, there were three males (37.5%) and five females (62.5%). Table 1 shows the socio-demographic characteristics of the patients with cardio-pulmonary manifestations of rheumatoid arthritis. Serositis and arrhythmia were the leading manifestations.

Table 1: Socio-demographic characteristics of the patients with cardio-pulmonary rheumatoid arthritis

Demography	No.	(%)
Age (years)		
18-24	1	12.5
25-34	2	25
35-44	3	37.5
45-54	2	25
55 and above	-	-
Sex		
Male	3	37.5
Female	5	62.5
Occupation		
Student	1	12.5
Artisan	2	25
Civil servant	4	50
Professional	1	12.5

Table 2 shows the cardio-pulmonary manifestations detected in the patients. Three people developed the manifestations after eight years of diagnosis of rheumatoid arthritis, two people developed symptoms about four years of diagnosis, while three others were not very sure of the time but ranges between three to six years. Table 3 shows the extra-articular manifestations of rheumatoid arthritis among patients seen in the rheumatology clinic.

Table 2: Cardio-pulmonary manifestations of rheumatoid arthritis encountered in our patients

Cases	Female	Male	Total
Pericardial effusion	2	1	3
Atrial fibrillation	3	1	4
Ventricular ectopic	0	1	1
Congestive cardiac failure	3	2	5
Pleural effusion	6	2	8
Pulmonary nodule	0	1	1
Pulmonary fibrosis	2	1	3

Table 3: Extra-articular manifestations of rheumatoid arthritis among patients seen in the rheumatology clinic.

Affected tissue/organ	Extra-articular manifestation
General symptoms	Weight loss Fever Early morning stiffness Fatigue Generalized muscle weakness Depression
Skin	Rheumatoid nodule Cutaneous vasculitis Raynaud's phenomenon
Eyes	Keratoconjuctivitis sicca Scleritis Episcleritis
Pulmonary system	Pulmonary nodule Pleural effusion Pulmonary fibrosis
Cardiovascular system	Pericardial effusion Atrial fibrillation Ventricular ectopics Congestive cardiac failure
Nervous system	Mononeuritis multiplex Sensory neuropathy Cervical myelopathy
Renal system	Analgesic nephropathy
Haematology system	Anaemia Felty's syndrome

Laboratory and radiology results: Erythrocyte sedimentation rate was elevated in all the patients, rheumatoid factor was significantly positive in all the patients, and all of them also had sub-cutaneous nodules. Chest-X-ray revealed pleural effusion in two males and six females, while five patients had cardiomegaly and features suggestive of heart failure. Plain radiograph also showed pulmonary nodule in one patient, while one male and two females had pulmonary fibrosis. Pulmonary function test showed restrictive pattern in patients with pulmonary fibrosis. Cardiovascular work-up with electrocardiography showed atrial fibrillation in four patients, while one had ventricular ectopics. Echocardiography showed a male and two females with pericardial effusion.

Mortality and morbidity: Four patients out of the eight patients with cardio-pulmonary manifestations are still being followed up in the clinic. Mortality was higher in men than women. A male (33.3%) died of pulmonary fibrosis, while two males and a female (60%) died of heart failure. Three males and a female died with a male to female mortality of 37% versus 12.5%.

Discussion

Rheumatoid arthritis is characterized by extra-articular manifestations. Many different tissues and organs can be involved in addition to the characteristic peripheral polyarthritis[17]. The extra-articular manifestation has a significant impact on mortality and morbidity. Availability of more efficacious drugs has led to a better control of disease activity and therefore a lower frequency of extra-articular manifestations of rheumatoid arthritis[18].

Eight of our patients developed cardio-pulmonary manifestations of rheumatoid arthritis out of a total of twenty-one patients diagnosed of rheumatoid arthritis over a three year period. Pulmonary manifestation was the leading of the systems as manifested by radiological finding of pleural effusion. Women were three times more affected than men. This is however not surprising because women were predominantly affected in our cohort, and this follows the trend as reported by earlier studies[19].

Pleural effusion was the leading pulmonary manifestation. The pleural effusion in our patients was not detected clinically but was detected on chest radiograph when being investigated for breathlessness and cough. Mantoux and plain chest X-ray were able to rule out infective causes of pleural effusion like tuberculosis. Chest X-ray was also able to rule out lung malignancy. Pleural effusion however has been reported in the literature to be more common than pericardial effusion in patients with rheumatoid arthritis[20].

Three patients had complication of pulmonary fibrosis. Our patients with pulmonary fibrosis presented with progressive breathlessness and cough. Lake and Proudman[21] however documented that the presentation of pulmonary fibrosis in rheumatoid arthritis is similar to that of idiopathic pulmonary fibrosis, but response to immunosuppressive is usually better. Pulmonary fibrosis in our patients was detected clinically and further confirmed by pulmonary function test. The investigation of choice is however High Resolution Computerized Tomography (HRCT)[22,23] but this was not available at our centre. A study of pulmonary function in rheumatoid arthritis patients in Nairobi by Biomdo *et al*[24] among 166 rheumatoid arthritis patients found a prevalence abnormality of 38.5%. Obstructive ventilatory (20.4%) abnormality was the leading abnormality, followed by restrictive pattern (16.8%) and least was the mixed pattern (1.2%). Age and rheumatoid arthritis disease activity were the independent factors associated with pulmonary function abnormalities[24].The single male with pulmonary fibrosis died while the females are still being followed up in the clinic.

Four of our patients presented with atrial fibrillation, while one presented with ventricular ectopic. Arrhythmia is an important cause of mortality in rheumatoid arthritis and may be secondary to ischaemia, conduction abnormality due to rheumatoid nodule, amyloidosis or congestive cardiac failure[25]. It has been shown that QT-dispersion and corrected QT- dispersion intervals were significantly longer in rheumatoid arthritis compared with healthy controls, and it was suggested that QT- dispersion may be a useful marker of cardiovascular morbidity and mortality in rheumatoid arthritis[26].

Congestive cardiac failure was the leading cardiac complication of rheumatoid arthritis in this study. Five individuals had congestive cardiac failure comprising two males and three females. Two males and a female died of congestive cardiac failure with a male to female mortality ratio of 2 to1. This study has shown an excess of cardiovascular mortality among males over females. An earlier study however documented that the excess mortality associated with extra-articular manifestations is greater in men than in women[27].

The pericardial effusion found in our patients was generally asymptomatic because of its small volume. It was detected by echocardiography while investigating them for heart failure. Ibrahim-Sayo *et al*[27] in a study of patients with rheumatoid arthritis at the Kenyatta National Hospital found cardiac abnormalities echocardiographic prevalence of 62.5%. Pericardial effusion was the leading cardiac lesion (39.4%). Tricuspid valve was affected commonly with 15.4% of patients presented with tricuspid regurgitation. Pulmonary hypertension was found in 5.5% of patients[28].

Three of our patients died of cardiovascular disease while one died of pulmonary disease. This study has shown an excess of cardiovascular mortality over the pulmonary disease. Several studies have shown that cardiovascular disease account for the major part of excess mortality in rheumatoid arthritis[29]. People with other extra-articular manifestations of rheumatoid arthritis tend to have higher cardiovascular co-morbidity such as congestive cardiac failure and arrhythmias than people without extra-articular manifestations of rheumatoid arthritis. A study in people with severe rheumatoid vasculitis demonstrated a more frequent cardiovascular co-morbidity than rheumatoid arthritis patients without vasculitis[29]. The excess of cardiovascular death in our patients also confirmed the findings from earlier studies.

Five of our patients developed congestive cardiac failure and three eventually died from the disease. Earlier studies have shown that patients with rheumatoid arthritis are at significantly higher risk for congestive cardiac failure[30]. The risk in them cannot however be explained by any increase incidence of traditional cardiovascular risk factors[31,32]. It has been shown that rheumatoid arthritis is associated with increased left ventricular mass which is independently related to disease duration, while the systolic function is typically preserved[32]. Congestive cardiac failure presentation may be subtle but mortality from the complication is significantly more than non-rheumatoid arthritis patients[31].

One of our patients died at the age of 33 years, while the other ones died at age 34, 37 and 40 years. Early mortality was observed in our patients with cardio-pulmonary involvement as compared with other rheumatoid arthritis without cardio-pulmonary disease. Earlier studies have claimed that there is a relative concentration of risk for cardiovascular events in younger rheumatoid arthritis patients, therefore higher mortality in younger individuals with rheumatoid arthritis[4,34].

Extra-articular complication in rheumatoid arthritis is associated with delayed diagnosis, delayed institution of appropriate anti-rheumatic drugs, and inappropriate dosage of the medications[35]. All the patients were already on prednisolone as at the point of visit to our hospital, three patients were on methotrexate, prescribed by the referring doctor. None of the patients was on the triple disease modifying anti-rheumatic drugs that we normally prescribe for rheumatoid arthritis patients.

The limitations of this study include small number of rheumatoid arthritis patients probably due to low awareness. Being a retrospective study, there is a likelihood of missing information. Inability to perform pleural fluid analysis is also a limitation to this study.

Conclusion

Cardiac and pulmonary involvements in rheumatoid arthritis are associated with increased mortality. The clinician must therefore be familiar with the clinical presentations of extra-articular involvement of rheumatoid arthritis and its management.

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Conflict of interest: The authors declare that there was no conflict of interest.

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Research article

The epidemiology of rheumatic disorders in a rural area of the Democratic Republic of Congo (DRC): A COPCORD study

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Abstract

Objective: To determine the prevalence of rheumatic diseases in a rural area of DR Congo.
Methods: A cross-sectional study was performed in six randomly chosen villages of the health division of Gombe-Matadi, in Kongo-Central province (near Kinshasa), from 15th October to 15th November 2012. Investigators questioned all individuals living in these villages, using the COPCORD Core questionnaire (CCQ). Age, sex and rheumatic complaints were noted. X-rays, and laboratory tests (C-reactive protein, erythrocyte sedimentation rate, blood cells count, uric acid and some serological assays) were performed.
Results: In total, 1500 individuals were questioned. Rheumatic complaints were reported by 743 individuals (49.5%), of whom 424 women and 319 men (sex ratio H/F 0.8). Their average age was 48.8±15.4 years. The encountered diseases were: osteoarthritis in 552 patients (prevalence of 36.8%), spondylarthropathies in 57 patients (prevalence of 3.8%), soft tissue rheumatism in 78 patients (5.2%), rheumatoid arthritis in 21 patients (1.4%), juvenile arthritis in 19 patients (1.26%), infectious arthritis in 11 patients (0.73%), rheumatic fever in 9 patients (0.6%) and gout in 1 patient (0.06%).
Conclusions: All types of rheumatic diseases can be found in rural areas and some of them like SpA, RA were found with very high frequencies. Also, clinical and demographic differences were observed compared to literature data.

Key words: Rheumatic diseases, Rural area, DR Congo

Introduction

To know the prevalence of musculoskeletal disorders is a capital preoccupation of The Community Oriented Program for Control of Rheumatic Diseases (COPCORD) is an emanation of the International League of Associations for Rheumatology (ILAR) with the collaboration of the World Health Organization (WHO) since 1981[1]. This program is adapted for recognition, prevention and control of rheumatic disorders in the developing world such as sub-Saharan Africa.

Many studies are realized in urban and rural areas in the world[2,8]. But in DR Congo, only the epidemiology of rheumatoid arthritis in urban areas (Kinshasa) was the population-based study conducted as per the COPCORD guidelines[3]. This study was initiated to determine the prevalence of rheumatic disorders in a rural area of the Democratic Republic of the Congo.

Materials and Methods

This was a cross-sectional study conducted from 15th October to 15th November 2012 in the health division of Gombe-Matadi, at the South-western part of the DR Congo. Six villages of this health division (Yanda, Lukengo, N'Kamba, Nzundu, Ntimansi and Ngombe-Kinsuka) were randomly selected. One thousand six hundred and forty inhabitants live in the six villages. Only 1500 inhabitants were interviewed, and then underwent clinical examination, X-rays, and laboratory tests. The 140 others habitants didn't complete the clinical examination or one of other types of the study for diverse reasons. Four investigators performing the screening were physicians in training for internal medicine for at least 3 years and with at least 6 months of training in rheumatology. These physicians were trained for the present study by a rheumatologist.

The COPCORD core questionnaire was used and comprised the following main sections: background information, work history, articular symptoms (pain-tenderness-swellings-stiffness during the

last week and in the past), functional disability, history of treatment and evaluation in the past, extra-articular symptoms of some rheumatic diseases. After a pretest with 30 subjects, the questionnaire was translated in Kikongo (the local common language) and asked to all participants. People who presented rheumatic complaints were examined by the investigators. X-rays and laboratory tests were performed at Masensa-Kikiunga (N'Kamba Hospital). The immunology's analysis was performed at the LOMO laboratory of Kinshasa. X-rays were analysed by 2 radiologists of the University Hospital of Kinshasa. The diagnosis that was finally retained for each patient was validated by a rheumatologist. International criteria of diagnostics were used for case definitions.

The statistical analysis had used SPSS 21 program. The Chi-squared test, t-student and ANOVA were used respectively to compare proportions, average of two groups and average of more than two groups. The odds ratio was calculated for measuring the strength of the association between two factors. The level of statistical significance (α) was set to 0.05 (The p-value was fixed to 0.05). The present study was approved by the ethics committee of the University of Kinshasa.

Results

Table 1 shows the distribution of patients according to their age and sex. In total, 1500 persons (91.6% of inhabitants) responded to the questionnaire. Musculoskeletal complaints were noted in 743 persons (49.5% of the study population). The mean age was 46.9 ± 16.9 years for males and 50.7 ± 14.2 years for females (p = *0.001*) with the ratio male (n=319) to female (n=424) was 0.75.

Table 1: The distribution of patients according to their age and sex

Age (years)	Male No. (%)	Female No. (%)	All
<18	16 (5.0)	11 (2.6)	27(3.6)
18-29	37 (11.6)	20(4.7)	57 (7.7)
30-39	48 (15.0)	50 (11.8)	98 (13.2)
40-49	64 (20.1)	101 (23.8)	165 (22.2)
50-59	71 (22.3)	135 (31.8)	206 (27.7)
60-69	65 (20.4)	61 (14.4)	126 (17.0)
70-79	13 (4.1)	36 (8.5)	48 (6.6)
≥ 80	5 (1.6)	10 (2.4)	15 (2.0)
Total	319 (42.9)	424 (57.1)	743 (100)

Table 2 shows the prevalence of principal's symptoms (complaints) in musculoskeletal diseases. In descending order: Joint pain, stiffness and joint swelling were the most musculoskeletal complaints in this study.

Table 2: Prevalence of musculoskeletal complaints

Manifestations	Effective	(%)
Joint pain	741	99.7
Joint swelling	125	16.8
Stiffness	163	21.9
Limited movement	103	13.9
Extra articular manifestations	32	4.3

Table 3 gives the distribution of participants according to the topographical sites of the rheumatic complaints and the types of pain. It emerges from the observations that among the participants, some people had more complaints located in at least two joints. Also, some participants reported having pain of two types. Thus, in descending order of frequency, the sites of the most encountered complaints were the lumbar spine, the hand, the knee and the hip. As for the type of pain, the mechanical type followed by inflammatory type were the most frequent.

Table 3: Topographical sites (joint distribution) of musculoskeletal complaints and type of pain (n = 743)

Variables	No.	(%)
Joint distribution		
Hand	201	27.1
Wrist	70	9.4
Elbow	35	4.7
Shoulder	10	1.3
Cervical spine	15	2.0
Dorsal spine	8	1.1
Lumbar spine	202	27.2
Hip	133	17.9
Knee	140	18.8
Ankle	95	12..8
Type of pain		
Mechanical	500	67.2
Inflammatory	400	53.8
Psychic	33	4.4
Neurological	5	0.7

Table 4 shows the distribution of the prevalence of rheumatic diseases encountered in this study by sex. This study shows also that except the gout, IR, and SpA, the prevalence of rheumatic diseases varied significantly (p < 0.05) between females and males; the female predominance was characteristic for PR, URA, ARF, soft tissue rheumatism and IR. By decreasing prevalence, the most common pathologies were: OA (36.8%); ABR (5.2%); SpA (3.8%); URA (3.3%); RA (1.4%). Women were 1.6 times more likely to develop RA than men and there was a statistically significant relationship between RA and sex (95% CI, OR: 1.3-2.1, p = 0; 003). On the other hand men have 1.8 times more chance of developing OA compared to women; And there was a statistically significant association between OA and sex (95% CI, OR: 1.4-2.2, p = 0.0001).

Table 4: Prevalence of musculoskeletal diseases (n=1500)

Musculoskeletal diseases	All	Male	Female	OR IC95%	P-value
	No. (%)	No. (%)	No. (%)		
RA	21 (1.4)	4 (0.5)	17(2.3)	1.6 (1.3-2.1)	0.003
URA	49 (3.3)	10 (1.3)	39(5.2)	1.7 (1.4-1.9)	0.0001
OA	552 (36.8)	315 (42.4)	237(31.9)	1.8 (1.4-2.2)	0.0001
SpA	57 (3.8)	30 (2.7)	27(1.8)	1.0 (0.6-1.2)	0.77
Soft tissue rheumatism	78 (5.2)	35 (2.3)	43(2.9)	0.7 (0.5-1.2)	0.28
IJA	10 (0.7)	9 (0.6)	1 (0.1)	2.1 (1.1-4.8)	0.013
IR	11 (0.7)	0 (0.0)	2 (0.1)	0.7 (0.5-1.0)	0.15
Gout	7 (0.5)	7 (0.5)	3 (0.2)	2.2 (0.6-8.7)	0.22
ARF	9 (0,6)	0 (0.0)	9 (100)	-	0.022
Osteoporosis	7 (0.5)	1(0.1)	6 (0.8)	1.0 (1.0-1.3)	0.05
Femoral necrosis	1(0.07)	0(0)	1(0.1)	1.0(0.9-1.0)	0.31
limitedness lumbar canal	1(0.07)	0(0)	1(0.1)	1.0(0.9-1.0)	0.31
Scoliosis	1(0.07)	0(0)	1(0.1)	1.0(0.9-1.0)	0.31

RA: Rheumatoid Arthritis; URA: Undifferentiated Reactive Arthritis; SpA: spondylarthropathy; IJ A: Idiopathic Juvenile Arthritis (n=1500); Soft Tissue Rheumatism (Epicondylite 61,5% ; scapulohumeral periarthritis 38,4% ; Carpal tunnel syndrome 6,4%;Tarsal Canal Syndrome 2,6%; Tenosynovitis of De Quervain 15,4%.); ARF: Acute Rheumatic Fever; IR: Infectious Rheumatism.

Table 5 shows the average age of participants with musculoskeletal diseases found in this study. Before 50 years of age, patients developed preponderantly ARF, gout, IJA, IR, ABR and OA; and beyond 50 years of age, RA, URA and SpA. The difference was statistically significant ($p < 0.05$) between the average age in the presence of RA, ARF and IJA, and that in their absence. In a nutshell, the average age of patients varied across the kind of rheumatism; and the statistical significance of the difference between their average ages in the presence and the absence of disease was also inconstant according to the kind of rheumatism.

Table 5: Average age of participants by presence or absence of disease

Rheumatic diseases	Average age ± SD (Standard deviation)		P-value
	Presence	Absence	
RA	61.4±13.4	49.0±15.2	0.0001
URA	52.4±12.9	49.1±15.3	0.126
OA	48.4±15.8	49.7±14.9	0.117
SpA	51.7±16.8	49.2±15.2	0.215
Soft Tissue Rheumatism	45.9±17.5	49.4±15.1	0.055
ARF	14.1±2.1	49.4±15	0.0001
Gout	44.6±13.4	49.2±15.2	0.338
IJA	16.5±1.5	49.4±15	0.0001
IR	29.5±13.4	49.2±15.2	0.067
Osteoporosis	59.7±7.2	49.2±.15.3	0.06
Femoral necrosis	63.0	49.2±.15	0.36
Limitedness lumbar canal	50.0	49.2±.15.2	0.95
Scoliosis	38.0	49.2±.15.2	0.46

RA: Rheumatoid Arthritis; URA: Undifferentiated Rhumatism Arthritis; SpA: Spondylarthropathy; IJA: Idiopathic Juvenile Arthritis; IR: Infectious Rheumatism; ARF: Acute Rheumatic Fever; OA: Osteoarthritis

In Table 6, the rheumatic patients encountered in this study are ranked according to whether they are obese or not. The table shows that 1.3 times more likely to have female rheumatism than male; There was also a statistically significant relationship between obesity in rheumatism and sex (95% CI: 1.1-1.6, p = 0.003).

Table 6: Obesity distribution by sex in rheumatism population

Obesity	Male No. (%)	Female No. (%)	OR (IC 95%)	P-value
Yes	32 (8.5)	58 (15.8)	1.3 (1.1-1.6)	0.003
None	348 (91.5)	310 (84.2)		

Discussion

This study provides the prevalence of musculoskeletal diseases in a rural area of DR Congo. It was the first experience of COPCORD study in a rural area of the country. In the overall population, this study shows a prevalence of 49.5% of musculoskeletal complaints with predominance in women ($p<0.05$) and the mean age of the males was inferior as compared to the females ($p<0.001$). This prevalence is superior to that found in Europe[4,5], the US[6], Chile, Brazil and Mexico[7], urban areas of Iran[8], and

in South Africa[9]. Nevertheless, this overall prevalence was inferior as compared to the study of Davatchi *et al*[10] in rural areas of Iran. We think that the age of female rheumatics was high because females lose progressively their hormonal protection as they approach menopause. This finding is corroborated by the literature[4,11].

The mechanical pain was found to be the dominant type in this study. This is supported by the predominance of OA. Lumbar and knee pains are more frequent. This result corroborates the study of Davatchi *et al*[10] which shows the predominance of dorsolumbar pain. We think that the use of hoe, pickaxe and machete as rudimentary instruments of the farmers and the genuflexion due to the influence of the Kimbanguistes' religion explain the lumbar and knee locations.

Osteoarthritis was the predominant rheumatic disease in our study. We can attribute that to the ageing of the population and the mechanical constraints by agriculture work with rudimentary tools. The average age of patients with OA was 48.4 ± 15.8. This average age shows that OA occurs prematurely in this population. Quid about the ethnicity, genetic and biochemical component part. The masculine predominance correlates with the context of age inferior to 50 years old[4,11,12]. This study also shows that obesity was associated with musculoskeletal complaints and the female gender (Table 6). So, the obesity favors OA through mechanical constraints on joints and the effect of adipokines[12,13].

Soft tissue rheumatism: The high prevalence (5.2%) corroborates the results of hospital study in Kinshasa University Hospital[14]. The female predominance corroborates the publications of Guillemin[4] and Cofer[15].

Spondylarthropathy: This study indicates a prevalence of 3.8%. The fact that the MRI had not been performed for the diagnosis of sacroiliitis may constitute a limit of this study since clinical examination and X-rays may not detect an early sacroiliitis. HLA typing may also be an additive argument for the diagnosis of spondylarthritis. This limit may be corrected by a study on sponylarthritis in Congoleses which is currently conducted and which includes HLA typing and the MRI. This prevalence was very high compared to worldwide estimations. Nevertheless, in Alaska the prevalence reported in Eskimos was higher as compared to this study[11]. The average age of the participants with SpA was 51.7± 16.8. This corroborates the studies of Mijiyawa *et al* [16], Houzou *et al*[17], Moustafa *et al*[18] and Bela *et al*[19]. No statistically significant difference was noticed between sex (p=0.77). This results corroborates with other studies[9-16].

Rheumatoid arthritis: The prevalence of RA was 1.4% in the rural area of Gombe–Matadi in DR Congo. This prevalence is higher than that found in the urban area of Kinshasa[20]. But many studies show very high prevalence notably Reyes Lierna GA *et al*[21] with prevalence of 2.7% in Cuba; Lutalo SK *et al*[22] with prevalence of 2% in rural Zimbabwe; Meyers *et al*[23] with 2.2% in the Xhosa tribe of South Africa; Gabriel *et al*[24] and Silman *et al*[25] with prevalence of 5.3% in Indian Pima and Chippewa.

Gout: The prevalence of 0.7% for gout found in this study is low when compared to the US and Europe according to the study of Roddy *et al*[26]. The predominance in males corroborates the literature. In the past, it was said that gout did not affect females, but the current study identified female cases as found in a hospital's case series study in Kinshasa by Divengi Nzambi *et al*[27].

Infectious rheumatism: The predominance of IR was 0.7%. This prevalence corroborates the results of Malemba and Mbuyi-Muamba[14] in a hospital context.

Idiopathic Juvenile Arthritis (IJA): Considering that there were only 27 individuals under 18 years, the prevalence of IJA must be revisited with another study on a more large population.

Osteoporosis: The prevalence of osteoporosis was 0.5%. This prevalence was certainly underestimated because it was not technically possible to determine the mineral density of bones with absorptiometry and there is no local standard to diagnose osteoporosis. The standard radiography suggests the diagnosis only when 30% of bone is lost[28].

Limitation of study

It should be noted that the present study has suffered from the unavailability of certain diagnostic tools such as Magnetic Resonance Imaging (MRI) and the knowledge of the typical HLA..

Conclusion

The prevalence of rheumatic disorders in the rural area of Gombe-Matadi in DR Congo is very high and needs attention of the health authority of the country. Osteoarthritis, soft tissue rheumatism and chronic inflammatory rheumatism were the dominant conditions. There was discrepancy to an extent related to demographic and clinical findings in some pathologies as compared to the literature.

Disclosures

None

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Research article

Prevalence of abnormal liver function tests in rheumatoid arthritis

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Abstract

Objective: To determine the prevalence of Abnormal Liver Function Tests (LFTs) in patients with rheumatoid arthritis at the rheumatology out-patient clinic, Kenyatta National Hospital (KNH).

Design: Cross-sectional descriptive study.

Setting: Rheumatology out-patient clinic at KNH.

Participants: One hundred and seven RA patients.

Results: The overall prevalence of abnormal LFTs in the study population was 57%. The most common abnormal LFTs were direct bilirubin and alkaline phosphatase (ALP), which were elevated in 34.6% and 15% of the study population, respectively. Abnormal direct bilirubin was associated with longer duration of disease; adjusted Odds Ratio (OR) 0.54 (0.34, 0.86) p-value 0.009 and higher disease activity, adjusted OR 2.79 (1.23, 6.25) p-value 0.014. Abnormal ALP was significantly associated with BMI, adjusted OR 0.205 (0.074, 0.57), p-value 0.002 as well as duration of disease, adjusted OR 1.14 (1.013, 1.29), p-value 0.031.

Conclusion: This study found the prevalence of liver dysfunction in patients with rheumatoid arthritis to be high, at 57%, and recommends regular monitoring of liver function tests in patients with rheumatoid arthritis.

Introduction

Rheumatoid Arthritis (RA) is a systemic, chronic, progressive inflammatory disease characterized by symmetric joint polyarthritis that progresses to severe joint destruction[1]. As a systemic illness, RA has many extra-articular manifestations and co-morbidities, many of which have been studied in our local setting, and have been found to correlate with disease activity[2-5]. The liver has however been overlooked as a target organ in patients with RA. Rheumatoid arthritis can affect the liver in many ways[6,7]; dysfunction is thought to arise from the disease itself, independent autoimmune disease, infections such as viral hepatitis or as a consequence of anti-inflammatory drugs such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or Disease Modifying Anti-Rheumatic Drugs (DMARDs)[6]. The most common DMARDs used in treatment of RA in our setting are methotrexate and leflunomide, which can be hepatotoxic. The risk of hepatotoxicity while on treatment with DMARDs may be increased in the presence of hepatitis or alcohol intake.

LFTs may be abnormal in up to 50% of patients with RA and this has been shown to correlate with disease activity[7,8]. The 'rheumatoid liver' has long been a topic of interest and previous studies noted histological changes in the liver of RA patients who were not on treatment with DMARDs such as fatty change, cellular necrosis, chronic passive congestion and gross atrophy[9-12]. Studies have also investigated use of multiple DMARDs, which were thought to predispose patients with RA to a higher risk of developing hepatotoxicity[13,14].

With increasing awareness and knowledge of the RA, more patients are being diagnosed early and started on treatment, which may be life-long. Effective treatment modalities may have hepatotoxic effects. Abnormal LFTs are in themselves an independent predictor of mortality[15]. Due to high mortality from both RA as well as abnormal LFTs, such a subset of patients could therefore be at a higher risk. This is especially so because we currently have limited ways of managing liver injury in our setting. It is therefore important for us to monitor liver dysfunction in patients with RA.

Materials and Methods

This was a cross-sectional descriptive survey carried out among 107 RA patients at the outpatient rheumatology clinic of KNH. Using an estimate of 146 RA patients on follow up at KNH, a minimum sample size of 106 RA patients was calculated. Consecutive sampling was used to recruit participants. History and clinical examination were carried out, as per the data capture form. Blood samples were collected from patients for LFTs and Erythrocyte Sedimentation Rate (ESR).

LFTs analysis was carried out in the KNH renal laboratory using the Biolys Superior 50i, an automatic biochemistry analyzer. It was able to analyze the following parameters; Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma Glutamyl Transferase (GGT), Alkaline Phosphatase (ALP), albumin, total protein, total and direct bilirubin using the manufacturer's protocol. The laboratory provided reference ranges for the tests. Determination of ESR was done at the Department of Haematology Laboratory, University of Nairobi, using the Wintrobe method. Both laboratories undergo internal and external quality control measures and are run by qualified laboratory technologists.

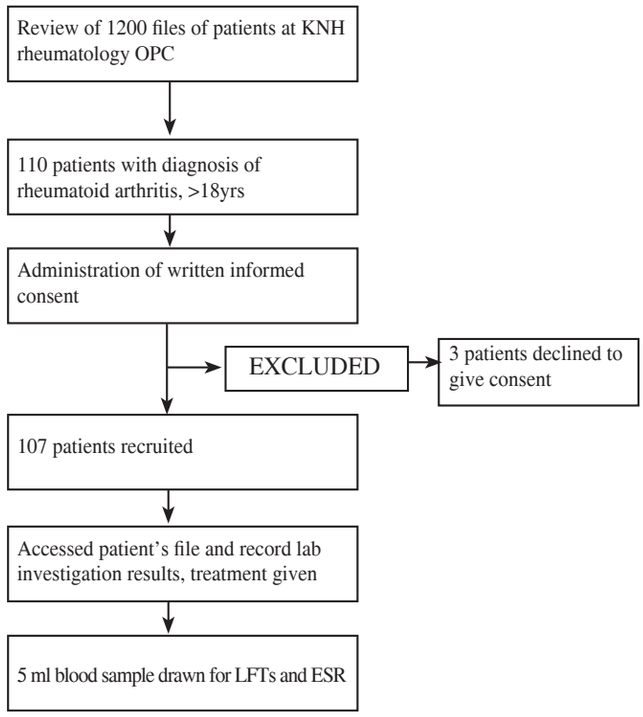
Patients were reported as having abnormal liver function tests if they had any elevations in the liver enzymes ALT, AST, ALP, GGT above the upper limit of the reference range, a rise in total or direct bilirubin above the upper limit and reduction of the albumin and protein levels below the lower limit of the reference range.

Data analysis: The prevalence of abnormal LFTs was calculated as number of abnormal LFT results as a percentage of the total number of LFT results. Association where the predictor and outcome were categorical was demonstrated using chi-square tests and odds ratios whereas Analysis of variance (ANOVA) tests were used to show relationships between categorical outcomes and continuous predictors. Where both predictor and outcome were continuous, Pearson correlation coefficients were used to characterize the association. Linear regression analysis was used to identify independent predictors of outcomes. Model building was done using a forward step-wise approach to identify the most parsimonious model. The level of significance was set at 0.05. Stata version 13 was used for data analysis.

Results

The study was done from 14th February to 21st April 2016 and enrolled 107 patients. All patients enrolled into the study gave written informed consent and had blood samples collected.

Figure 1: Shows the study flow chart



A. Demographics of the study participants

The study population was 107 patients, and 90.7% of the participants were females. The median age was 50 years, ranging from 18 to 81 years (Age of the study participants was not normally distributed and was negatively skewed; mean was therefore not described). Majority of the study participants had been diagnosed to have RA for over 5 years. Table 1 summarizes the characteristics of the study population.

Table 1: Characteristics of the study population

Variable			
Age	Median 50 (35, 62)	Min 18	Max 81
		No.	(%)
Gender	Male	10	9.3
	Female	97	90.7
Duration diagnosed with RA (years)	<1	12	11.2
	1-5	36	33.6
	>5	59	55.1

B. Medication and alcohol use

Methotrexate was the most commonly used DMARD in our population, with 60% of RA patients using it. Fourteen percent were on both methotrexate and leflunomide. Use of herbal medication was surprisingly high at 22.4%. Most study participants were non-smokers. Alcohol intake was slightly higher, with approximately 7.5% reporting current alcohol intake and 15% having stopped taking alcohol (Table 2).

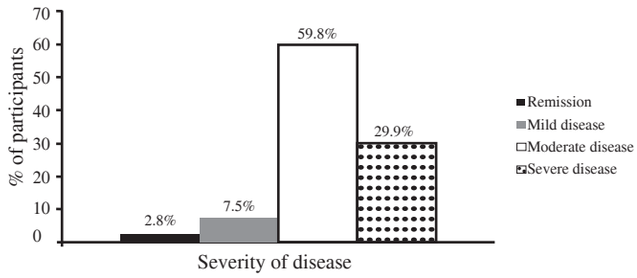
Table 2: Medication use among study participants

Drug	Use No. (%)	Duration <3 months No. (%)	3 months - 1 year No. (%)	> 1 year No. (%)
NSAID	86 (80.4)	2 (2.3)	23 (26.1)	63 (71.6)
Methotrexate	65 (60.7)	1 (1.5)	10 (15.4)	54 (83.1)
HCQS (mg/day)	44 (41.1)	1 (2.2)	6 (13.3)	38 (84.4)
Steroids - prednisone	49 (45.8)	2 (4)	7 (14)	41 (82)
Sulfasalazine (grams/day)	8 (7.5)	2 (22.2)	sz0 (0)	7 (77.8)
Leflunomide	25 (23.4)	4 (15.4)	4 (15.4)	18 (69.2)
Statin	4 (3.7)	2 (40)	0 (0)	3 (60)
Antiepileptic drugs	2 (1.9)	1 (50)	0 (0)	1 (50)
Oral contraceptive pills	8 (7.6)	1 (12.5)	2 (25)	5 (62.5)
Herbal medication	24 (22.4)	16 (15)	3 (2.8)	5 (4.7)

Disease activity among study participants

Active disease was present in 97% of the study participants and only 3% were in remission. Most of the patients, 61%, had moderate disease activity at the time of the study, despite some being on multiple DMARDs. Use of HCQS was found to be associated with a high DAS score, reflecting poor control of disease. Patients who were on HCQS were 1.7 times more likely to have poor disease control (OR=1.7, 1.14-2.55, p=0.011). A high BMI was also found to be associated with more severe disease (OR=1.06, 1.02-1.11, p=0.002). Figure 2 shows disease activity of participants.

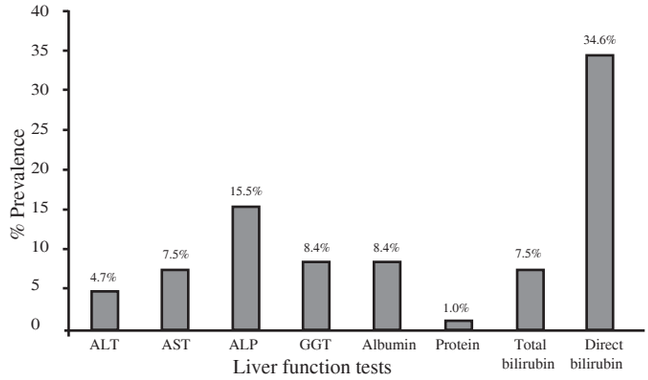
Figure 2: Disease activity of study participants



C. Prevalence of abnormal LFTs in RA

Among the RA patients, 61 (56%) had at least 1 abnormal LFT result. The most common abnormality was elevated direct bilirubin, which was found in 34.6% of RA patients. ALP was elevated in 15.5% of patients. Abnormal GGT and albumin values were found in 8.4% of patients. AST and total bilirubin were elevated in 7.5% of patients. Less than 1% of patients had low protein. Participants who had abnormality in both ALP and GGT were only 6 (5.4%). Participants who had elevations of more than twice the upper limit of normal range for the enzymes were fewer, with 5.6% having abnormal direct bilirubin, 1.9% with abnormal AST, 1.9% with abnormal GGT, 1% with abnormal ALP and total bilirubin and 0.9% with abnormal ALT. Figure 3 illustrates the prevalence of abnormal LFTs among participants.

Figure 3: Prevalence of abnormal LFTs in RA



D. Correlates of abnormal LFTs

Abnormal direct bilirubin: With longer disease duration, RA patients were almost three times more likely to have elevated direct bilirubin, OR 2.79 (1.23, 6.25), with a p value of 0.014. Though not significantly associated, being female and having a high education level seemed to be protective against development of abnormal direct bilirubin. Drugs such as HCQS, especially at high doses were also protective against abnormal direct bilirubin (Table 3).

Table 3: Adjusted odds ratios for abnormal direct bilirubin

Variable	Crude OR (95% CI)	P-value	Adjusted OR	P-value
DAS28	0.593 (0.396, 0.888)	0.011	0.54 (0.34, 0.86)	0.009
RA duration	2.144 (1.099, 4.181)	0.025	2.79(1.23, 6,25)	0.014
Gender	0.313(0.082, 1.190)	0.088	0.603(0.43,1.03)	0.054
Education level	0.659(0.402, 1.081)	0.099	0.6(.33, 1.09)	0.096

Abnormal ALP: Fifteen percent of the study population had abnormal ALP. Notably, abnormal ALP was significantly associated with BMI with an adjusted OR of 0.205 (0.074, 0.57), p-value 0.002 as well as duration of disease, with an adjusted OR 1.14 (1.013, 1.29), p-value 0.031.

Other independent predictors of elevated ALP included occupation and use of oral contraceptives. Having an occupation appeared to be protective for elevated ALP, OR 0.41 (0.16, 1.01) with a p-value of 0.05. However, use of OCP was up to 22 times predictive for elevated ALP OR 22.3 (1.72, 290.12), p-value 0.018. Having been started on any DMARD and drugs such as HCQS, methotrexate and prednisone were noted to be protective against development of abnormal LFTs (Table 4).

Table 4: Adjusted ORs for abnormal ALP

Variable	OR (95% CI)	P-value	Adjusted OR	Adjusted P-value
BMI	1.168 (1.051,1.298)	0.004	0.205 (0.074, 0.57)	0.002
MTX dose	0.829 (0.683,1.008)	0.06	-	-
RA duration	0.247 (0.108, 0.564)	0.001	1.14 (1.013, 1.29)	0.031
Occupation	0.434 (0.227, 0.83)	0.012	0.405(0.16, 1.01)	0.053
Anti CCP	0.1 (0.017, 0.705)	0.02	-	-
DMARD started	0.304 (0.079, 1.166)	0.083	-	-
MTX duration	0.243 (0.061, 0.971)	0.045	-	-
Folate	0.122 (0.007, 2.19)	0.154	-	-
HCQS	0.16 (0.034, 0.748)	0.02	-	-
HCQS duration	0.105 (0.011, 1.014)	0.05	-	-
Prednisone	0.215 (0.057, 0.809)	0.023	-	-
OCP	9.577 (1.458, 62.906)	0.019	22.3 (1.72, 290.12)	0.018

Discussion

The overall prevalence of abnormal liver function tests in the study population was 57%. The most common abnormality was elevated direct bilirubin in 34.6% of participants, followed by elevated ALP in 15%. This study showed a low prevalence of ALT and AST abnormality at 4.7% and 7.5% respectively. Significant associated factors for elevated direct bilirubin included disease activity and duration of disease. Elevated direct bilirubin was more common in patients with a low disease activity and longer duration of disease. Duration of disease was a significant associated factor for both elevated ALP and direct bilirubin. Direct bilirubin and ALP may be elevated in case of liver disease and suggest intrahepatic biliary obstruction.

Previous studies have noted liver dysfunction in RA at variable levels. Lefkovitz *et al*[16] found a depressed albumin level as the most common LFT abnormality, which was in 37% of patients. Fewer patients had elevated ALP (15%) and bilirubin levels (0%). This study had a similar prevalence of ALP abnormality but higher bilirubin levels. Notably, these were patients who had not yet been started on DMARDs and the difference in this population may well be an effect of treatment. Webb *et al*[7] found that 18% of RA patients had elevated ALP, 1.9% of patients had elevated ALT and 0.5% of patients had elevated AST. In a review of RA patients on methotrexate, Amital *et al*[17] found a total of 45% of the population had at least one abnormal result, most commonly ALP and albumin. This study is similar, and shows an overall prevalence of abnormal LFTs at 57%, with the common abnormal LFTs being direct bilirubin and ALP. A study done among RA patients on a combination of methotrexate and leflunomide by Curtis *et al*[13] demonstrated LFT abnormalities in 33% of RA patients. Studies done among patients who were on DMARDs have revealed variable LFT abnormalities that have been attributed to the drug regimen, citing high dosage of drugs such as methotrexate, lack of folate supplementation and combination of drugs such as methotrexate and leflunomide. The lower prevalence of abnormal ALP in this study population of 15% in comparison to the systematic review by Salliot *et al*[19], which had a prevalence of 20%, may be explained by use of folate supplementation, which the study participants on methotrexate were on as well as the small number of patients on multiple DMARD combination. Folate supplementation is used in all our study patients on MTX

and this has been proven to reduce adverse events of MTX, including gastrointestinal effects and liver function test abnormalities [20,21].

This study also reveal an elevation of direct bilirubin, which may not be explained by the effect of RA on the liver. An isolated elevation of direct bilirubin may be difficult to infer much from, though many recent studies have been evaluating elevated bilirubin as a protective factor in many inflammatory diseases such as RA, SLE, stroke, atherosclerosis and vasculitis[18]. This could explain why elevated direct bilirubin was associated with low disease activity.

This study shows no correlation of abnormal ALP with disease activity. There was however a protective effect of using DMARDs, especially prednisone and HCQS. Studies by Cockel *et al*[8] and Kendall *et al*[22] demonstrated that the abnormal LFTs, mostly ALP elevation, subsided with disease remission as well as steroid use in patients with RA. Lefkovitz *et al*[16] also demonstrated a definite relationship between abnormal albumin and high disease activity. Kendall *et al*[22] found the pathogenesis of abnormal LFT to be obscure and was unable to ascribe this to hepatotoxic drugs, alcohol or hepatitis. The high disease activity of the study population despite treatment could explain the lack of correlation. This study found that 97% of patients with rheumatoid arthritis in the rheumatology outpatient clinic have active disease. This is higher than in the study by Owino *et al* in 2007[23], who found that at least 88% of RA patients had high disease activity. High disease activity among the RA patients may not be surprising, given that patients who have been on DMARDs for a long duration will have poor response with time. The ERAN cohort in the UK similarly noted high disease activity, despite patients being on DMARDs[24].

With longer disease duration, RA patients were almost three times more likely to have elevated direct bilirubin; OR 2.79 (1.23, 6.25), with a p-value of 0.014. The effect of duration of disease could represent a cumulative effect of either the disease or the drugs on abnormal liver function. Drugs such as HCQS were protective against abnormal bilirubin results. Elevated ALP was significantly associated with BMI with an adjusted OR of 0.205 (0.074, 0.57), p-value 0.002 as well as duration of disease, with an adjusted OR 1.14 (1.013, 1.29), p-value 0.031. Kent *et al*[25] showed an effect of obesity on liver function tests in RA patients using methotrexate. Other independent predictors of elevated ALP included occupation and use of oral contraceptives. Having an occupation appeared to be protective for elevated ALP, OR 0.41 (0.16, 1.01) with a p-value of 0.05. However, use of OCP was up to 22 times predictive for elevated ALP, OR 22.3 (1.72, 290.12), p-value 0.018. Having been started on any DMARD and drugs such as HCQS, methotrexate and prednisone were noted to be protective against development of abnormal LFTs.

Study limitations: This was a cross-sectional study and we were unable to follow up patients with serial LFT measurements. We were unable to ascertain causes of liver dysfunction, especially those which may result from infection or autoimmune disease. LFTs are non-specific and were only used to detect liver dysfunction.

Conclusion

This study reveals a high prevalence of abnormal LFTS, in 57% of RA patients. Such a high burden of liver dysfunction necessitates that LFTs should be a requirement in providing quality care to any patient with rheumatoid arthritis. Abnormal direct bilirubin was associated with a low disease activity and longer duration of disease. Duration of disease was a significant associated factor for both elevated ALP and direct bilirubin. Patients with rheumatoid arthritis who have had the disease for longer should be on the health provider's watch list and LFTs should be done often. None of the patients with abnormal LFTs had clinically evident liver disease, which therefore illustrates the importance of frequently monitoring LFTs among these patients. Moreover, most of the study population did not have previous liver function test results. This study therefore recommends regular monitoring of liver function tests in patients with rheumatoid arthritis, especially in those who have long-standing disease. Establishment of a prospective cohort would also be useful as well to determine the intervals at which monitoring liver function should be done.

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Case report

Late onset Pompe disease- new genetic variant: Case report

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Abstract

Pompe's disease (acidmaltase deficiency, glycogen storage disease type II) is an autosomal recessive disorder caused by a deficiency of lysosomal acid-1, 4-glucosidase, resulting in excessive accumulation of glycogen in the lysosomes and cytoplasm of all tissues, most notably in skeletal muscles. A case is presented of late-onset Pompe's disease with progressive respiratory failure for about 2 years requiring constant Oxygen supplementation. On physical exams except weight loss and breathlessness everything else was normal.

Alpha glucosidase enzyme activity was reduced 22 (56-296). GAA gene mutation showed a heterozygous missence variation in exon 9 of the GAA gene (chr17.78083769;C>C/G; Depth:141x) that results in the amino acid substitution of Arginine for Proline at codon 451 (p.Pro451Arg:ENST00000302262) was detected. The variant c.1352C>C/G (p.Pro451Arg) detected had an autosomal recessive inheritance pattern. This mutation has not been reported before and it presents with severe progressive respiratory failure. The patient was not given enzyme replacement therapy due to cost but received high protein therapy and Oxygen supplementation using Oxygen extractor machine. She is worsening due to respiratory failure.

Conclusion: This is a new genetic variant isolated of late-onset Pompe disease which presents with almost pure progressive respiratory failure.

Introduction

Pompe disease is a lysosomal storage disorder caused by the deficiency of acid α-glucosidase[1-4]. Deficiency of the lysosomal acid alpha-glucosidase enzyme causes accumulation of glycogen in the lysosomes. The build-up of glycogen causes progressive muscle weakness (myopathy) throughout the body and affects various body tissues, particularly in the heart, skeletal muscles, liver and the nervous system.

The clinical spectrum of Pompe disease is very heterogeneous with regard to the age of onset, disease manifestations and rate of disease progression[3,5]. A vacuolar myopathy is the classic description of the pathology, but in clinical practice the findings can vary substantially from virtually normal muscle to severely abnormal, "end-stage muscle," with prominent necrosis[6]. Muscle biopsy findings vary not only from one patient to the next, but also from one muscle to the next within an individual patient[7]. If the muscle chosen for biopsy is clinically unaffected, a falsely normal biopsy result may be obtained. Thus, a normal muscle biopsy does not exclude the possibility of late-onset Pompe's disease, and clinical suspicion must remain high in patients with appropriate phenotypes despite normal biopsy results. Muscle imaging may allow a more accurate selection of muscle biopsy sites.

A case is presented of adult-onset Pompe disease with an uncommon clinical presentation characterized by severe isolated respiratory failure. The patient has normal muscle biopsy but deficient alpha glucosidase enzyme activity.

Case report

This was a 54 year old black African lady, who suffered from asthma since childhood and is on seretide inhaler. Informed consent was obtained from the patient before publication. Since December 2015, she presented with history of progressive difficulty in breathing and breathlessness which was not remitting on anti-asthma treatment. She has never smoked but

she was living with her husband who stopped smoking 10 years ago. By February 2016 her Oxygen saturations were low to 69% room air and she started depending on Oxygen supplementation. Other diagnosis entertained were Chronic Obstructive Pulmonary Disease (COPD), sarcoidosis, connective tissue disease and probable small septum primum defect due to severe RA overload. No family history of similar illness was elicited.

On investigation, a CT pulmonary angiogram was suggestive of possible pulmonary sarcoidosis. A chest X-ray and lower limb dopplers ultra sound were reported to be normal. Bronchoscopy also revealed a normal airway. Bronchial aspirate was negative for Tuberculosis (TB) stain, TB Polymerase Chain Reaction (PCR) was not detected and culture showed no growth of any organisms, cytology was normal and negative for fungal staining. Echocardiography showed severe pulmonary hypertension, PASP 117mmhg (millimeter of mercury), severely dilated Right Atrium with Tricupsid Regurgitation+++ and Right Ventricular overload with flattening and paradoxical motion of the septum. Left ventricle size was normal with EF 65%.

Other tests done were full blood count, urinalysis, kidney functions, calcium levels, D-dimers, International Normalized Ratio (INR), Aldolase level, Creatine phosphokinase (CPK) level, Lactate Dehydrogenase *(*LDH) level, blood sugar level, liver function tests, Erythrocyte Sedimentation Rate (ESR), Angiotensin Converting Enzyme, serum proteins and magnesium levels which were all normal. Human Immunodeficiency Virus *(*HIV*)* test, anti-double stranded DNA (anti-dsDNA), antinuclear antibody (ANA), Lupus anticoagulant, Anti-phospholipid antibodies, Venereal Disease Research Laboratory test (VDRL), Perinuclear Anti-Neutrophil Cytoplasmic Antibodies (p-ANCA), Cytoplasmic Antineutrophil Cytoplasmic Antibodies (c-ANCA), Extractable Nuclear Antigens (ENA) and Anti-Cyclic Citrullinated Peptide (anti-CCP) were done and were reported negative. Only C-reactive protein was slightly elevated to 8.05mg/L. Nerve conduction study and electromyography done was normal. Muscle biopsy done of biceps muscles showed no muscle abnormality and lipofuscin staining was negative. Glucosidase level was found to be deficient at 22 (56-296) suggestive of POMBE Disease. GAA gene mutation showed a heterozygous missence variation in exon 9 of the Acid Alpha-Glucosidase (GAA) gene (chr17.78083769;C>C/G; Depth:141x) that results in the amino acid substitution of arginine for proline at codon 451(p.Pro451Arg:ENST00000302262) was detected. The variant c.1352C>C/G(p.Pro451Arg) detected had an autosomal recessive inheritance pattern and it suggested a new variant of Pompe disease with severe respiratory involvement. She could not start on myozyme due to cost. She is currently not able to walk for 20 metres without Oxygen and clinically she is deteriorating.

Discussion

Pompe disease is an autosomal recessive metabolic disorder[8] which damages muscle and nerve cells throughout the body. It is caused by an accumulation of glycogen in the lysosome due to deficiency of the lysosomal acid alpha-glucosidase enzyme. It is the only glycogen storage disease with a defect in lysosomal metabolism, and the first glycogen storage disease to be identified, in 1932 by the Dutch pathologist J. C. Pompe.

The build-up of glycogen causes progressive muscle weakness (myopathy) throughout the body and affects various body tissues, particularly in the heart, skeletal muscles, liver and nervous system. More alpha glucosidase present in the individual's muscles means symptoms occur later in life and progress more slowly. Type of Pombe depends on onset i.e infantile-onset form and late onset.

Respiratory symptoms may occur during the night, with apnoea or hypoventilation worsening the clinical course[9]. Hagemans *et al*[10] did not find any correlation between the age of 29 patients with late-onset Pompe disease and the presence, in some cases, of severe respiratory insufficiency without severe limb girdle muscle weakness, and highlighted that respiratory function should be monitored independently from the degree of peripheral muscle weakness. The case presented has basically respiratory failure.

The following is a list of symptoms seen in Pompe disease[10-14] starting with musculoskeletal system. A patient can present with musculoskeletal progressive proximal muscle weakness (trunk and lower limbs), gait abnormalities, muscle pain, difficulty when climbing stairs, frequent falls, scapular winging and difficulty chewing or jaw muscle fatigue. Respiratory system patient can present with respiratory complications caused by weakening of the diaphragm and other respiratory muscles, respiratory failure, orthopnea, exertional dyspnea, respiratory tract infections, daytime somnolence, morning headache and nocturnal hypoventilation. In cardiac they may have arrhythmias. Gastrointestinal system patients can present with feeding and swallowing difficulties and poor weight gain/maintenance. Creatine Kinase (CK) levels may be normal to elevated, with or without symptoms.

The disease is caused by a mutation in a gene (acid alpha-glucosidase: also known as acid maltase) on long arm of chromosome 17 at 17q25.2-q25.3 (base pair 75,689,876 to 75,708,272). To date, almost 300 distinct GAA mutations have been identified, although not all are considered pathogenic[15]. Muscle biopsy depends on muscle isolated, severity of disease and duration of disease. The occurrence of progressive, sometimes fatal, respiratory failure is primarily due to the inability of the respiratory muscles to generate normal levels of pressure and airflow during in- and expiration. These events significantly impair the removal of airway secretions and, therefore, recurrent infections, even pneumonia and atelectasis, which can eventually result in severe respiratory failure, were reported[16]. Respiratory symptoms may occur during the night, with apnoea or hypoventilation worsening the clinical course[17]. Pellegrini *et al*[18] did not find any correlation between the age of 29 patients with late-onset Pompe disease and the presence, in some cases, of severe respiratory insufficiency without severe limb girdle muscle weakness, and highlighted that respiratory function should be monitored independently from the degree of peripheral muscle weakness. When Pompe disease presents in children or adults, the predominant sign is usually progressive muscle weakness, generally beginning with the trunk and proximal muscles of the lower limbs[17]. Early respiratory involvement resulting from degeneration of the diaphragm and other respiratory muscles may manifest as respiratory insufficiency, including orthopnea and indications of sleep-disordered breathing such as morning headaches and daytime fatigue[18].

Treatment of Pompe disease: Cardiac and respiratory complications are treated symptomatically. Physical and occupational therapy may be beneficial for some patients. Myozyme was FDA approved for Pompe disease in 2006

Prognosis: The prognosis for individuals with Pompe disease varies according to the onset and severity of symptoms. Without treatment the outcome is poor. On myozyme (enzyme replacement herapy) it can delay onset of use of ventilator.

Investigational therapies: Gene therapy is also being studied as another approach to therapy for individuals with Pompe disease. In gene therapy, the defective gene present in a patient is replaced with a normal gene to enable the produce of the active enzyme and prevent the development and progression of the disease in question. Modifications to existing enzyme replacement therapy in an effort to improve effectiveness includes exploring ways to improve the uptake of recombinant acid alpha-glucosidase by muscle cells.

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Rheumatic disease in a Nigerian lady with sarcoidosis: Case report

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Abstract

Sarcoidosis is a rare disease. It is a systemic granulomatous disease that primarily affects the lungs and lymphatic systems of the body. It has not been reported in rheumatology practice in Nigeria. The essential factors for diagnosis include compatible clinic-radiologic features, histologic proof of non-caseating epithelioid granulomas, and exclusion of similar diseases. The patient was a 63 year old lady who had a skin lesion overlying the upper lip. She developed cough which was associated with occasional chest pain. She had multiple joint pains, fever, oral ulcers and weight loss with associated anorexia. She developed significant hair loss, fatigue, redness of the eyes; with poor vision, and hearing impairment of about 6 years duration at the time of presentation. Essential findings were those of hearing impairment and a few crepitations in the lung bases. Her chest radiograph revealed bilateral hilar lymphadenopathy. The antinuclear antibody and anti double stranded DNA were both negative while serum angiotensin converting enzyme (sACE) was elevated (58.5IU). A punch biopsy of the skin overlying her upper lip revealed granulomatous dermatitis. Her electrolytes, urea and creatinine, liver function tests and full blood count were essentially normal.

Key words: Sarcoidosis, Granulomatosis, Joint pains, Serum angiotensin converting enzyme

Introduction

Sarcoidosis is a systemic granulomatous disease that primarily affects the lungs and lymphatic systems of the body[1]. The cause of sarcoidosis remains unknown, however genetic and environmental factors have being incriminated. The possible agents involved in its aetiology are micro organisms, organic and inorganic dusts such as aluminium, zircomium and talc[1]. Sarcoidosis occurs globally and has its highest geographic prevalence in northern European countries (5-40 cases per 100,000 people)[2]. The disease appears to be slightly more frequent in women than men[3]. Sarcoidosis may present at any age but prevalence peaks between 20 and 40 years of age, with a second peak in women over 50 years[3]. Sarcoidosis appears to be three to four times more common in blacks than whites[4]. Immunogenetic differences between patients may determine their clinical manifestations of sarcoidosis, and could underlie the heterogeneity of the disease[5,6]. Blacks tend to present with more acute and severe disease than whites, who tend to present with asymptomatic and chronic sarcoidosis[7].

Being a multisystemic disease, sarcoidosis also does affect the musculoskeletal system. To the best of our knowledge, it has not been reported in rheumatology practice in Nigeria. We present a case of a middle aged Nigerian lady with sarcoidosis attending a rheumatology clinic.

Case report

The patient was a 63 year old lady who was apparently well until about 10 years prior to presentation when she developed a lesion on the skin overlying the upper lip. She developed cough which was productive of sputum but no associated hemoptysis. There was only occasional chest pain but no difficulty with breathing. She had multiple joint pains involving the shoulders, knees, ankles and wrists. She had experienced fever, oral ulcers, and weight loss with associated anorexia. She also developed significant hair loss, fatigue, redness of the eyes; with poor vision and hearing impairment of about 6 years duration at the time of presentation.

She had a skin nodule on the left foot with associated numbness of the digits. There was a history of neck pain radiating down to the limbs. She only occasionally takes alcohol but does not smoke. She is neither hypertensive nor diabetic. She has never worked in an industry. Essential findings were those of hearing impairment and a few crepitations in the lung bases. Her chest radiograph revealed bilateral hilar lymphadenopathy while

radiography of the cervical spine showed spondylosis. The antinuclear antibody and anti double stranded DNA were both negative while serum angiotensin converting enzyme (sACE) was elevated (58.5IU). A punch biopsy of the skin overlying her upper lip revealed granulomatous dermatitis. This consisted of focal thinning and mild acantholysis of the epidermis. The papillary dermis exhibited band-like zone of inflammation characterized by foamy histiocytes, macrophages with melanin incontinence, lymphocytes and a few poorly formed giant cells. Thyroid function test showed minimally elevated T3 and T4 with a normal thyroid stimulating hormone. Her electrolytes, urea and creatinine, liver function tests and full blood count were essentially normal. Her erythrocyte sedimentation rate was 79mm/Hr. Her serum calcium was within normal limits (9.2mg/dl). She is presently on methotrexate, folic acid, prednisolone and omeprazole.

Discussion

Due to its nonspecific presentation, the diagnosis of sarcoidosis can be challenging. It has been shown recently that the diagnosis is often delayed[8]. The essential factors for diagnosis include compatible clinico-radiologic features, histologic proof of non-caseating epithelioid granulomas, and exclusion of similar diseases[1,9].

The reported case has a myriad of symptoms and laboratory features in keeping with sarcoidosis. The age of the patients fits in to the second peak of patients presenting with sarcoidosis[4]. Though 63 years old, her symptoms started 10 years prior to presentation hence in keeping with an earlier report by Giovinale *et al*[10] who described a 53 year old with systemic sarcoidosis. Being female is in tandem with the greater frequency of sarcoidosis in the female gender[1]. Cough is a common presentation in sarcoidosis as it primarily affects the lungs in more than 90% of patients[11]. There are four stages of pulmonary sarcoidosis. Patients with stage I or II disease may have no symptoms, whereas stages III and IV can be characterized by progressive dyspnea, loss of lung function, and fibrosis[9]. Twenty-five percent of patients have skin involvement[11]. Lesions can range from nonspecific maculopapular eruptions, such as plaques and nodules, to erythema nodosum and lupus pernio[11]. The reported case had a lesion on the skin overlying the upper limb whose biopsy revealed granulomatous dermatitis. Lupus pernio consists of indurated plaques and discoloration of the nose, cheeks, lips, and ears and usually indicates a chronic disease course that is unlikely to result in spontaneous remission[11] as has been in the reported case. The presence of granulomas alone is not diagnostic as the same lesions may also be observed in chronic berylliosis, tuberculosis, histoplasmosis, coccidioidomycosis, lymphoma, Hodgkin's disease, bronchogenic carcinoma, foreign body granuloma, schistosomiasis, syphilis, and leprosy[12]. The reported case had articular involvement. Osteoarticular involvement in sarcoidosis is uncommon[9]. The incidence is around 3–13% and is clinically relevant only in 2–5% of cases, often presenting an asymptomatic course[13].

Patients with bone involvement often also have lung disease[14] (up to 90% of cases) and skin involvement (in a proportion that rises to 25%) mainly in the form of lupus pernio as is the case in the reported patient. The presence of acute polyarthritis associated with lymphadenopathy and erythema nodosum is called Löfgren syndrome[15]. In the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other granulomatous disorders statement on sarcoidosis, constitutional symptoms, such as fever, weight loss, fatigue and malaise, were mentioned as being present in approximately one-third of patients[16]. Neurosarcoidosis is a rare manifestation which may present as cranial nerve palsies, meningitis, seizures, and neuropsychiatric symptoms[17,18]. The most common neurologic manifestation of sarcoidosis is cranial neuropathy secondary to nerve granulomas, raised intracranial pressure, or granulomatous meningitis[19]. The facial nerve is the most frequently affected cranial nerve while the vestibulocochlear nerve is involved in 1–7% of cases of neurosarcoidosis[19] as in this case. Bilateral hilar lymphadenopathy is characteristic as was seen in this case and usually accompanied by paratracheal lymphadenopathy[20]. Serum angiotensin converting enzyme is increased in 30 to 80% of patients with sarcoidosis as was in this case[21]. Serum Angiotensin Converting Enzyme (ACE) has a poor predictive value in sarcoidosis and can also be elevated in several disorders such as tuberculosis, multiple sclerosis, and Guillain-Barre Syndrome[21].

Conclusion

Sarcoidosis is a rare multisystemic disorder with protean clinical, laboratory and radiologic manifestations. The musculoskeletal system is not excluded from its presentation. The presence of arthritis, hilar adenopathy and skin manifestation should raise the suspicion about Löfgren syndrome.

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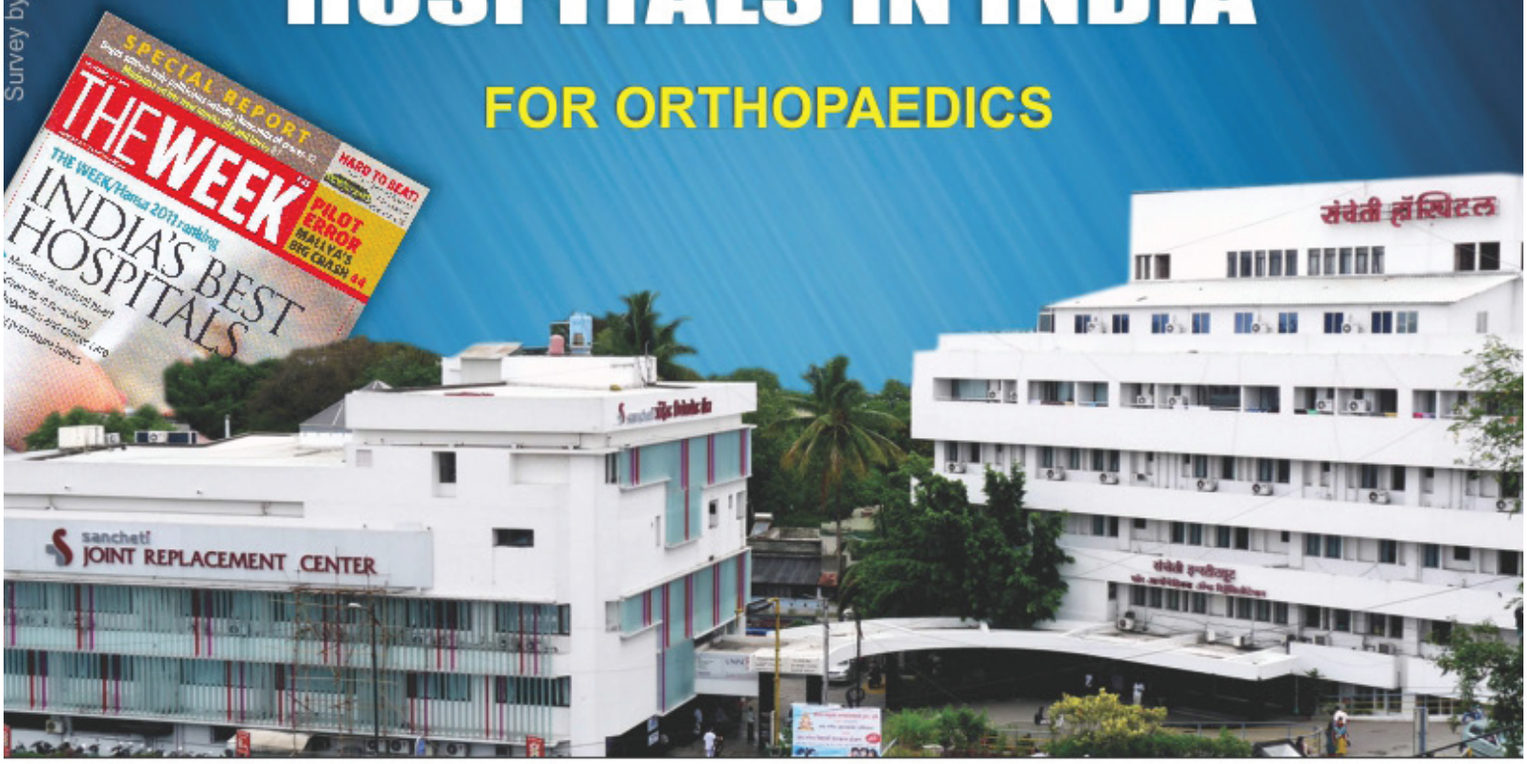

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