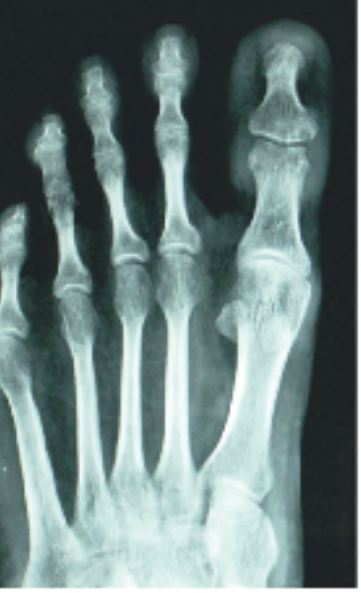

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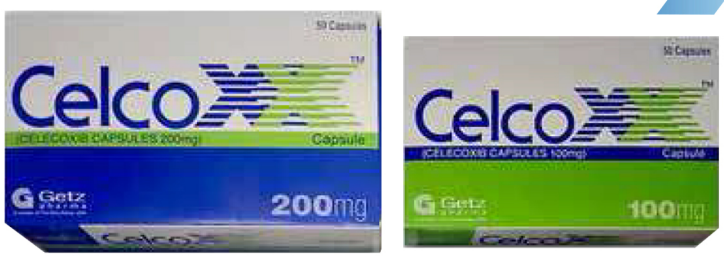

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Emerging value of stem cell therapy in rheumatic diseases

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Rheumatic Diseases (RDs) including Rheumatoid Arthritis (RA) and osteoarthritis, are characterized by immune dysregulation and chronic progressive inflammation that leads to irreversible joint damage[1]. Recently, research has focused on Mesenchymal Stem Cells (MSCs) application in RDs due to their low immunogenicity and immunomodulatory properties[2]. MSCs have been widely investigated in RDs not only for their immunomodulatory action but also owing to their regenerative properties and therapeutic potency[1]. Activated T lymphocytes play an important role in the pathogenesis of RD. MSCs possess immunoregulatory activities but such functions of MSCs from bone marrow of Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SSc), and Ankylosing Spondylitis (AS) patients are impaired. Adipose tissue-derived MSCs are an optional pool of therapeutically useful MSCs, but biology of these cells in RD is poorly known[3].

Mesenchymal stem cells have a therapeutic potential in Rheumatoid Arthritis (RA) due to their immunomodulatory and differentiation effects[4]. Circulating interferon-γ (IFN-γ) was found to improve the clinical efficacy of MSC therapy in patients with RA[5]. Moreover, there was a sufficient immunoregulatory effect of autologous MSCs on regulatory T cells in patients suffering from refractory RA[6].

In the last years, a considerable progress has been made in the treatment of spondyloarthritides. Nonetheless, there remains a considerable number of patients who are unresponsive to all current therapies[2]. As MSCs can dampen inflammation and play an effective role in osteoarthritis, it was expected to be a potential solution for numerous human conditions. However, in RA and Spondyloarthritis (SpA), subsets of MSCs might conversely fuel synovitis and enthesitis[7].

Stem cell therapy has been proved to be an effective therapeutic approach to treat Systemic Lupus Erythematosus (SLE), the detailed underlying mechanisms are not fully understood[8]. Intra-renal injection of human bone marrow derived mesenchymal stem cells is a promising route for treatment of lupus nephritis in mice[9].

Haematopoietic Stem Cell Transplantation (HSCT) can cure Chronic Granulomatous Disease[10] and MSC infusion might be a potentially successful therapy for intractable drug-resistant Behcet disease patients with concomitant leg ulcer[11].

In Systemic Sclerosis (SSc), determined tissue repair leads to progressive fibrosis of the skin and internal organs. The key roles of Mesenchymal Stem Cells (MSCs) include initiating and regulating tissue repair[12]. MSCs represent a promising therapeutic advance due to their trophic and pleiotropic properties. MSCs display anti-fibrotic, angiogenic, and immunomodulatory actions that are imperative in the treatment of SSc[13]. The diversity in extent, severity, and progression of skin and internal organ involvement gives rise to challenges in determining optimal therapeutic options for SSc as disease modifying anti-rheumatic drugs (DMARDs) are lacking. In this scenario, it is not surprising that SSc was one of the first autoimmune diseases challenged with high-dose immunosuppressive treatment and stem cell therapy[14]. Since stem cell-based treatments have developed as a novel approach to rescue from several autoimmune diseases, it seems that stem cells, especially MSCs as a powerful regenerative tool can also be advantageous for SSc treatment via their remarkable properties including immunomodulatory and anti-fibrotic effects[15]. MSCs are characterized by a broad availability and no or low acute toxicity[16].

Mesenchymal Stem Cells (MSCs) have been demonstrated to exert great potential in the treatment of various autoimmune diseases. Although MSCs is an effective therapeutic approach for Sjögren Syndrome (SS), the underlying mechanisms are still elusive17. MSCs have been revealed to suppress CD4 + T cell activation and autoimmunity in both mouse models and patients with primary SS[18].

MSC-based cell therapy is a relatively safe treatment that holds great potential for Osteoarthritis (OA), evidenced by a positive effect on pain and knee function for a short term[19,20]. Using low-dose (25 million) and adipose-derived stem cells is likely to achieve better results[19]. In spite

that using stem cell therapy for knee osteoarthritis helps in pain improvement, but its effect on cartilage regeneration has not yet been explored[21].

In the near future, MSC therapy may be considered a potentially promising therapeutic option added to the management armamentarium of many rheumatic diseases.

Conflict of interest: None.

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Review article

Fibromyalgia: Reviewing the epidemiology and gender-based differences in Africa

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Abstract

Objectives: Fibromyalgia is a complex disorder which presents with chronic widespread musculoskeletal pain, together with other symptoms like fatigue, sleep disturbances and cognitive disturbance. The cause remains unclear but it is postulated that there are abnormalities in neurohormonal profile and central sensitization to pain as the main mechanism. It is known to occur more commonly in females than males. This study set out to look at these differences in terms of epidemiology and gender differences.

Data source: We conducted online and public library searches using the English language.

Data extraction: We reviewed several papers and research work focusing on epidemiology and differences in gender presentation. The period of the search was between the years 1990 up to 2020.

Conclusion: Fibromyalgia is a commonly occurring rheumatologic condition. Gender differences exist with regard to epidemiology, clinical presentation and health seeking behaviors. Population based studies would be of use to establish the prevalence in Africa. More studies would be necessary to explain the gender differences noted in the many aspects of the disease including response to treatment.

Key words: Fibromyalgia, Fibromyalgia in women, Gender differences and impact of fibromyalgia

Introduction

Fibromyalgia is a condition characterized by chronic widespread musculoskeletal pain together with tenderness in areas known as pressure points. The condition has other symptoms apart from musculoskeletal ones. These include a disturbance in sleep patterns whereby patients present with poor unrefreshing sleep. Other associated symptoms include fatigue, irritable bowel syndrome and cognitive symptoms[1]. With regard to the widespread pain, inflammation is not a feature of fibromyalgia and therefore the patients do not suffer consequences of joint damage or deformities as is seen with other painful inflammatory conditions[2].

The cause of this condition is unknown. Several studies have been done to link it with certain causative factors and so far, it has been linked with Parvovirus B, Human Immunodeficiency Virus (HIV) and Hepatitis C virus infections. It is thought that these infections may act as a trigger to fibromyalgia[3]. There is a high prevalence of sleep disturbances in patients with fibromyalgia. These may include difficulty in falling asleep and poor unrefreshing sleep. There are notable abnormalities in sleep studies of patients with this condition. These may play a role in worsening symptoms of fibromyalgia[4]. The main focus of recent studies has been on the alterations in the neuroendocrine system of patients suffering from fibromyalgia. It has been noted that they tend to have abnormalities in hormonal profile alterations like serotonin[5] and substance P[6]. This has led to suggestions that it is a neurohormonal condition with central sensitization as the main mechanism in fibromyalgia[7]. This would then explain why the medications used to treat it are those whose main mechanism of action is in the central nervous system[8]. The hypothalamus-pituitary-adrenal axis has also been thought to play a role in the pathogenesis of this condition. A study done in women suffering from both fibromyalgia and chronic fatigue syndrome found that they tend to have low cortisol levels compared to healthy controls[9].

Fibromyalgia can occur on its own or in association with other rheumatologic conditions. It has been found to be prevalent in patients with rheumatoid arthritis, systemic lupus erythematosus, Sjogrens syndrome, osteoarthritis and also chronic fatigue syndrome[10]. Other non-rheumatological diseases have also been associated with fibromyalgia and these include diabetes mellitus[11].

Population based studies have put the disease at a prevalence of 2% in the

general population. In terms of gender, fibromyalgia is commonly seen in females compared to males. The reason for this is unclear. When it comes to age, it is mainly seen in middle aged women but the prevalence rises as they advance in age. The prevalence thus rises from 18-30 years and peaks at 55-64 years. Women also present with longer disease duration and have more tender points compared to men[12].

There is no specific laboratory or imaging modalities that can be used to diagnose fibromyalgia. The American College of Rheumatology has over the years developed sets of criteria that can be used for diagnostic purposes. This entails the presence of widespread pain present for at least three months. Widespread pain is defined as pain in all the four quadrants of the body together with presence on both right and left side of the body. Physical extermination is then carried out to assess for tenderness in 18 established areas on the body[13]. Previously, assessment of tender points was required but this has since been removed from the latest criteria. This entails calculation of widespread pain index on 19 sites together with assessment of 41 defined somatic symptoms[14].

The impact of this condition can be felt both at the individual and society level. At the individual level, fibromyalgia as much as it does not cause joint deformities, the disease can be debilitating in several aspects. The impact of symptoms like sleep disturbance, fatigue and depression can be assessed using the revised Fibromyalgia Impact Questionnaire (FIQR) tool. Additionally, pain, tenderness and their severity can also be assessed by the FIQR. The total score can be used to assess disease activity and also help with guiding management of the patient[15].

Other tools that help to assess the quality of life in fibromyalgia include EuroQol, the Medical Outcome Study (MOS) Sleep Scale, the Brief Pain Inventory- Short Form (BPI- sf) and the Hospital Anxiety and Depression Scale (HADS). Using these tools, it has been noted that the quality of life of patients with fibromyalgia is adversely affected by their pain, poor sleep patterns and chronic fatigue[16]. Assessment of the quality of life has been done in other studies with similar findings. The findings from one such study which looked at the focus groups in 48 women revealed that fibromyalgia has a substantial negative impact on patients' lives[17].

This can be seen well in advance of the diagnosis being made. A study in the United Kingdom revealed that fibromyalgia patients have a higher rate of clinic visits, prescriptions and diagnostic procedures up to 10 years before the diagnosis is made[18]. At the society level, fibromyalgia is associated with higher utilization of healthcare facilities. This could be in a bid to establish a diagnosis thus many hospital visits and unnecessary tests are done before a diagnosis is reached. In addition, many treatment modalities may be sought. This is as a result of the complex nature and myriad symptoms that the patient may present with[19].

Comparing the epidemiology in Western and African populations

Population based studies done in Western populations have estimated the prevalence to be between 2-4%[20]. In the United States, the prevalence was estimated to be 2.0% from a population of 3004 patients in a study done in Wichita[21]. In Europe, a study done in 5 countries estimated the prevalence in the general population at 4.7 % and it was found to be associated with both age and gender[22].

In Africa, there is paucity of data regarding the prevalence of fibromyalgia. Several countries have however sought to do prevalence studies in their own populations, some at community level and others at facility level. One such study was done in West Africa (Nigeria) where they studied 114 patients diagnosed by a rheumatologist. It was however noted that the ACR criteria may not be a sensitive tool to use in sub-Saharan Africa[23]. In Kenya, several studies have been done with regard to fibromyalgia. The first one was done by Dokwe *et al*[24] where they sought to establish prevalence of the disease in patients attending the medical outpatient clinics. They found a prevalence rate of 13% with middle-aged women contributing to 97.7% of the cases[24]. With regard to the associated conditions linked to fibromyalgia, Malombe *et al*[25] studied the disease in HIV positive patients who had musculoskeletal symptoms. They found a prevalence of 17.9% with a notable higher disease activity using the FIQR tool in comparison to the SIQR in those without fibromyalgia[25]. Umar *et al*[26] studied the presence of fibromyalgia in diabetic patients and they found that 27.9% of these patients had the condition. A majority of the patients were females (88.2%) and poor control of their underlying diabetes (using HBA1C measurements) was an associated finding[26].

Fibromyalgia in women

Differences exist between both genders when it comes to many things like biology and behavior. Consequently, the two genders may differ when it comes to disease manifestations, epidemiology and also pathophysiology of some conditions. In general, there is a female preponderance when it comes to most of the rheumatologic conditions. Certainly, common conditions like rheumatoid arthritis[27], systemic lupus erythematosus[28], systemic sclerosis[29] and even osteoarthritis[30] are seen more in women compared to men. The explanation towards this has remained elusive. It has been thought that these difference in occurrences could be due to the hormonal profile in both genders. Hormones like estrogen have been seen to play a role in auto reactivity of the immune cells (in mice studies) which then could explain some of the gender differences[31].

Fibromyalgia is no exception when it comes to these findings. In the USA, it has been found to be seven times more common in women. This was done via a population survey which interviewed about 3000 patients and further evaluated 391 who had symptoms of chronic

pain[12]. Another population based study revealed that those with fibromyalgia were more likely to be female and of a younger age group. The study population was however a predominantly male population[32].

In Africa, there is paucity of data with regard to fibromyalgia in women. What the previously mentioned studies found was that there is indeed an increased female to male ratio. In the Nigerian study, this was found to be at 1.5;1[23]. Dokwe *et al*[24] found a female preponderance of 97.7% in patients attending the medical out-patient clinics. The overall duration of symptoms was 5.8 years pointing towards the chronicity of symptoms before diagnosis was made. They also assessed the frequency of symptoms where they found that pain, fatigue and stiffness were the most common presentations in these patients[24].

Malombe *et al*[25] studied the HIV positive population and of the 68 patients out of 380, 88% were female. Fibromyalgia was found to be independently associated with the female gender with an odds ratio of 2.75. Other associations included unemployment and retired status. On the contrary, fibromyalgia was not associated with clinical stage of HIV, CD4 count or anti-retroviral regimen[25].

Basis of the gender differences

Female hormones are also believed to play a role in both the incidence and severity of fibromyalgia. This is evidenced by the fact that it tends to occur in women of child bearing age. In paediatric fibromyalgia, it has been shown that the prevalence between both genders remains similar until puberty whereby it tends to be higher in girls compared to boys[33]. Other findings have been that the level of progesterone and testosterone are inversely proportionate to the level of pain in fibromyalgia. This was a study done in women with fibromyalgia whereby hormone levels were assessed daily over a period of 25 days and compared against the symptom of pain. Additionally, fibromyalgia pain was highest during menstrual phase when hormone levels were low suggesting that sex hormones have a role to play in the symptomatology of fibromyalgia[34].

Racial differences have also been seen when it comes to the prevalence in females. For instance, a study done in USA comparing African-American women to Caucasian women found a prevalence of 3% and 2% respectively[35]. Other differences between the races have been seen whereby racial minorities were found to have greater levels of mood disturbance and depression than their Caucasian counterparts[36].

Notable differences in both genders exist when it came to disease presentation where it was seen that women with fibromyalgia were more likely to have connective tissue diseases. Men were found to have medical conditions linked to their diagnosis of fibromyalgia. In terms of clinical differences, women tend to have a higher tender point count compared to men when the ACR 1990 criteria was used[37]. They also tend to have more pain at these sites. Other differences in this study that compared 40 men and 40 women with fibromyalgia found that men had severe symptoms with decreased physical function together with lower quality of life[38].

It is a known finding that fibromyalgia is associated with cognitive symptoms like anxiety and depression. A study done to establish differences in the two genders with regard to this found that the odds of being female were 112% when anxiety was reported as a symptom. Curiously, in this study, depression was more associated with the male gender[39].

Effects of fibromyalgia from the women's perspective

The main symptom of pain is described as present throughout, unpredictable and fluctuating. Several patients were asked to describe their symptoms and below is an excerpt

''My body is stiff and then I get pain, like a hard pain in my back and then I'm tired, tired, tired all the time and it feels like I can't open my eyes properly for the whole day."

Other women felt as though their bodies were unfamiliar to them. Other symptoms described include sensitivity to cold, tender skin and swellings as well. The main finding from this study is that women felt that there's a double burden associated with fibromyalgia. This results from the symptomatology and also not being able to be understood/believed by those around them including healthcare workers[40].

The diagnosis of fibromyalgia has profound effects on patient's relationships with others. This includes family members, workmates and the community at large. At the family level, effects on the spouse can be varied from those who offer support during the illness while in others, fibromyalgia can lead to the end of a relationship[41]. Guilt is also one of the negative feelings that women living with fibromyalgia experience when it comes to feeling inadequate about not being able to take care of their children. Additionally, their spouses may have to take up more household roles in the family and this may further worsen the guilt feelings[42].

The physical and cognitive symptoms of fibromyalgia may affect the productivity of women living with fibromyalgia. It has been seen that this may lead to stigma and lack of social acceptance by the medical community and other people around them. In addition, those who are working may end up changing jobs frequently or take up lesser roles because of the difficulty in performing tasks brought about by their pain or cognitive symptoms like poor memory[42].

Conclusions

Fibromyalgia is a debilitating condition whose cause is unclear. The prevalence is noted to be higher in middle aged females with differences in disease presentation. The reason for the gender differences are unclear but there is evidence that sex hormones may have a role to play in this. More research is needed to explain these differences. The effects of the disease can be felt both at individual and

society level with increased utilization of resources both for diagnosis and treatment. There is paucity of data on fibromyalgia in Africa. We recommend that more studies be done to establish the prevalence and characteristics in the female gender.

Conflicts of interest: None to declare.

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Prevalence and spectrum of rheumatic and musculoskeletal diseases in a Lagos hospital community: an under-reported non-communicable disease in Africa

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Abstract

Background: Rheumatic and Musculoskeletal Diseases (RMDs) previously known as the musculoskeletal (MSK) diseases are a major cause of chronic pain and functional disability. While there are few hospital based reports of RMDs and its individual conditions in Nigeria, community data of these conditions are even rarer.
Objectives: To determine the prevalence and spectrum of RMDs as well as the factors associated with MSK pain in Nigeria.
Design: This was a cross-sectional survey of staff and patients' relatives at a Lagos tertiary hospital.
Methods: We prospectively collected data on 350 respondents using a pre-tested interviewer-based study questionnaire and the Health Assessment Questionnaire-Disability Index (HAQ-D1) questionnaire. Clinical information was recorded and laboratory tests done for all participants. Data was analysed with descriptive statistics using Statistical Package for Social Sciences (SPSS) version 21. Ethical approval was obtained for the study.
Results: A total of 268 (76.6%) respondents completed the study comprising 176 (65.7%) females and 92 (34.3%) males with a mean age of 57.3±12.4 years (range 20-70 years). RMDs and MSK pain (current/past) were diagnosed in 59 (22%) and 162 (60.4%) respondents respectively most of whom were female (n=38, 64%) and middle aged (n=31, 52.5%). Osteoarthritis (25.5%), limited joint mobility (18.6%), lumbosacral spondylosis (10.1%) and DeQuervain's tenosynovitis (10.1%) were the most frequent RMDs. The median HAQ-DI was 0.8 (IQR 0.1-1.8) with significant disability (HAQ-DI≥1) in 57.5% of the subjects with RMDs. Respondents with MSK pain had higher proportions of truncal obesity (BMI>30) (n=89, 54.9%, p=0.016), family history of arthritis (n=93, 57.4%, p=0.001), abdominal obesity (n=97, 60%, p=0.002), hypertension (n=102, 63%, p=0.001), elevated acute phase reactants (n=57, 35.2%, p=0.003) and hyperuricemia (n=61, 37.6%, p=0.001) than respondents without MSK pain with no significant predictors of MSK pain documented after multivariate regression analysis.
Conclusions: RMDs and MSK pain are common among Nigerians occurring in 22% and 60.4% respectively resulting in significant functional disability. Osteoarthritis was the most frequent presentation of MSK pain while obesity, hypertension, hyperuricaemia, positive family history of arthritis and elevated acute phase reactants were all associated with MSK pain.

Key words: Prevalence, Spectrum, Rheumatic musculoskeletal diseases, Community

Introduction

The term "Rheumatic and Musculoskeletal Diseases"(RMDs) represent over a hundred conditions which include many types of arthritis and autoimmune inflammatory diseases that affect the bones, joints, connective tissue and other components of the musculoskeletal (MSK) system[1]. RMDs are Non-Communicable Diseases (NCDs) and patients with such conditions often present with MSK pain, joint swelling, joint stiffness, constitutional and organ-based symptoms as well as functional disability.

Studies have shown that, at any given time, 30–40% of the general population have MSK signs and symptoms such as pain, swelling or limited mobility[1,2]. In 2010, data from the World Health Organization's (WHO) Global Burden of Disease (GBD) study showed that the prevalence and burden of MSK conditions were exceptionally high throughout the world[3]. As a group, these conditions caused 21.3% of the total Years Lived with Disability (YLDs) globally[3]. Although, there is a growing prevalence of MSK disorders worldwide, probably due to population growth, ageing, low physical activity and obesity[4], a recent meta-

analysis of 20 population and 7 hospital-based studies showed paucity of MSK prevalence data from Africa[5].

In Nigeria, there are hospital based retrospective reports of isolated RMDs such as lupus, rheumatoid arthritis, Soft Tissue Rheumatism (STR), gouty arthritis, and osteoarthritis (OA) with very few published studies on the spectrum of these conditions in community settings[6-9]. The scarcity of data from sub-Saharan Africa may be attributable to a relative neglect of NCDs by policy makers as well as limited access to rheumatology and orthopaedic services. Thus, this study seeks to examine the prevalence and spectrum of RMDs as well as its associated functional disability among the non-patient community in a Lagos tertiary hospital.

Materials and methods

This was a cross-sectional study done within a hospital community - the Lagos State University Teaching Hospital (LASUTH), Lagos – Nigeria over 6 months. Apart from its large non-patient population, the study area was chosen due to its strategic location in the densely populated city of Lagos. The typical non-patient population included: medical staff, allied health staff, academic and non-academic staff of College of Medicine as well as a large community of patients relatives. Verbal and written informed consent was obtained from every respondent using signature or thumbprint.

Non-probability convenient sampling method was used to recruit consenting respondents into the study. The minimum sample size was 156 based on a 12% prevalence figure obtained from a Kenyan pilot community study[10], a confidence interval of 1.96 and a tolerable sampling error of 0.05[11]. Socio-demographics, clinical and MSK history (current pain or pain within the last one week) as well as physical examination findings were documented using pre-tested questionnaires. Blood samples were taken for serum uric acid and erythrocyte sedimentation rate while standard radiographs were done where indicated to confirm the diagnosis.

Pain intensity was assessed using the Numerical Rating Scale (NRS)[12] while functional disability was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI)[13]. The diagnosis of RMDs was based on relevant American College of Rheumatology (ACR) criteria[14-20], Brighton criteria[21] and Southampton criteria[22]. Rheumatic conditions that could not be classified using above criteria were diagnosed clinically using case definitions developed by the authors.

The functional disability assessed by HAQ-DI was reported as median with interquartile range (IQR). Degree of disability was categorized with score ≥1 indicating significant disability as follows: mild (>0 but <1), moderate (1-2) and severe (>2)[13]. Pain intensity was assessed using NRS and reported as; no pain (NRS-0), mild (NRS 1-3), moderate (NRS 4-6) and severe (NRS 7-10)[12].

Data analysis was done using IBM SPSS version 21. Socio-demographics and prevalence figures for MSK pain and clinically diagnosed RMDs were summarized as percentages. Bivariate statistics was used to compare categorical variables between respondents with MSK pain and subjects without MSK pain. Multivariate logistic regression was used to determine independent predictors of MSK pain in the study subjects with $p < 0.05$. The study was approved by the ethics committee of the Lagos State University Teaching Hospital (LASUTH).

Results

Socio-demographic characteristics of the study subjects

Two hundred and sixty eight adults consented and completed the interview-based questionnaires. The mean age of all subjects was 57.3±12.4 years with a range from 20 to 78 years. Majority of the subjects were female (n=176, 65.7%), middle aged (n=140, 52.2%), civil servants (n=110, 41%) and had tertiary education (n=108, 40.3%). The socio-demographic characteristics of the study population are as shown in Table 1.

Table 1: Socio-demographics characteristics of the study population

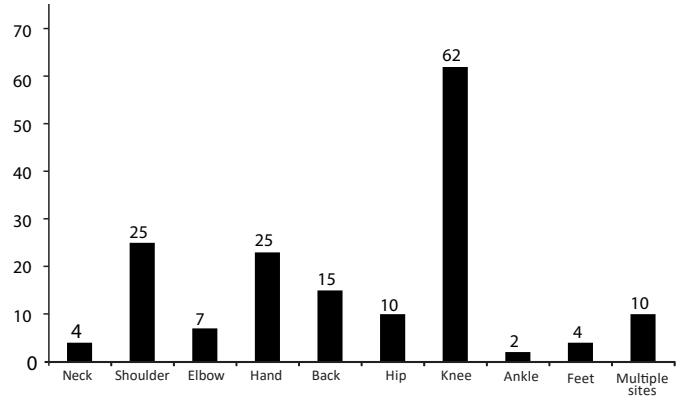
Variables	All subjects (n=268) No. (%)	Subjects with MSK pain (n=162) No. (%)	Subjects without MSK pain (n=106) No. (%)	P-value
Male	92(34.3)	50(39.6)	42(30.9)	0.140
Female	176(65.7)	112(60.4)	64(69.1)	
Family history of MSK conditions	93(34.7%)	91(56.2)	2(1.9)	0.001
Age range (years)				0.847
18-45	38(14.2)	24(14.8)	14(13.2)	
46-64	141(52.6)	83(51.2)	58(54.7)	
≥ 65	89(33.2)	55(34)	34(32.1)	
Occupation				
Private sector worker	95(35.4)	64(39.5)	31(29.2)	0.359
Civil servants	110(41.0)	61(37.7)	49(46.2)	
Trading	26(9.7)	14(8.7)	12(11.3)	
Retired	21(7.8)	12(7.4)	9(8.5)	
Others	10(3.7)	8(5.0)	2(1.9)	
Artisan/Apprentices	6(2.2)	3(1.9)	3(2.8)	
Religion				
Christianity	162(60.4)	104(64.1)	58(54.7)	0.392
Islam	101(37.7)	54(33.3)	47(44.3)	
Others	5(1.9)	4(2.5)	1(1.0)	
Marital status				
Single	70(26.1)	34(21.0)	36(34.0)	0.001
Married	174(65.0)	110(67.9)	64(60.4)	
Widowed	20(7.5)	16(9.9)	4(3.8)	
Separated/divorce	4(1.4)	2(1.2)	2(1.8)	
Education				
Primary	79(29.5)	42(25.9)	37(34.9)	0.154
Secondary	51(19.1)	33(20.4)	18(17.0)	
Tertiary	108(40.2)	72(44.4)	36(34.0)	
None	30(11.2)	15(9.3)	15(14.1)	
Smoking history	19(7.1)	10(6.2)	9(8.5)	0.470
Alcohol history	48(17.9)	28(17.3)	20(18.9)	0.741
Generalised hypermobility	85(31.7)	70(43.2)	15(14.2)	0.003
History of hypertension	118(44.2)	102(63)	16(15.1)	0.001
History of diabetes	48(17.9)	29(17.9)	19(17.9)	0.428
Abdominal obesity	125(46.7)	97(60.0)	26.4(8.3)	0.002
Hyperuricemia	73(27.2)	61(37.7)	12(11.3)	0.001
Elevated acute phase reactants	67(25)	57(35.2)	10(9.4)	0.003
Obesity by BMI definition	146(54.4)	89(54.9)	57(53.7)	0.005
History of trauma	57(21.3)	29(17.9)	28(26.4)	0.096

N= Frequency; %=Percentage; MSK=Musculoskeletal

Prevalence and associations of musculoskeletal pain in the study subjects musculoskeletal pain

As shown in Table 1, 162 subjects had MSK pain among 268 subjects recruited, accounting for the period prevalence of 60.4%. Current MSK pain was documented in 75.9% of subjects with MSK. Subjects with MSK pain were predominantly middle aged females, married, and significantly older than subjects without MSK pain {Median (IQR) years-42(31-55) vs 34(25-46), P=0.001)}. Family history of MSK conditions, hypertension, elevated acute phase reactants, hyperuricemia, abdominal obesity and generalised hypermobility were significantly more frequent in subjects with MSK pain than those without pain. As shown in Figure 1, knee, shoulder and hand were the common sites of MSK pain in decreasing order.

Figure 1: Sites of musculoskeletal pain in subjects with MSK pain



Clinically diagnosed Rheumatic Musculoskeletal Diseases (RMDs)

As shown in Table 2, 59 subjects from the 268 subjects with MSK pain had clinically diagnosed RMD, giving a period prevalence of 22% with females constituting 44 (74.6%). Osteoarthritis (n=15, 6.7%) was the most frequent condition documented in our study subjects. This was followed in decreasing order by limited joint mobility (n=11, 4.1%), lumbosacral spondylosis (n=6, 2.2%), de Quervain's tendinitis (n=6, 2.2%), carpal tunnel syndrome (n=5, 1.9%) and adhesive capsulitis (n=4, 1.5%). Taken together, soft tissue rheumatism was the most common RMD as it represented 62.7% of the subjects with RMDs.

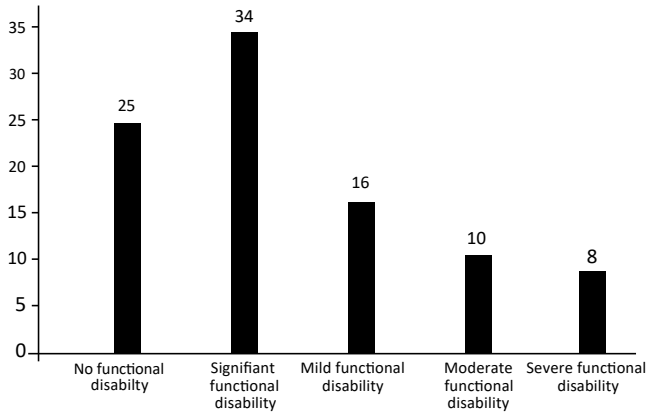
Table 2: Frequency and pattern of Rheumatic Musculoskeletal Diseases (RMDs)

Rheumatic Musculoskeletal Disease	Frequency (n)	Percentage of RMDs (n=59)	Percentage of all subjects (n=268)
Osteoarthritis	15	25.4	6.7
Limited joint mobility	11	18.6	4.1
Lumbosacral spondylosis	6	10.1	2.2
Adhesive capsulitis	4	6.7	1.5
Finger tenosynovitis	5	8.4	1.9
de Quervain's tenosynovitis	6	10.1	2.2
Rotator cuff tendinitis	1	1.6	0.4
Carpal tunnel syndrome	5	8.4	1.9
Subacromial bursitis	2	3.3	0.7
Plantar fasciitis	1	1.6	0.4
Cervical spondylosis	1	1.6	0.4
Fibromyalgia	1	1.6	0.4
Lateral epicondylitis	1	1.6	0.4

Pain severity and functional disability in study subjects with MSK pain and RMDs

The majority of subjects (n=67, 65.4%) with current MSK pain reported moderate intensity of their pain. The median NRS for pain severity in subjects with current pain was 4(IQR 3-5), also suggesting moderate intensity of pain. As shown in Figure2, the median HAQ-DI was 0.8(IQR 0.1-1.8), indicating mild disability from RMDs overall though significant disability (HAQ-DI≥1 was found in 57.5% of the subjects with RMDs.

Figure 2: Functional disability in subjects with rheumatic musculoskeletal disease



Predictors of MSK pain in study subjects

The results of chi-square analysis showed that family history of MSK conditions, generalised hypermobility, hypertension, hyperuricemia and abdominal obesity were significantly associated with presence of MSK pain. However, further tests of these independent variables using logistic regression with presence of MSK pain as outcome variable showed no significant independent predictors of MSK pain.

Discussion

This cross-sectional study showed that 60.4% of our study subjects self-reported either past or current MSK pain. This prevalence is higher than previous prevalence reports from other African studies[8,23]. A hospital based study from Sagamu, South Western Nigeria, found a prevalence rate of 15.1% out of 3,124 patients seen at the Medical Outpatient Department (MOPD) during the study period[8] while Singwe-Ngandeu *et al*[23] found 536 cases of RMDs (9.4%) out of 12,494 patients referred to the MOPD of General Hospital, Yaoundé over a one year period.

The distribution of MSK pain across socio-demographic lines in our study showed that it was more prevalent in females, middle aged subjects, private sector workers and civil servants. In addition, majority of subjects with MSK pain were married and had tertiary education. Although, not statistically significant, the possible explanation for this socio-demographic distribution may be due to metropolitan nature of the study site and study population which included predominantly staff of the medical school and hospital including patient's relatives.

Most of our subjects reported knee as the commonest site of their MSK pain. Notably, there have been conflicting reports on the commonest site of MSK pain reported in most studies, while some reported knee as the most frequent site[24,25], a North Central Nigeria study documented low back as the most affected MSK pain site[7]. These contrasting findings may be due to differences in occupation, lifestyle as well as background RMD in the populations studied.

As in previous African studies[7,8,23], osteoarthritis was the most prevalent condition observed in our study subjects while lumbosacral spondylosis was the next in the series particularly when STR are counted individually. In a meta-analysis study conducted in Iran, osteoarthritis (16.9%), chronic low back pain (15.7%) and STR (4.6%) were observed in decreasing order as the commonest RMDs among 19,786 respondents[26]. Similarly, the 2004-2010 India bone and joint decade, after excluding non-specific MSK symptoms, found osteoarthritis (4.39%) and STR as the first and second most prevalent MSK condition respectively, among 55,000 subjects surveyed in their study population[27]. Similarly, taken together, all STR accounted for 62.7% of RMD in our study, making OA, the second most frequent condition. (n=15, 25.4%).

The bivariate data analysis showed that family history of MSK conditions, history of hypertension, obesity, abdominal obesity, hyperuricemia, elevated acute phase reactant and widespread hypermobility were associated with MSK pain. Further analysis using a multivariate logistic regression model did not find independent predictors of MSK pain. These finding contrasts with the previous Nigerian study which showed that family history of MSK symptoms and male sex were independently associated with MSK diseases among Nigerian subjects[7]. Elsewhere in Mexico, older age, physically demanding work and female sex were documented predictors of MSK symptoms[28]. Although, the predictors of MSK pain identified in various studies vary, most have not shown consistent association with MSK pain[29].

MSK diseases are one of the leading causes of disability worldwide[2-4] and reports from South America and Asia showed high burden of disability due to RMD[30]. In this study, the median HAQ-DI was 0.8, indicating mild disability. In Africa, there is paucity of reports on physical disability in subjects with RMD. Despite the high disability (significant HAQ-DI =57.5%) reported in this study and by Laatar *et al*[25] in Tunisia (significant HAQ-DI =60%), the report from Jos, Nigeria was a far cry from our figure as the significant functional disability in their study population was only 14.7%[7].

This variation in functional disability in various studies may be attributable to non-uniformity of disability assessment tools used in various studies and differences in understanding and cultural interpretation of HAQ questions by the subjects. The associated co-morbid conditions such as diabetes, hypertension, and obesity identified in our subjects may also contribute to the burden of disability.

Limitations

This was a cross-sectional study done among a non-patient community in the hospital, implying a quasi-community study. Therefore, it is neither a true hospital-based study nor a community survey. Thus its findings should be interpreted with caution for a general population. We suggest further testing of our findings with a large population-based study or a hospital based cohort study with a large sample size.

In conclusion, MSK pain is common in a Lagos tertiary hospital community and the knee was the most frequently affected site. MSK pain was common in females, middle aged and married persons and those with a family history of MSK conditions. History of hypertension, hyperuricemia, generalised hypermobility, obesity, abdominal obesity and elevated acute phase reactants were associated with MSK pain. While osteoarthritis was the commonest diagnosed RMD, high physical disability and moderate intensity of pain were also recorded in our subjects.

There is a need to increase awareness at all levels about the burden and impact of RMDs in Africa, a continent already grappling with the twin menace of infectious diseases and poverty. Government investment in rheumatic and musculoskeletal disease education both for healthcare workers and the general population is

paramount in reducing MSK burden. Access to rheumatic and musculoskeletal services should be improved in sub-Saharan Africa, where there is dearth of rheumatology manpower and lack of diagnostic and management tools[31].

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Factors associated with extra-articular manifestations of rheumatoid arthritis in Abidjan, Côte d'Ivoire

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Abstract

Objective: The aim of this study was to identify factors associated with extra-articular manifestations of rheumatoid polyarthritis in Abidjan, Côte dIvoire.
Design: A descriptive and analytical retrospective study.
Methods: The study was conducted at the Rheumatology Department of Cocody's University Teaching Hospital in Abidjan from January 2009 to December 2018. The study participants were 106 patients with rheumatoid arthritis diagnosed on the basis of ACR 1987 and ACR/EULAR 2010 criteria, with extra articular manifestations.
Results: The study included 129 cases of rheumatoid polyarthritis and 106 of them had extra-articular manifestations. The hospital frequency of extra-articular manifestations in rheumatoid arthritis was 82.17%. Our sample population were 92 females (86.79%) and 14 males (13.21%) with an average age of 44.69 years. The average duration of disease progression was 62.36 months. Extra-articular manifestations observed were largely dominated by general signs (83.86%) and haematological manifestations (78%). Other cases included rheumatoid nodules (10%), abarticular manifestations (7.62%) and dry syndrome in 8.70% of cases. Visceral manifestations were cardiovascular (3.77%), neurological (1.89%) and pulmonary in 1% of cases. Only articular deformities (OR=2.4; IC 95% = [1.4-6.3]; P=0.03) were significantly associated to the presence of extra-articular manifestations.
Conclusions: Extra-articular manifestations are very common during the rheumatoid arthritis in Abidjan. Joint deformities are the major factors significantly associated to the presence of extra-articular manifestations.

Key words: Associated factors, Extra-articular manifestations, Rheumatoid arthritis, Abidjan

Introduction

Rheumatoid Arthritis (RA) is the most common chronic inflammatory rheumatism. It is characterized by polyarthritis and Extra-Articular Manifestations (EAMs) with a frequency of around 40% of patients[1]. These EAMs may appear either at the onset or during the evolution of the disease[1]. No actual classification is known for these EAMs. On the other hand, Turesson *et al*[2] issued criteria to be included or considered as EAMs: it was a set of visceral and organic manifestations. RA with EAMs, is considered by some authors to be severe and associated with increased mortality and patients suffering from it should be treated and monitored early and aggressively[3-5]. It therefore seems important to identify these manifestations. Some authors have identified factors associated with the presence of EAMs[6,7]. In our context, the knowledge of these frequency of EAMs and the research of the associated factors motivated the realization of our study. The main objective of the study was to identify the factors associated with EAMs of RA in Abidjan, Côte dIvoire.

Materials and methods

A retrospective (descriptive and analytical) study was conducted within the Rheumatology Department of the University Teaching Hospital of Cocody in Abidjan over a period of 10 years ranging from January 2009 to December 2018. It included 106 patients with rheumatoid arthritis who met the ACR 1987 and ACR-EULAR 2010 criteria, with EAMs. Incomplete records (records that lack critical information to support the diagnosis) and records of patient's loss of sight were not included.

We recorded at socio-demographic data (age, sex), clinical data (diagnostic delay, axial and peripheral joint damage, duration of morning stiffness, presence of joint deformities), biological data (sedimentation rate (ESR), C Protein Reactive (CRP), Rheumatoid Factors (RF), anti-cyclic citrullinated peptide antibodies

(anti-CCP antibodies) and radiographic (bone erosions). We looked for an association between the various socio-demographic, clinical, biological and radiographic factors and the presence of EAMs through appropriate statistical tests: the Pearson Chi Square test for qualitative variables, the Student t-test and the Anova test for quantitative variables. The association was significant if the Odd Ratio was consistently above or below 1 with a 95% confidence interval not containing the value 1 and risk p strictly below 0.05. The study was done in accordance with the Helsinki declaration on ethical principles.

Results

The hospital frequency of EAMs in RA was 82.17%, representing 106 out of 129 patients recorded during the study period. Our sample consisted of 92 females (86.79%) and 14 males (13.21%) with an average age of 44.69 years. The average duration of disease progression was 62.36 months at the time of diagnosis. RF and anti-CCP antibodies were positive respectively in 43% and 44% of patients. The different EAMs diagnosed were general signs (fever 53 cases, altered general condition 94 cases), haematological signs (inflammatory anaemia 74 cases, thrombocytosis 10 cases, leukopenia 6 cases, Felty syndrome 2 cases), rheumatoid nodules (10 cases), secondary Sjögren's syndrome (xerostomia and xerophthalmia 2 cases each), abarticular manifestations (8 cases) and vasculitis (3 cases). The visceral manifestations was cardiac (myocarditis 1 case), pulmonary (interstitial pulmonary fibrosis 11 cases, pulmonary nodule 1 case) and neurological (cervical spinal cord compression 2 cases). Tables 1 and 2 show socio-demographic, clinical, biological and radiographic data recorded and the association between these factors and the EAMs. We also looked for a correlation between these factors and the main general signs (fever) and haematological (anaemia) respectively in Tables 3 and 4.

Table 1: Correlation between socio-demographic and clinical data with EAMs

Sociodemographic and clinical data	Presence of EAMs	Absence of EAMs	P	OR IC95%
Mean age (years)	44.69	51.39	0.47	
Gender				
Female	92	21	0.3	
Male	14	02		
Average diagnostic delay (months)	62.36	65.55	0.8	
Morning stiffness				
≥ 1 hour	78	14	0.4	
< 1 hour	17	07		
Joint deformities	54	07	0.03	(OR=2.4) [1.4-6.3]
Cervical spine involvement	49	07	0.14	
Peripheral joint damage	104	22	0.17	

EAMs = Extra-Articular Manifestations

Table 2: Correlation between para-clinical data and EAMs

Para-clinical data	Presence of EAMs	Absence of EAMs	P-value
Mean ESR (mm)	80	12	0.19
Mean CRP (mg/l)	86	18	0.24
Positive RF	52	47	0.1
Positive anti-CCP antibodies	43	26	0.47
Bone erosions	69	08	0.35

EAMs = Extra-Articular Manifestations; ESR = Sedimentation Rate; CRP = C Protein Reactive
RF = Rheumatoid Factors; anti-CCP antibodies = Anti-Cyclic Citrullinated Peptide Antibodies

Table 3: Correlation between clinical and para-clinical data and fever

Para-clinical data	Presence of fever	Absence of fever	P-value
Average diagnostic delay (months)	59.66	65.67	0.5
Morning stiffness ≥ 1 hour	46	46	0.06
Cervical spine involvement	23	34	0.2
Joint deformities	28	33	0.4
Positive RF	32	32	0,18
Positive anti-CCP antibodies	31	41	0.2
Bone erosions	38	42	0.3

RF = Rheumatoid Factors; anti-CCP antibodies = Anti-Cyclic Citrullinated Peptide Antibodies

Table 4: Correlation between clinical and para-clinical data and anaemia

Para-clinical data	Presence of anaemia	Absence of anaemia	P-value
Average diagnostic delay (months)	57	74.1	0.13
Morning stiffness ≥ 1 hour	64	28	0.09
Cervical spine involment	37	20	0.4
Joint deformities	40	21	0.4
Positive RF	40	24	0.1
Positive anti-CCP antibodies	51	21	0.2
Bone erosions	53	27	0.3

RF = Rheumatoid Factors; anti-CCP antibodies = Anti-Cyclic Citrullinated Peptide Antibodies

Discussion

At the socio-demographic level: Our hospital frequency (82.17%) was very high and reflected the fact that EAMs were commonly present in RA. This observation was also made in the literature but with much lower proportions than ours, ranging from 17.8% to 40.9%[7-9]. We did not find a significant difference in age in our study, although the high age of onset is recognized as a predictor of EAMs[7]. The clear predominance of elderly women was noted in our study and is well known by the various studies in sub-Saharan Africa and other countries[6, 9, 10-12]. Although the male sex is significantly associated in terms of prediction (risk is doubled) with the presence of EAMs and also with the occurrence of mortality, this link was not confirmed in our study[7,15].

At the clinical level: The disease had an average progression time of 62.36 months at the time of diagnosis. This reflected a long diagnostic delay that is recognized as a predictor or associated with the development of a EAMs when adjusted for age and sex[9,10]. This situation could have favored the appearance of EAMs because these patients suffering from RA did not have early and adequate management. Some publications have mentioned the fact that EAMs may appear at the onset of the disease but most often in progress[9]. Various EAMs were recorded in our study and were dominated by general signs (fever and alteration of general condition) and haematological manifestations including inflammatory anaemia. In Europe, rheumatoid nodules were the most common EAMs[3,9,16]. There were only 10 cases of rheumatoid nodules in our study (10%). However, they were rarely diagnosed in Nigeria with a frequency of 1%[9]. In our study, the other visceral or organic manifestations had similar, proportions to those found in the literature [3,9]. In sum, our high frequency of general signs could not be found in other studies and their presence reflected the systemic character of RA in our context, thus confirming Cojocaru *et al*[1] and Bartels *et al*'s[17] assertions that these EAMs appeared at an active and evolved phase of the illness[1,17]. There was no association in our study between most of the clinical factors studied and the EAMs. Only the presence of joint deformities was significantly associated to the occurrence of EAMs in our study (OR= 2.43; IC 95% = [1.4- 6.3]; P= 0.03) although according to some publications the presence of a disability predicted the presence of severe EAMs [3,9,18].

At the paraclinical level: There was an inflammatory syndrome with an average ESR and CRP of 60.38 mm and 66.59mg/l, respectively. No association was found in our study between the inflammatory syndrome and the EAMs. However, a severe RA with high activity was a risk factor for EAMs[18,19]. According to Cojoracu *et al*[1], many EAMs were linked to an active and severe RA. The positivity of RF and anti-CCP was not significantly associated with the presence of EAMs in our study. In the literature, it was rather noted that the positivity of RF was significantly related to the occurrence of EAMs and that in multivariate analysis, the positivity of RF was a predictive factor of mortality[2,6-8,20]. In addition, the presence of RF is a risk factor for disease progression and aggravation and for an increase in the frequency of EAMs[20]. The functional prognosis takes into account disabilities and bone erosions, which are the most striking elements of the severity of the disease. Bone erosions are a reflection of this joints destruction. They were not associated with the presence of EAMs according to our study. However, they were recognized as factors associated with the occurrence of severe EAMs[6].

Conclusion

EAMs are very common in RA in Abidjan. RA with presence of EAMs is more common in adult females. The diagnostic delays are long. The main EAMs are general signs and haematological manifestations. Only joint deformities are significantly associated with the presence of EAMs in our study.

The authors declare no conflict of interest.

We obtained the consent of the patients.

The study was cleared by the relevant ethics committee.

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Ocular manifestations in chronic inflammatory rheumatism

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Abstract

Objective: To contribute to the study of the characteristics of Chronic Inflammatory Rheumatism (RIC) in Guinea.
Design: Cross-sectional study.
Methods: The study was carried out over a period of nine months on patients with chronic inflammatory rheumatism and the ocular manifestations.
Results: The study population consisted of 28 patients including 10 men and 18 women, the mean age was 39.07 ± 16.04 years. The different types of rheumatism encountered were: rheumatoid arthritis (n=18), ankylosing spondylitis (n=8) systemic lupus erythematosus (n=1), juvenile idiopathic arthritis (n=1). All patients presented with ocular manifestations (100%): sicca syndrome (n=24), allergic conjunctivitis (n=5), ametropia (n=5), cataract (n=3), anterior uveitis (n=3), episcleritis (n=1), keratitis (n=1) and glaucoma (n=1).
Conclusion: Ocular manifestations during inflammatory rheumatism are frequent, the sicca syndrome was dominant.

Key words: Guinea, Inflammatory rheumatism, Ocular manifestations

Introduction

Chronic Inflammatory Rheumatism (RIC) are systemic diseases with articular and extra-articular manifestations, including ocular damage sometimes affecting all segments of the eye. Thus, the rheumatological history must be researched, regardless of the reason for ophthalmology consultation[1]. RICs can be autoimmune (rheumatoid arthritis, certain forms of juvenile idiopathic arthritis) or even autoinflammatory (spondyloarthritis: of which ankylosing spondylitis (APS) is the most frequent, juvenile spondylarthritis, rheumatism of enterocolopathies, psoriatic arthritis[2]. Ocular manifestations may exist during the course of these rheumatisms: frequent ocular manifestations have been reported in the course of Gougérot-Sjögren Syndrome (SGS) in 15% of RA[3]. Spondyloarthritis is the cause of uveitis. Inflammatory ophthalmologic lesions of rheumatoid arthritis are represented by keratitis, scleritis and episcleritis, which most often occur in old polyarthritis, which is often nodular and often seropositive[4]. Lars can be directly linked to the disease, but they can be the consequence of the therapies used. Hydroxychloroquine and methotrexate, widely used in the disease-modifying treatment of ICR are implicated in the occurrence of ocular symptoms and require ophthalmologic monitoring[5]. Several African studies have shown the importance of ocular involvement during RIC, particularly that of Sangha[6] in Ivory Coast who reported in 2014 a frequency of 37.5% (9/24) of ocular involvement in rheumatoid arthritis. In Guinea, no study has been carried out on this subject in our knowledge. Knowledge of these manifestations and the lack of previous studies motivated the realization of this study, the objective of which was to contribute to the study of the characteristics of RICs in Guinea.

Materials and methods

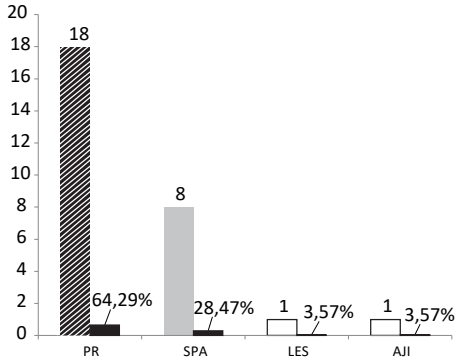
This was a cross-sectional study that lasted nine months, conducted in the Rheumatology Department of the Ignace Deen National Hospital and the Ophthalmology Department of the Armed Forces Medical and Surgical Center. This was a descriptive cross-sectional study of patients with chronic inflammatory rheumatism. The patients were randomly selected with ophthalmologic symptoms. This study was carried out from 1st February to 31st October 2017 and included patients with RIC confirmed by a rheumatologist and meeting the study criteria: rheumatoid arthritis (ACR / EULAR 2010 criterion), ankylosing spondylitis (Amor's criteria 1995), systemic lupus erythematosus (Petri 2012), juvenile idiopathic arthritis (ILAR criteria). Patients with other forms of rheumatism and those with other diseases with ocular involvement and patients who missed the ophthalmologic examination were excluded. We took into account the unconstrained informed consent of patients. The study was done in accordance with the Helsinki declaration on ethical principles. They had all

carried out a complete ophthalmologic examination including: measurement of visual acuity from far and near, the examination with the slit lamp, the fundus, break up time, Schirmer's test. 1-distance visual acuity was measured using the <<letter MONOYER >> scale for patients who could read and the SNELLEN <<E>> scale for patients who were unable to read and near visual acuity measured with the Parineau scale for those who could read and the Rosano scale for patients who could not read. The average being 10 / 10th. (i) Visual acuity is lowered or has an abnormality only when it is less than 10/10. (ii) The slit lamp examination allowed the examination of the appendages (conjunctiva, eyelashes, eyelids and eyebrows) and of the anterior segment (cornea, anterior chamber, iris, pupil, lens and anterior vitreous). (iii) The fundus examination was performed after complete pupillary dilation obtained after instillation of mydriaticum and neosynephrine either directly through the ophthalmoscope. (iv) Break-up time: This is the test most frequently performed by the practitioner due to its speed of execution and its simplicity. (v) Schirmer's test: This involves instilling a small amount of fluorescein in the butt of eye bag. We were interested in epidemiological data and the main ocular manifestations. Data analysis was carried out using Epi info 7.0.2.1.

Results

During the study period, ocular manifestations were observed in 28 cases of RIC. The workforce consisted of 18 women (64.29%) and 10 men (35.71%), for a sex ratio of 0.55. The mean age was 39.07 ± 16.04 years (range: 15 and 73 years). The different types of rheumatism encountered were: rheumatoid arthritis (n = 18), ankylosing spondylitis (n = 8), systemic lupus erythematosus (n = 1), juvenile idiopathic arthritis (n = 1) (Figure 1). Patients presented with abnormal visual acuity and manifestations on slit lamp examination, Schirmer's test, break up time. These ocular manifestations found are identifiable in Table 1.

Figure 1: Distribution of patients by type of RIC



RA=Rheumatoid Arthritis; AS=Ankylosing Spondylitis; SLE=Systemic Lupus Erythematosus; JIA=Juvenile Idiopathic Arthritis

Table 1: Distribution of patients according to the ophthalmologic examination

Ophthamologic examination	Workforce	(%)
Visual acuity normal	19	67.86
Lowered slit lamp exam	9	32.14
Normal	7	25.00
Appendices ⟶ Conjunctival irritation	18	64.29
Anterior segment *⟶ Opalescence of the lens	3	10.71
BUT		
Positive ≥ 15 s	24	85.71
Negative ≤ 15 s	5	14.29
Schirmer test		
Positive	27	96.43
Negative	1	3.57
Fundus		
Normal	26	92.86
Papillary	1	3.57
Optic atrophy	1	3.57

All patients presented with ocular manifestations (100%): sicca syndrome (85.71%), conjunctivitis allergic (17.86%), ametropia (17.86%), cataract (10.71%), anterior uveitis (10.71%), episcleritis (3.57%), keratitis (3.57%) and glaucoma (3.57%) (Table 2).

Table 2: Distribution of patients according to ophthalmologic diagnosis

Diagnosis	Number of cases	(%)
Ametropia	5	17.86
Cataract	3	10.71
Allergic conjunctivitis	5	17.86
Episcleritis	1	3.57
Glaucoma chronic	1	3.57
Superficial punctate keratis	1	3.57
Dry eye syndrome	24	85.71
Chronic anterior uveitis	3	10.71

Table 3: Distribution of patients according to rheumatologic diagnosis and ophthalmologic diagnosis

	RA		AS		JIA		SLE	
Diag Ophthalmo.	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Ametropia	3	10.71	1	3.57	0	0.00	0	0.00
Cataract	2	7.14	1	3.57	0	0.00	0	0.00
Allergic conjunctivitis	4	14.29	0	0.00	1	3.57	0	0.00
Episcleritis	0	0.00	1	3.57	0	0.00	0	0.00
Chronic glaucoma	1	3.57	0	0.00	0	0.00	0	0.00
Superf point keratis	1	3.57	0	0.00	0	0.00	0	0.00
Dry eye	15	53.57	8	28.57	0	0.0	1	0.57
Anterior uveitis	1	3.57	2	7.14	0	0.00	0	0.00

RA=Rheumatoid Arthritis; AS=Ankylosing Spondylitis; SLE=Systemic Lupus Erythematosus; JIA=Juvenile Idiopathic Arthritis

Of the patients with rheumatoid arthritis, 15 had dry eyes, or 53.57% (Table 3). Artificial tears, antiseptic eye drops, and antibiotic eye drops were the most prescribed with 81.71% and 71.43% of cases, respectively. Glasses were recommended to 4 patients (14.29%) (Table 4).

Table 4: Distribution of patients according to ophthalmologic treatment

Treatment	Number of cases	(%)
Artificial tears	24	81.71
Antibiotic eye drops	20	71.43
Antiseptic eye drops	20	71.43
Glasses	4	14.29
Automatic refraction	1	3.57

Discussion

This study focused on patients with chronic inflammatory rheumatism whose ocular manifestations was studied. In our series the patients were relatively young (mean age = 39.07 years). The results were lower than that reported by Singwe-Ngandeu *et al*[7] in Cameroon (52.7 ± 5.3 years). The female predominance found in our patients could be explained by the frequency of rheumatoid arthritis which affects more women according to the literature. Polyarthritis was common with 64.29% of cases. The mean duration of development of chronic inflammatory rheumatism study was 6.44 years with a long mean consultation time (4.19 years). This period is longer than that reported by Diouf[8] in Senegal (3.7 years). This long delay in our series would be due to socio-cultural factors (the doctor is sometimes after the marabouts and traditional therapists) and socio-economic (the poverty of the populations and the remoteness of the centers of competence, delaying diagnosis as well as management). Pain is a major symptom but in chronic inflammatory rheumatism its management is rarely independent of that of their inflammatory component. The choice of the treatment depended on the type of chronic inflammatory rheumatism mode presentation, its evolutionary stage and prognostic factors. Methotrexate, glucocorticoid and hydroxychloroquine combination was the most prescribed disease-modifying treatment. In Africa, these classic background treatments are used[9]. This would be linked to the inaccessibility of the cost of biotherapies. Regarding ocular manifestations according to some authors, dry eye syndrome is a disorder common to chronic inflammatory rheumatism. According to the literature, its prevalence varies between 17.6% and 85%. Cases of anterior uveitis have been observed in patients with AS (35.50%). Among the patients with rheumatoid arthritis (53.57%) had dry eyes. Artificial tears, antiseptic eye drops, and antibiotic eye drops were the most prescribed with 81.71% and 71.43% of cases, respectively. Glasses were recommended in 4 (14.29%) patients.

All of these patients were on anterior background treatment, uveitis is often associated with SPA and appears to be the predominant ocular manifestation in this form of chronic inflammatory rheumatism[10,11]. At an early stage, the manifestation of retinal toxicity to synthetic antimalarials is reversible. The risks of retinal toxicity are related to the dose (greater than 6.5 mg / kg / day), the dose and the duration of treatment. In a study of 526 patients, Mavrikakis *et al*[12] reported that an absence of retinal toxicity was noted during the first six years of treatment with hydroxychloroquine.

Conclusion

This study has shown that during chronic inflammatory rheumatism, ocular manifestations are frequent hence the need for the rheumatologist to look for these extra-articular manifestations as part of multidisciplinary management involving an ophthalmologist.

Conflict of interest: None to declare.

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Research article

Profiles of vitamin D among patients with rheumatoid arthritis at the Kenyatta National Hospital

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Abstract

Background: Rheumatoid Arthritis (RA) is an autoimmune, chronic debilitating condition of undetermined cause. It affects numerous extra- articular organ systems. Vitamin D is a steroid hormone synthesized in the skin by the action of ultraviolet B (UVB) irradiation. Active vitamin D is important in the inhibition of T cell proliferation and down-regulation of key inflammatory cytokines responsible for the pathogenesis of RA. There is growing evidence demonstrating the association between vitamin D insufficiency and higher incidence of RA as well as increased severity of disease and increased functional disability in RA patients.

Objective: The purpose of this study was to determine serum vitamin D levels among patients with rheumatoid arthritis at the Kenyatta National Hospital (KNH) and its association with disease activity and functional disability.

Design: This was a descriptive cross-sectional survey.

Methods: The study involved subjects with RA at the Kenyatta National Hospital. Consecutive sampling technique to recruit patients with rheumatoid arthritis, having met the 2010 American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) classification criteria was selected. Ten mls of peripheral blood was collected from the recruited subjects to determine serum vitamin D levels. Every participant had their demographics, clinical history and disease duration documented. Clinical Disease Activity Index (CDAI) was used to assess disease activity and severity. It comprised of number of tender joint out of 28 joints (T-28), number of swollen joints out of 28 (S-28) global health assessment score by both the physician and the patient level of disability was determined by the standard Modified Health Assessment Questionnaire (MHAQ). Data analyzed was correlated to determine their association with serum vitamin D levels. SPSS version 21 was used to analyze the data collected and this entailed descriptive statistics, chi-square, ANOVA and students'-test to compare and correlate vitamin D levels with age, duration of disease, CDAI score and modified HAQ score in RA.

Results: Eighty one patients with a mean age of 48.7 (SD 13.9), median of 48.0 (IQR 40.0-59.0) were evaluated. The female to male ratio was 4:1. The mean serum 25-VD concentration was 34.9ng/ml (SD11.6). Thirty five participants (43.2%) had insufficient vitamin D levels (<30ng/ml), whereas 46 study participants (56.8%) had sufficiency of vitamin D. Majority of the patients 54 (67.5%) had low disease activity. Fourteen subjects 17.5% had high disease activity and while 2.5% were on remission. Functional disability was assessed using the modified health assessment questionnaire. Thirty eight participants (46.5%) demonstrated no disability, 33.8% had mild disability while 9% had severe disability. Correlation between vitamin levels with age, duration of disease, CDAI and HAQ did not attain statistical significance.

Conclusion: Vitamin D insufficiency is high among patients with rheumatoid arthritis with no correlation with age, duration of disease, functional disability and disease activity.

Key words: Rheumatoid arthritis, Vitamin D, Disease activity, Functional disability, Cytokines

Introduction

Rheumatoid Arthritis (RA) is a chronic debilitating autoimmune disorder whose origin is not fully understood[1]. It is believed to be due to the breakdown of self-tolerance, and B and T lymphocytes are key in the occurrence of the disease[2]. Importance of T and B lymphocytes is further proved by the introduction of Biologic Disease Modifying Antirheumatic Drugs (DMARDS) in the mitigation of RA, which target both T and B lymphocytes and their cytokine profile[3]. Vitamin D is a hormone existing in the skin as an inactive molecule, pre-vitamin D, which is metabolized in the skin by action of ultraviolet irradiation[4]. Vitamin D has multiple extra skeletal

roles potentiated through its receptor, the Vitamin D Receptor (VDR). In the immune system, it acts as an immunomodulator, a property key in the regulation of B and T cells[5]. Multiple studies have found serum vitamin D to be considerably lower in rheumatoid arthritis patients compared to controls, and these levels have an inverse relationship with the activity and severity of disease in RA[6].

Significance of the study

The deficiency of 25-VD is associated with the occurrence, increased disease activity and a more aggressive disease in RA. Among the black population, various studies have shown vitamin D insufficiency even in healthy subjects due to increased melanin concentration impairing vitamin D absorption. These studies have however found considerably reduced levels of vitamin D in RA individuals in the black population compared to those without the disease[7]. In studies where vitamin D was included as part of wholesome RA management, it was noted that there was substantial improvement in disease severity in the subjects[8,9]. In Kenya, and sub-Saharan Africa, the burden of vitamin D insufficiency in RA individuals is unknown.

Objective

To determine serum vitamin D levels among patients with rheumatoid arthritis in Kenyatta National Hospital and to associate it with age, disease activity and functional disability.

Materials and methods

This was a descriptive cross-sectional study conducted in the rheumatology outpatient clinic at KNH. We included patients aged 18 years and above with a documented diagnosis of rheumatoid arthritis who gave written informed consent. The sample size was calculated using the finite population correction factor and a minimum sample size of 81 was achieved. Patients were recruited by consecutive sampling technique. Data collection was done using a structured demographic data collection tool, CDAI form and Stanford health assessment questionnaires.

Inclusion criteria

(i) Patients above 18 years.
(ii) Confirmed to have RA (as per the 2010 revised ACR/EULAR criteria for the classification of RA.
(iii) Willing to participate and signed an informed consent.

Exclusion criteria

(i) Patients taking multivitamin supplements or any form of vitamin D supplementation.
(ii) Pregnant and lactating mothers

Study variables

Dependent variable

Serum 25-hydroxycholecalciferol: Determined by serum immunoassay. The vitamin D was analyzed using High Performance Liquid Chromatography (HPLC). It was extracted from serum using acetronitryl with 0.4% acetic acid. This was injected into a chromatographic column, Polaris C18-A 3µ 150 x 2.0mm. HPLC uses isocratic mode with eluent (MeCN: 0.4% Acetic acid) as the mobile phase. The flow rate was 0.3mls/min and oven temperature 30 degrees Celsius, and detector will be UV-V at wavelength of 280nm. The amount of vitamin D3 was determined by matching the retention of pure standard and a calibration code.

Independent variables

(i) *CDAI score:* To determine disease activity and severity.
(ii) *Modified HAQ:* To determine functional disability in rheumatoid arthritis patients. It was determined by the Stanford HAQ 8-Item disability scale.
(iii) *Duration of disease from time of diagnosis*: This was stratified at five-year.

Data management and analysis

Each study questionnaire was assigned with a unique study serial number to prevent duplication of data collection. A computer that is protected with a pass word was used to enter the data collected in Microsoft access. The data entered in Microsoft access was integrated into the Statistical Package for Social Sciences (SPSS) software version 21. The socio-demographic characteristics, medical history and vitamin D levels were used to determine the means, standard deviations, medians, proportions and frequencies for continuous data and proportions, frequencies and percentages for categorical data and correlation analysis. Statistical findings where p value of less than 0.05 were considered significant. The findings of this study were presented using tables and graphs.

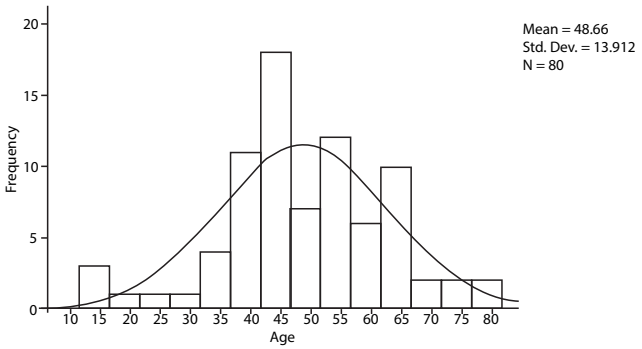
Results

The study participants were relatively young patients with a mean age of 48.7 (median 48). Sixty-five (81.3%) of the participants were female, while 15 (18.8%) were male, giving a female to male ratio of 4:1. Majority of the patients were married, 70% and 55% had received secondary education. Serum 25-VD concentrations ranged from 19.08 to 57.56. The mean (SD) serum 25-VD concentration in this study population was 34.9 ng/ml with a median of 33.6 (11.2) ng/ml and an inter-quartile range of 24.0 - 44.2ng/ml (Table 1). Thirty five (43.2%) participants had insufficient vitamin D levels. No patient was found to have severe vitamin D deficiency of <10ng ml. Ten percent of the subjects had serum vitamin D levels below 20ng/ml.

Table 1: Socio-demographic characteristics of the study participants (n= 81)

Characteristic	Frequency (%)
Age	
Mean (SD)	48.7 (13.9)
Median (IQR)	48.0 (40.0-59.0)
Range	14-78
Age (years)	
<30	5 (6.3)
30-45	33 (40.0)
46-60	27 (33.8)
Above 60	16 (20.0)
Sex	
Male	16 (18.8)
Female	65 (81.3)
Marital status	
Single	18 (22.5)
Married	55 (70.0)
Widowed	7 (7.5)
Level of education	
None	4 (5.0)
Primary	10 (11.3)
Secondary	44 (55.0)
Tertiary	23 (28.7)

Figure 1: Age distribution of the study participants- Histogram



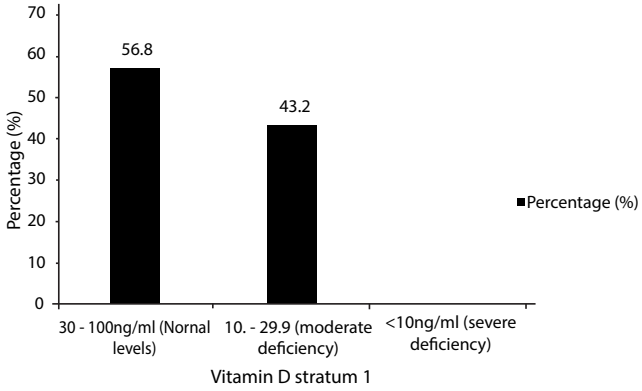


Table 2: Laboratory characteristics of the study population

Characteristic	Frequency (%) (n=80)	95% CI
Serum vitamin D		
Mean (SD)	34.9 (11.6)	
Median (IQR)	33.6 (24.0-44.2)	
Range	16.0-64.4	
Serum vitamin D Stratum 1		
>100 (toxicity)	0	
30 -100ng/ml (Normal levels)	46 (56.8)	(47.2-69.5)
10.-29.9 (Moderate deficiency)	35 (43.2)	(21.6-42.7)
< 10ng/ml (Severe deficiency)	0	
Serum vitamin D Stratum 2		
≥ 20	72 (90.0)	(80.7-95.3)
< 20ng/ml	9 (10.0)	(4.7-19.3)

Table 3: CDAI score in patients with RA

Characteristic	Frequency (%) (n=80)	95% CI
Mean (SD)	14.3 (17.1)	
Median (IQR)	7 (5.0-14.5)	
Range	2-74	
CDAI score		
Remission <0-2.8	3 (2.5)	(0.6-8.6)
Low activity 2.9-10	54 (67.5)	(56.0-77.3)
Moderate activity 10.1-22.0	10 (12.5)	(6.5-22.2)
High activity 22.1-76	14 (17.5)	(10.2-27.9)

We estimated the disease activity of the patients using the CDAI score. Majority of the patients 54 (67.5%) had low disease activity, while 10 (12.5%) had moderate disease activity. Fourteen subjects 17.5% had high disease activity while 2 (2.5%) patients were on remission.

Table 4: HAQ in patients with RA

Characteristic	Frequency (%) (n=80)	95% CI
No disability 0	38 (46.5)	(36.3-58.9)
Mild disability 1	27 (33.8)	(23.8-45.3)
Moderate disability >1 <2	6 (7.5)	(3.1-16.2)
Severe disability >2	9 (11.3)	(5.6-20.8)

Functional disability was assessed using the modified health assessment questionnaire. Thirty-eight (46.5%) participants demonstrated no disability, 27 (33.8%) had mild disability; 6 (7.5%) participants had moderate disability, while 9 (11.3%) had severe disability.

Discussion

The study population was on long term follow up for rheumatoid arthritis (RA). The mean (SD) serum 25-VD concentration in this study population was 34.9 ng/ml with a median of 33.6 (11.2) ng/ml. We found a prevalence of vitamin D deficiency of 10%, and insufficiency of 43.2%. This is lower than what is reported in RA patients in other studies done in Europe, Asia, North America and North Africa. A study done in the US showed a vitamin D insufficiency and deficiency of 84% and 43% respectively[10]. In Amsterdam, 37% of the subjects had vitamin D deficiency while 39% had insufficient levels[11]. An Egyptian study demonstrated 99.1% of patients with RA to have vitamin D insufficiency[12]. In Africa, despite adequate tropical sun exposure, vitamin D levels are thought to be low because of low dietary calcium intake, and increased vitamin D turnover because of high infectious disease burden. Increased melanin is also thought to inhibit proper sun penetration thus leading to reduced vitamin D conversion. There are suggestions that skin colour may influence vitamin D levels. Racial differences in vitamin D deficiency have been reported, with 47%, 54%, 26% and 41% in Asian American, African American, White and Mexican Americans respectively. There is no study reporting the prevalence of vitamin D deficiency in the Kenyan population[13]. Studies have however reported the prevalence of vitamin D deficiency in cancer and HIV patients. Among men with prostate cancer, vitamin D deficiency was found in 88.9%[14]. In a study done among HIV-infected patients in Nairobi, 39% were vitamin D deficient, while 34% were insufficient[15].

Some of the differences observed in vitamin D levels across different populations may be attributable to the cut-off levels adopted by the authors. There are no universally accepted cut-off levels for deficient, insufficient and sufficient vitamin D levels. Recent investigations have suggested that the threshold for vitamin D deficiency should be the 25-VD level below which PTH secretion begins to rise. The authors of these studies have proposed that the cutoff value for vitamin deficiency may be as high as 32ng/ml[16-18] although most studies have adopted <20ng/ml, <30ng/ml and > 30ng/ml for deficiency, insufficiency and sufficiency respectively. For instance, Nesby-O'Dell *et al*[20] used a lower cut-off of 10ng/ml for insufficiency, thereby possibly underestimating the number of subjects with deficiency.

The prevalence of vitamin D deficiency mirrors population vitamin D levels. In normal populations where the prevalence of vitamin D deficiency is high, the same is reflected, at a higher prevalence among RA patients. For instance, in India, a study on vitamin D status in the normal population found a prevalence of 40-100% deficiency in the general population[21]. It is thought that the high prevalence of vitamin D deficiency in the general population in Middle East, India, Turkey and Pakistan is due to inadequate exposure to sunlight because adults, especially women, are covered in veils[21]. In Kenya, a normal population study found a mean vitamin D level of 65.5ng/ml (26.25-114.75) [22].

In our study, all the 81 (100%) patients were on DMARDS which are the cornerstone drugs in the management of RA. These drugs have been shown to mitigate RA manifestations as well as reducing disease activity and improving quality of life. The use of DMARDS in the patients might be the explanation to reduced functional disability and reduced disease activity in the patients. Also, proper follow up and management in a tertiary institution with specialist doctors may be the explanation for better disease control in the patients.

Conclusion

This study found a relatively high prevalence of vitamin D insufficiency in the study population. In long- term rheumatoid arthritis patients, looking for other correlates of disease mitigation like vitamin D levels is prudent. The study however cannot show the causal association between disease activity, age and functional disability with vitamin D levels.

Recommendations

This study recommends further studies needs to be done to explore:

(i) Vitamin D profile – case-control studies in patients with and without rheumatoid arthritis.

(ii) Interventional studies analyzing the impact of vitamin D replacement on rheumatoid arthritis outcomes in patients with vitamin D deficiency.

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A prospective cohort of gouty arthritis patients presenting with hyperuricemia and chronic kidney disease stage 3 and 4 for the safety, efficacy and renal effect of febuxostat at Changhai Hospital, Shanghai, China

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Abstract

Background: Hyperuricemia (HU) is a risk factor for the onset of Chronic Kidney Disease (CKD) and accumulating evidence significantly associates it with disease progression. A major challenge in treating hyperuricemia with traditional Urate-Lowering Drugs (ULDs) are the adverse effects associated with the accumulation of these drugs or their metabolites in CKD patients. Due to these unwanted effects, doses of ULDs are down-regulated to levels commensurate with the kidneys' ability to excrete their metabolites. This leads to suboptimal efficacy. Febuxostat, a selective Xanthine Oxidase (XO) inhibitor has demonstrated high efficacy in reducing Serum Uric Acid (SUA) levels and is well tolerated in mild kidney disease. However, its efficacy, safety and renal effects have not been studied in patients with advanced kidney disease, hyperuricemia and gout.

Objective: To evaluate the safety, efficacy and renal effects of febuxostat in patients with HU, gout and CKD stage 3 and 4.

Design: This was a 16-week prospective study, single-center, open-label, self-controlled trial.

Methods: Thirty five patients included received febuxostat 40mg/day. Changes in kidney function tests; SUA levels; liver function tests and full blood count were evaluated. Gout was diagnosed based on 2015 ACR/EULAR criteria, and GFR was estimated using the MDRD formula.

Results: Febuxostat decreased SUA levels to a target <360micromol/L for uncomplicated gout in 5 (36%), n=14, and SUA decreased to a target<300micromol/L for complicated gout in 5 (24%), n=21. Changes in eGFR and SUA were statistically significant, with p=0.001 for both at 95% confidence interval. Mean absolute eGFR from baseline to week 16 represented 9.04 ml/min (19.05%), and was attributed to febuxostat (R^2= 0.9556, 96%). Changes in LFTs and full blood count were insignificant. No drug- related AE were reported.

Conclusion: Febuxostat, as a ULD was safe and effective in controlling SUA levels in patients with gout, hyperuricemia and CKD stage 3 and 4. The drug also exerted renoprotective effects in this patient group. The reduction in SUA by febuxostat was associated with improvement in eGFR and overall kidney function, although a causal relationship wasn't evaluated in this study.

Key words: Chronic kidney disease, Febuxostat, Hyperuricemia, Uric acid, Safety, Efficacy, Renoprotective effects

Introduction

Hyperuricemia has been associated with adverse outcomes in CKD. Recently, evidence has accumulated showing that HU has a role in the pathogenesis of hypertension, metabolic syndrome, cardiovascular disease and the progression of CKD, indicating the necessity for treatment even in the absence of symptoms of gouty arthritis[1]. HU is well known to be even more prevalent in patients with CKD[2,3] and has been reported to be a risk factor for kidney dysfunction[4-6]. The mechanism underlying the progression of kidney dysfunction by activation of XO has also been reported by Liu *et al*[7]. Activation of XO increases Reactive Oxygen Species (ROS) production and oxidative stress, as well as Uric Acid (UA) production, and causes vascular damage and organ dysfunction. Indeed, ROS is known to inactivate Nitric Oxide (NO) production and activates Renin-Angiotensin System (RAS), resulting in endothelial dysfunction and/or tubular injuries [8,9]. Alternatively, UA salts activate inflammasomes, triggering inflammation and leading to the development of tubular injuries[10,11]. Antihyperuricemic XO inhibitors are believed to suppress renal dysfunction via oxidative stress reduction and suppression of endothelial dysfunction and tubular injuries[12].

The incidence and prevalence of gout and HU are increasing worldwide secondary to a multitude of factors,

especially changes in dietary intake and lifestyle in both developed and developing countries[13].

According to Saag and Choi[13], global prevalence rate of gout ranges between 2.6% and 36%. Prevalence of HU in mainland China is estimated at 13.3% (19.4% in men and 7.9% in women) and that of gout stands at 1.1%[14]. These estimates are similar to the United Kingdom and Germany where prevalence stands at 1.4%. In the European Union (EU), the statistics are somewhere between 0.9% and 2.5%[15] with a twofold preponderance towards men[16,17].

These figures are comparable to those observed in other developed countries, such as the United States where diagnosed gout cases have been estimated at 2.13%[18]. The authors[18] found males to be more than twice as susceptible to have gout as their female counterparts. Additionally, citizens older than 65 years were observed to have the highest estimated prevalence standing at 4.9% diagnosed gout cases.

Accumulating data support an increase in the prevalence of gout that is potentially attributable to recent shifts in diet and lifestyle, improved medical care, and increased longevity[13]. The authors[13] identify non-modifiable (age and sex) and modifiable (obesity, use of diuretics, high purine intake both in food and beverages) risk factors as major drivers of HU and gout. The disease burden of chronic gout is substantial, both in social and economic terms. Patients with acute gouty flares or chronic gout experience lower health-related quality of life due to pain, activity limitation, and disability[19,20]. Work-related activity and productivity are also negatively impacted in this population[21]. In addition, the small subset of patients suffering from chronic gout refractory to conventional therapy experience a disproportionally greater overall disease burden. Furthermore, gout usually exists with a multitude of comorbidities, not the least of which is CKD. This further compound the problem of treatment options[21]. HU is not only a risk factor for the onset of CKD[4], but it is also significantly associated with its progression[14] and it is more prevalent in patients with CKD[3]. The world over, CKD is estimated to affect between 11-14% of adults in industrialized countries[22,23].

A number of ULDs exist to manage HU. However, most of them are either used with caution or contraindicated altogether in CKD due to their untoward adverse effects[24]. Owing to this, doses of ULDs are downgraded, which leads to suboptimal efficacy[24]. Febuxostat has been shown to be highly efficacious in reducing SUA and is reported to be well tolerated in patients with mild-moderate kidney dysfunction[25]. However, very few studies have addressed the safety, efficacy and renal effects of febuxostat in subjects with a cocktail of hyperuricemia, gout and stages 3 and 4 CKD. This study has set out to evaluate the safety and efficacy of febuxostat at a dose of 40mg/ day in the management of HU in gouty arthritis patients with CKD stages 3 and 4.

Materials and methods

Study design: This study was a 16-week prospective, single-center, open-label, self- controlled trial to evaluate the safety, efficacy and renal effects of febuxostat in patients with HU, gout and CKD stage 3 and 4. HU was defined as SUA above 420umol/L, and CKD stage 3 as eGFR between 60 and 30ml/min/1.73m^2, while CKD stage 4 was eGFR below 30ml/min/1.73m^2. GFR was estimated using the Modification of Diet in Renal Disease (MDRD) formula, and gout was diagnosed in a step-wise manner using the combined 2015 American College of Rheumatology/ European League Against Rheumatism (EULAR) collaborative initiative gout classification criteria[26]. The domains of this classification criterion included clinical, laboratory and imaging. The entry criterion, which formed the first step, required the occurrence of at least one episode of pain, swelling or tenderness of a peripheral joint or bursa. The second step sought the presence of Monosodium Urate Monohydrate (MSU) crystals in a symptomatic joint, bursa or in a tophus. The presence of MSU was diagnostic for gout and no further scoring was required. If sufficient criterion were not met, step 3 studied clinical considerations: under pattern of joint or bursa involvement during symptomatic episode, a score of 1 was assigned to ankle or mid-foot involvement (without involvement of the first metatarsophalangeal (MTP) joint), and 2 was for involvement of the first MTP joint as part of monoarticular or oligoarticular episode. Under characteristics of symptomatic episode, erythema overlying affected joint (either patient reported or physician observed), inability to bear touch or pressure to affected joint and great difficulty with walking or inability to use affected joint was assigned 1 score each.

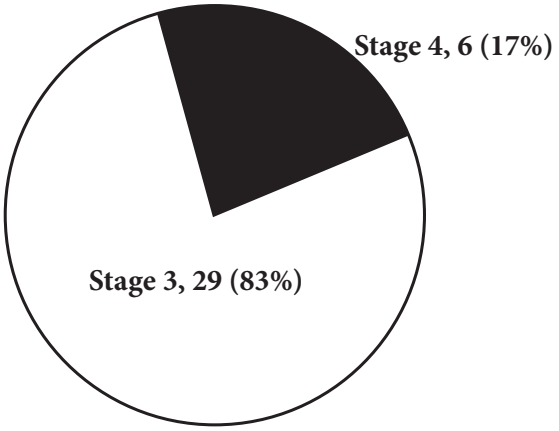
Study procedures: The first primary endpoint was the safety and tolerability of febuxostat. All suspected relationship between AEs and adverse reactions and the study drug was reported by the primary attending physician and evaluated based on the clinical course for AEs (timing of the event and reversal of event by cessation of the medication) and laboratory changes for the adverse reactions. 'Possibly' indicated that, although a relationship between the AE and the study drug could not be excluded, the probability that they were connected was considered to be fairly low. 'Probably' indicated that the probability that AE and the study drug were related and considered to be relatively high. The second primary end point included relative (%) change from baseline of SUA. The first secondary endpoint comprised of the achievement rate of the target SUA of 360 umol/L for uncomplicated gout and 300umol/L for complicated disease. Complicated gout is tophiceous gout or the presence of nephrolithiasis (as guided by the 2016 EULAR evidence-based recommendations for the management of gout)[5]. The final secondary endpoint studied the relative (%) changes in eGFR at 16 weeks from their baseline levels.

Data analysis: Statistical packages used for data analysis were SPSS (version 22, IBM 2013, USA) and MS Excel using the following methods therein: Descriptive statistics - measures of central tendency and dispersion were used to report the findings on the demographics and other study parameters. Inferential Statistics – the student t-test (Wilcoxon) and comparison of two means were used to test the hypothesis and ascertain general associations between various variables.

Results

Description of patients according to stage of renal failure: One hundred percent of the patients under study (n=35) had either stage 3 or stage 4 CKD. Twenty nine patients, representing 83% had stage 3 renal failure, and 6 (17%) patients had stage 4. Figure 1 depicts a graphical representation of patient distribution. All the study participants (n=35) were on febuxostat 40 mg once daily.

Figure 1: Patient distribution according to stage of renal failure

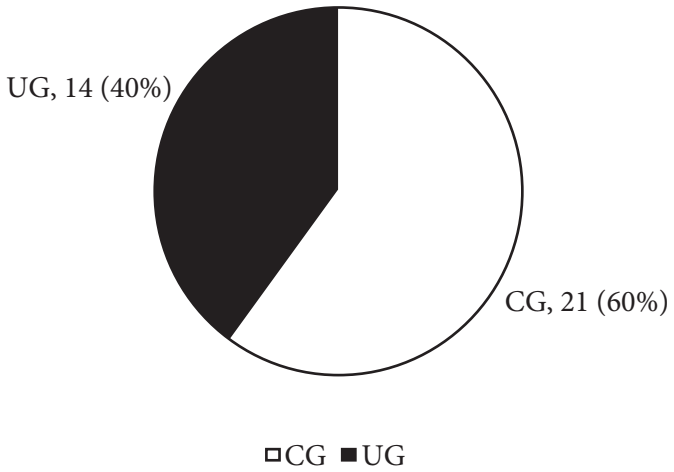


Presence of nephrolithiasis and tophi (complicated gout): Of the 35 patients studied, 35 patients, representing 100% had history of tophi and/or nephrolithiasis recorded. Out of these patients, 21, representing 60% had a history of nephrolithiasis and/or tophi (complicated gout) (Table 1, Figure 2), and 14 patients, representing 40% did not.

Table 1: Patient history of nephrolithiasis/tophi

Characteristics	Frequency	(%)
No	14	40
Yes	21	60

Figure 2: Patient distribution into complicated and uncomplicated gout



UG= Uncomplicated Gout; CG= Complicated Gout

Renal function parameters: Table 2 displays data on the renal functions using standard parameters of measurement. Foremost, descriptive statistics and trend line analysis has been done for the parameters of renal function for the period of 5 months. During a period of 5 months of assessment of patients on febuxostat, results on renal function were recorded. The parameters used to assess renal function were serum creatinine, BUN, UA and eGFR. For the purposes of the paired sampled t-test used, the month 1 was the baseline or the pre-test result and month 5 as the outcome or post-test after febuxostat treatment. Therefore, the descriptive statistics for each parameter are for month 1 and month 5.

Table 2: Descriptive statistics of renal parameters

Statistics			95% Confidence Interval
Mean	Serum creatinine(umol/L) at month 1	141.869	131.376 - 152.802
	Serum creatinine(umol/L) at week 5	125.923	111.444 - 143.787
	BUN (mmol/L) at month 1	9.4783	8.0175 - 10.8848
	BUN (mmol/L) at month 5	9.6289	7.9109 - 11.6472
	Uric acid (umol/L) at month 1	610.557	566.461 - 650.216
	Uric acid (umol/L) at month 5	347.266	327.634 - 368.859
	eGFR (ml/min) at month 1	47.4546	43.1637 - 51.6152
	eGFR (ml/min) at month 5	56.4886	50.0713 - 63.1101
Median	Serum creatinine (umol/L) at week 1	135.000	125.000 - 141.000
	Serum creatinine (umol/L) at week 5	113.000	105.000 - 127.000
	BUN (mmol/L) at month 1	8.3000	7.5000 - 10.0000
	BUN (mmol/L) at month 5	8.1000	7.3300 - 8.9000
	Uric acid (umol/L) at month 1	610.000	560.000 - 683.644
	Uric acid (umol/L) at month 5	340.000	310.000 - 364.000
	eGFR (ml/min) at month 1	50.7375	41.5642 - 54.9400
	eGFR (ml/min) at month 5	55.1867	49.4811 - 65.8852
Std. Deviation	Serum creatinine (umol/L) at week 1	34.2355	23.5661 - 43.0866
	Serum creatinine (umol/L) at week 5	48.6479	24.7631 - 69.2266
	BUN (mmol/L) at month 1	4.29422	2.91041 - 5.21149
	BUN (mmol/L) at month 5	5.64731	2.47575 - 7.82762
	Uric acid (umol/L) at month 1	129.6423	101.5358 - 154.1640
	Uric acid (umol/L) at month 5	61.2968	41.6308 - 77.9505
	eGFR (ml/min) at month 1	12.85501	9.33068 - 16.07469
	eGFR (ml/min) at month 5	19.77694	14.59987 - 24.08033

Renal function results: Table 3 shows a paired sampled t-test for renal function results of 1 month and 5 month categories.

Table 3: Renal function results

Paired samples T-test (n=35)								
Parameter		Paired Differences			95% Confidence	t	DF	P-value
		Mean difference	Std. Deviation	Std. Error Mean	Interval of the Difference			
Serum Creatinine	Srmcrtmonth1 Srmcrtmonth5	15.9457	32.3550	5.4690	4.8314 -27.0600	2.916	34	0.006
BUN	Bunmonth1bunmonth5	-0.15057	4.01324	0.67836	-1.52917- 1.22803	-0.222	34	0.826
Uric Acid	Urratemonth1 Urratemonth5	263.291429	118.8772	20.0939	222.4557 - 304.1272	13.103	34	0.001
eGFR	Egfrmonth1egfrmonth5	9.03394	11.28210	1.90702	5.15841 – 12.90948	4.737	34	0.001

Change in eGFR results over the study period (month 1 to month 5): The change in eGFR for all the patients (n= 35) was studied and recorded. Figure 3a and 3b show the absolute figures of the change in eGFR from month 1 to month 5.

Figure 3a: Changes in eGFR for 18 patients (from 1 to 18)

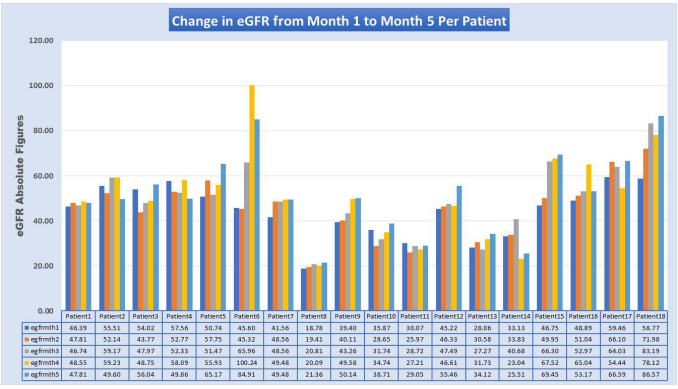
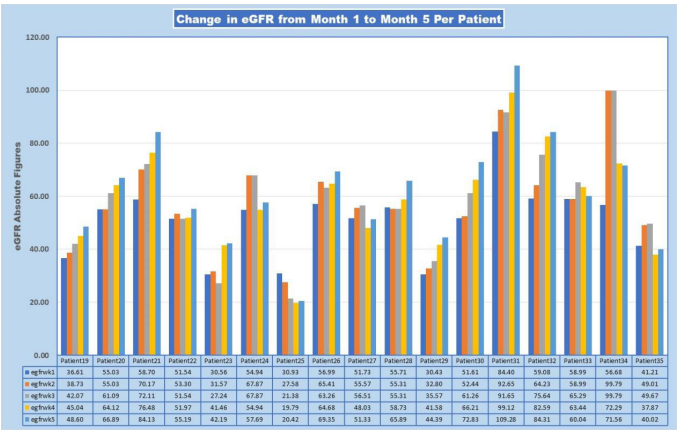


Figure 3b: Changes in eGFR for 17 individual patients (from 19 to 35)



Summary of changes in eGFR for 35 patients: To summarise the change in eGFR, Figure 4a depicts a graphical representation of the mean change every month for 5 months. The R^2 shown (0.9556) in the graph below indicates that 96% of changes in eGFR in patients across the period of 5 month is explained by the treatment given to the patients. Figure 4b shows this change in percentage form. The R^2 shown (0.9568) in the graph means that 96% of changes in eGFR in patients over the 5 month-period can be attributed to the febuxostat administered to the patients.

Figure 4a: Mean changes in eGFR for all the patients (n = 35)

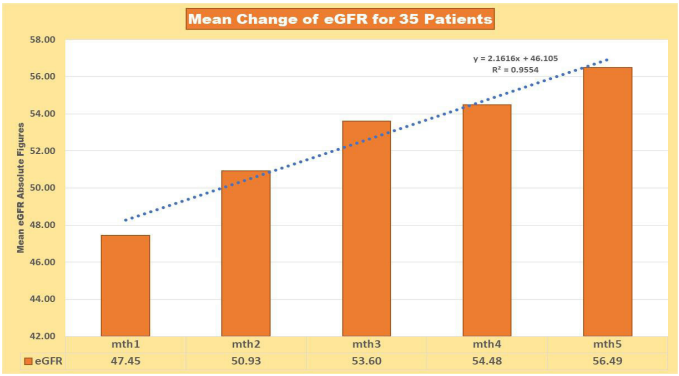
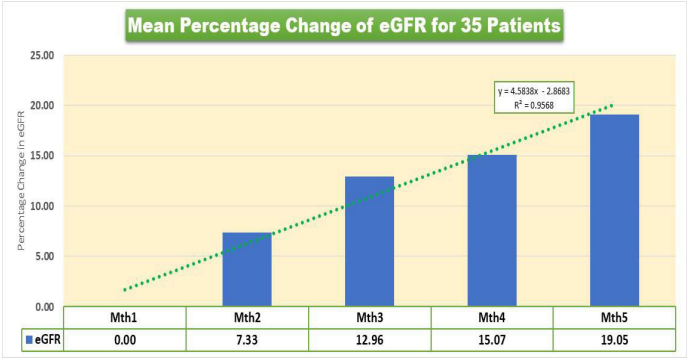


Figure 4b: Percentage change in eGFR for all the patients (n=35)



Full blood count results – Paired sample t-test test statistics: Using the paired sampled t-test. Table 4 shows the statistics test result of the named parameters.

Table 4: Full blood count results

Paired samples T-test (n=35)								
Parameter		Paired Differences			95% Confidence	t	df	P-value
		Mean difference	Std. Deviation	Std. Error Mean	Interval of the Difference			
WBC	Wbcmth1 Wbcmth5	-0.10667	1.82604	0.43040	-1.01474 – 0.80140	-0.248	17	0.807
RBC	rbcmonth1 rbcmonth5	-0.07643	0.37932	0.10138	-0.29544 – 0.14259	-0.754	17	0.464
Haemoglobin	hemmonth1 hemmonth5	-6.1111	13.9743	3.2938	-13.0604 – 0.8381	-1.855	17	0.081
PLT count	ptlcmonth1 ptlcmonth5	1.5000	52.3419	12.3371	-24.5290 – 27.5290	0.122	17	0.905

Liver function test statistics results: Using paired sampled t-test statistic, the following are the results for the parameters used in the study.

Table 5: Liver function results

Paired samples T-test (n=35)								
Parameter		Paired Differences			95% Confidence	t	df	P-value
		Mean difference	Std. Deviation	Std. Error Mean	Interval of the Difference			
ALT	Altcmonth1 altmonth5	-4.6000	17.9250	4.0081	-12.9892 – 3.7892	-1.148	19	0.265
AST	astmonth1 ast-month5	-4.4000	15.6555	3.5007	-11.7270 – 2.9270	-1.257	19	0.224
TB	tbmonth1 tb-month5	-1.5444	6.5998	1.5485	-4.8115 – 1.7227	-0.997	17	0.333
TP	tpmonth1 tp-month5	-1.5400	7.7723	3.4759	-11.9905 – 8.1105	0.443	4	0.681
ALB	Albmonth1 Alb-month5	0.7200	3.9865	1.7828	-4.2299 – 5.6699	0.404	4	0.707
ALP	Alpmonth1 Alpmonth5	-31.4000	34.1585	15.2761	-73.8133 – 11.0133	-2.055	4	0.109
LDH	Ldhmonth1 Ldhmonth5	5.8000	65.7548	29.4665	-75.8454 – 89.4454	0.197	4	0.853

Discussion

This study had three findings. We demonstrated that febuxostat was safe and tolerable in patients with stages 3 and 4 CKD; we showed that the drug was efficacious in reducing SUA levels in this patient group, and we proved that febuxostat possesses renoprotective effects by not only halting the process of renal dysfunction, but also reversing kidney injury and improving renal function indicators, such as eGFR.

Up until febuxostat was approved for use in HU and gout, there were several attempts at controlling SUA levels using ULD, like allopurinol in patients with CKD. These attempts proved futile for various reasons: Firstly, allopurinol, another XO inhibitor, is excreted in urine, and its serum concentration and AE increase in patients with CKD, requiring dose adjustments from early stages of CKD and resulting in poor control of SUA levels[12]. Secondly, Paisansinsup *et al*[27] report the rate of possible or definite AEs of allopurinol in CKD to range from 10.5% to 13.9% depending of the stage of CKD. Our study demonstrated that these statistics are much worse than the safety profile of febuxostat. Thirdly, the active metabolite of allopurinol, oxypurinol, which is associated with AE, is increased in patients with CKD[12]. Finally, Yamaguchi *et al*[12] reported several studies that have indicated severe Allopurinol Hypersensitivity Syndrome (AHS) in patients with CKD that could prove fatal. This syndrome has not been reported to occur with febuxostat, and our study recorded no cases related to hypersensitivity syndrome.

Becker *et al*[28] assert that although incidence is low and severity is mild-moderate, headache, dizziness, diarrhoea, nausea, rash, cramps and twitches (muscle-related adverse effects) and liver function abnormalities are AE frequently observed with febuxostat. Our study didn't record any patient- reported AE, and the analysis of liver function tests at baseline and at week 16 was statistically insignificant. Additionally, the increased rate of flares associated with febuxostat initiation were not observed in this current study since flare prophylaxis was

initiated concurrently with febuxostat according to a study by Khanna *et al*[29].

Schumacher *et al*[30] and Becker *et al*[28] raised concerns about increased cardiovascular events (non-fetal MI, non-fetal stroke and cardiovascular death) to the risk of events associated with febuxostat. For these events to likely occur, the patients should have a history of cardiovascular disease and/or risk factors for developing cardiovascular disease[30]. White *et al*[31] reported a higher risk of adverse cardiovascular events associated with febuxostat more than allopurinol. However, it can't be ascertained if these cardiovascular events could purely be attributed to febuxostat, or if there is a role of underlying HU which is in itself a risk factor for cardiovascular disease[32,33]. Although baseline CVS investigations such as echocardiogram were outside the scope of this study, we didn't record worsening cardiovascular status in patients with existing CVD, and we did not observe any new CVS pathology that we could tie to febuxostat.

Our study showed no evidence of haematologic abnormalities contrary to reports in the WHO newsletter[34] of 13 patients with agranulocytosis, and Kabayashi *et al*[35] who reported cases of acute neutropenia associated with febuxostat in patients with CKD. Although Choham[36] reported early severe immunological reactions like Stevens-Johnson syndrome (SJS) in patients taking febuxostat, the majority of these patients with immunological reactions also had a history of allopurinol hypersensitivity and/or renal impairment. Therefore, it is inconclusive if these reactions could purely be attributed to febuxostat. Our study recorded no cases of immunological reactions.

Several reasons have been advanced to support the impressive safety profile of febuxostat as compared to other ULDs. Firstly, febuxostat is primarily metabolized in the liver[12]; secondly, the drug is 49.1% excreted in urine and 44.9% through faeces[37]. Therefore, febuxostat possesses strong anti-hyperuricemic effect without serious AE even in patients with CKD without dose adjustments[38,39]. Thirdly, febuxostat is highly selective in its mechanism of action, and finally, the drug is not uricosuric and thus, is less likely to cause urolithiasis[37].

Hosoya and Ohno[40] studied pharmacokinetic and pharmacodynamic properties of febuxostat in patients with mild-to moderate kidney failure. They reported that although renal dysfunction caused an increase in systemic exposure to unchanged febuxostat, the noted increase was slight in patients with mild-to-moderate renal dysfunction. No AEs were observed, and unchanged febuxostat or its metabolites did not accumulate after repeated exposure[40]. Although our study did not collect and analyse pharmacokinetic and pharmacodynamic data, it can be assumed with confidence that the safety and tolerability of febuxostat is high even in the presence of advanced CKD.

The percentage of patients on febuxostat constant dose of 40mg/day who achieved target SUA levels of 360micromol/L or less for uncomplicated gout, as recommended by the 2016 EULAR evidence-based recommendations for the management of gout[15], was 36%, and those that reached SUA of 300micromol/L or less for complicated gout were 24%. A large study with longer follow-up time which addressed febuxostat efficacy in patients with moderate-to-severe renal dysfunction found febuxostat to reduce SUA levels to 360micromol/L in 44%, 46% and 60% of patients with mild renal dysfunction who were taking 80, 120, and 240mg/day of febuxostat, respectively[38]. Becker *et al*[39] reported that patients with CKD stage 3 on 40 and 80mg/day of febuxostat achieved SUA levels 360 micromol/L in 43.1% and 71.3% of cases, respectively. From the foregoing, 80 mg/day of febuxostat reduced SUA to 44% in mild CKD, and 40mg/day of febuxostat reduced SUA levels below 360 micromol/L in 43.1% in CKD stage 3. Our study evaluated patients with moderate-to-severe CKD with uncomplicated and complicated gout, while applying stringent SUA levels of below 300micromol/L for complicated gout. Additionally, febuxostat dose was kept at 40mg/day throughout the study period of 16 weeks. Although previous studies[39,38] have shown better efficacy at higher doses of febuxostat, our study was limited to 40mg/day due to cost constraints.

Our study found that febuxostat was efficacious in reducing SUA levels in patients with advanced renal dysfunction and complicated or uncomplicated gout. Before the advent of febuxostat, allopurinol was the only available ULD, but its dose needed downward adjustment to levels commensurate with the kidneys' ability to excrete its metabolites[12]. Furthermore, the efficacy of allopurinol is much less than that of febuxostat, more so with the reduced doses permissible in patients with kidney failure[39]. Nakaya *et al*[24] reported that in Japan physicians limit the dose of allopurinol to only 100mg/day in CKD stages 4 and 5, rendering its use as ULD in this patient group ineffective.

Iseki *et al*[4] and Koratala *et al*[6] have demonstrated that HU is a risk factor for the progression of kidney dysfunction in the general population and CKD patients. As a result, ULDs are expected to contribute to renal protection. Additionally, Becker *et al*[41] reported that in patients with either mild or no renal dysfunction, taking 40–120mg of febuxostat/day for 5 years improves eGFR by 1ml/min from baseline for every 60 micromol/L decrease in SUA.

In this study, we showed that lowering SUA resulted in improved eGFR in CKD patients, with an absolute mean improvement in eGFR from baseline to week 16 of 9.04 ml/min and a mean percentage change of 19.05%. Although we didn't evaluate the direct relationship between absolute change in SUA and absolute change in eGFR, our findings support the hypothesis postulated by Goicoechea *et al* [42] and Sircar *et al*[43] that lowering SUA levels by ULDs in patients with CKD ameliorates eGFR reduction, and is therefore, renoprotective. Whereas Levy *et al*[44] reported that renal dysfunction could be suppressed with ULDs in patients with controlled SUA levels at <360micromol/L, our study found that deterioration of kidney function could be suppressed in patients with SUA

levels controlled more strictly in patients with complicated gout.

The mechanism by which febuxostat is renoprotective is not well understood, although several theories have been advanced. Johnson *et al*[45] suggests that ULDs block RAS, resulting in a decrease in glomerular hypertension, which in turn preserves GFR. Additionally, the authors assert that ULDs confer a renoprotective effect by suppressing uric acid's oxidative stress on the endothelium.

HU and XO activation are vascular injury factors. XO activation increases oxidative stress, suppresses NO production, and activates RAS[9,46]. Sánchez-Lozada *et al*[46] reported that HU induces arteriolopathy of pre-glomerular vessels, impairing endothelial function and the autoregulatory response of afferent arterioles, resulting in glomerular hypertension. ULD, febuxostat is thought to improve these vascular events by inhibiting XO and suppressing HU.

Conclusion

Febuxostat, as a ULD was safe and effective in controlling SUA levels in patients with gout, HU and CKD stage 3 and 4. The drug also exerted renoprotective effects in this patient group. The reduction in SUA by febuxostat was associated with improvement in eGFR and overall kidney function, although a causal relationship was not evaluated in this study.

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Research article

Treatment of chronic inflammatory joint disease in Zanzibar: impact of the Covid-19 pandemic

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Abstract

Background: The Covid-19 pandemic has had a major impact on economies and health globally. It has also affected the availability of drugs such as hydroxychloroquine, commonly used in rheumatic disorders.

Objective: The aim of this study was to describe the impact of the Covid-19 pandemic among patients with chronic inflammatory joint disease.

Methods: A study on chronic inflammatory joint disease in Zanzibar was undertaken in July 2019 and is ongoing. So far, 38 participants have been recruited and were included in the present study. These participants were contacted for phone interview regarding information on self-reported disease activity, joint pain and swelling. Patients were also asked about adherence to medication, Covid-19 symptoms, household expenditure and quality of life during the pandemic.

Results: At baseline, 38 patients, mostly females (92%), had been enrolled. The mean age was 45 years and mean disease duration was 3.5 years. Majority had moderate and severe disease activity (58%). For this study, 33 patients were reached for interview. The majority reported joint pain (91%) and swelling (52%). Twenty four (73%) noted their disease activity to be better than before joining the ongoing study. Only 13 (39%) reported symptoms of Covid-19. Adherence was generally lower during the pandemic (52%) compared to baseline (58%) although this was not statistically significant. About a third of participants were unable to quantify their expenditure. Of the remainder, 13 (39%) participants reported a decrease.

Conclusion: The pandemic had a negative impact on patients due to lack of funds to purchase drugs and unavailability of drugs such as hydroxychloroquine which is cheaper compared to alternatives. We believe that the overall improvement in disease activity may be attributed to management that had been commenced prior to the pandemic.

Key words: Arthritis, COVID-19, Health expenditure, Zanzibar, Medication adherence

Introduction

Chronic Inflammatory Joint Diseases (CIJD) reduce health-related quality of life substantially due to pain and immobility, among others[1,2]. The prevalence is estimated to be 0.13-2.5%[3]. Coverage of effective Disease Modifying Anti Rheumatic Drugs (DMARDs) are low in African countries[2]. By large, rheumatic disorders have so far been neglected in low-income health systems, and many patients remain undiagnosed and untreated[4]. The Covid-19 pandemic has influenced health systems and economies all over the world, and there is now growing concern that this leads to disinvestments of essential non-Covid-19 services like DMARDs in rheumatic disease[5,6]. Therefore, there is a need to learn more about how Covid-19 indirectly affects patients with CIJD.

Evidence has shown that DMARD therapy in sufficient dosage significantly improves patient outcomes[7]. However, most studies that evaluate effect of DMARDs are conducted in settings with optimal access to drug therapy where patients can be reviewed regularly in the health system. This is not the case in many low-income countries. Additionally, the modes of routine care and patient reviews have had to undergo significant changes in such settings during the Covid-19 pandemic. Not much is known about how DMARDs influences patient outcomes in low-income settings like Zanzibar. A study in Egypt reported an increase in disease flares among patients with CIJD in the cities with more Covid-19 cases[8].

Covid-19 continues to affect people worldwide and the World Health Organisation estimates that over 65 million people had been infected and over 1.5 million had died by December 2020. Although it is difficult to make sound predictions about the disease[9], it is well known that it causes increased mortality for the elderly and those with underlying

health conditions[10]. Furthermore, many countries, including Zanzibar, have implemented restrictive public health policies like home office, home school, quarantine, closing restaurants and public transport regulations[11]. These restrictive policies have many negative societal and indirect health effects. There is an urgent need for the development of an effective vaccine to stop infections. Until then, it is important to maintain public health measures and protect the vulnerable from acquiring the disease, but also to get a better understanding of indirect health effects of Covid-19 on other diseases and their management in the health system[12].

In this case study we describe patient characteristics, disease activity, anti-rheumatic treatment as well as socio-economic factors in patients with CIJD in Zanzibar before and during the Covid-19 pandemic.

Materials and methods

Design: A mixed-methods descriptive study was undertaken. The first part is the quantitative component comparing findings at baseline and during the Covid-19 pandemic. The second part is qualitative and selected patient cases are presented to illustrate personal experiences and how the Covid-19 pandemic had affected them regarding their disease and its management.

Setting: The Zanzibar islands (Unguja and Pemba) are a semi-autonomous region of Tanzania, with a population of about 1.46 million[13]. The main referral hospital, Mnazi Mmoja Hospital, is based at Unguja island. This is currently the only hospital with rheumatology care, and where DMARDs are prescribed. A research project on treatment and diagnostics of patients with Rheumatoid Arthritis (RA), psoriatic arthritis and ankylosing spondylitis was initiated in 2019. Enrolled patients were closely monitored and included in a follow-up study. Before the pandemic, the included patients had started to improve vastly because of intensified treatment and follow-up that had already been initiated.

Study population: From September 2019, all patients with a clinical diagnosis of RA, psoriatic arthritis or ankylosing spondylitis were informed of the study and invited to participate. At the time of this write-up 38 patients had been recruited.

Inclusion criteria: Patients aged ≥18 years with a clinical diagnosis of RA, ankylosing spondylitis or psoriatic arthritis were included. Written and informed consent was obtained from all included patients. Prior to the phone interview, informed consent was acquired.

Quantitative data: The following data were registered at the first visit (the baseline visit): age, year since first symptoms, year of diagnosis, medication used in management, comorbid illnesses, tender and swollen joint count, lab results for complete blood count, liver function tests, erythrocyte sedimentation rate, chest X-ray reports and hand X-ray reports. Baseline disease activity score -28 (DAS 28) and Clinical Disease Activity Index (CDAI) were also registered. Questionnaires were completed for medication adherence, income and total household expenditure.

Data on total household expenditure was collected using specific questions on health and non-health expenditures of households in Tanzanian shillings. For the first three clinic visits, patients were asked to quantify how much they had spent on reaching the hospital, acquiring treatment and care, payment for alternative medicine and caretakers. They were also asked about total household expenditure on household items, food, clothing, utilities, transport, education, rent, healthcare, insurance, repairs and loans.

At the first visit, patients are informed of the diagnosis, educated on their disease, its progression and management. Key messages include chronicity of the disease, information concerning medical treatment and precautions in relation to pregnancy, as well as restriction of steroids and non-steroidal anti-inflammatory drugs to prescribed use. Medication was prescribed according to a pre-defined treatment protocol in adherence to internationally recommended guidelines which recommend early and targeted therapies using DMARDs[14].

Interview data: For the present study, all patients were contacted by phone for interview. Six of the interviews were conducted face-to-face. Patients were asked to describe their symptoms during the Covid-19 pandemic as compared to baseline. They were asked whether they had any painful or swollen joints, and whether they felt their disease had improved, stayed the same or deteriorated. Medication adherence was also investigated, and the following questions were addressed: When was the last time they took their DMARD, and was it taken on time as prescribed, or did they ever forget to take it? Did they ever run out of their medication, or experience difficulties obtaining it at their local pharmacy in terms of availability? Had there been difficulties obtaining funds to purchase their medication during the pandemic?

For Covid-19 symptoms, we used a questionnaire with a variety of symptoms categorised as systemic, respiratory, neurological, and gastrointestinal. Patients answered yes or no to whether they or any of their immediate family members had experienced any of these symptoms within the last month.

Concerning the household expenditure, participants were asked about monthly expenditure on the various parameters similar to that of the baseline visit. They were asked to give as exact figures as possible, and these were used for comparison.

Qualitative cases: Patients accounts and experiences are described to illustrate their personal experiences during the pandemic. The choice was of critical cases of patients who had undergone difficulties in managing their disease because of the pandemic. This was either from loss of income or unavailability of hydroxychloroquine.

Statistical analysis: Descriptive statistics were used for the presentation of patient baseline characteristics. Data from the interviews, self-reported disease activity and adherence are presented as percentages. Total household expenditure before and after the Covid-19 pandemic was assessed using the paired T-test.

Ethics: Ethical approval was obtained both from the Zanzibar Health Research Institute (ZAHRI) and Norway Research Ethics Committees (2019/472/REK vest), respectively.

Results

Thirty eight patients were included in the study (mean age 45 years, 92% women). Patient characteristics registered at the baseline visit (when the patient was included in the study) are presented in Table 1.

Table 1: Patient characteristics at baseline (n=38)

Characteristic	No. (%)
Gender (% women)	92
Age (mean, SD)	45 (13)
Disease duration (mean, SD years)	3.5 (3)
Time to diagnosis (mean, SD years)	2.6 (3)
Disease activity at baseline (n, %) *	
Remission	3 (8)
Low	12 (33)
Moderate	16 (41)
Severe	7 (17)
Medication at baseline (n, %)	
No DMARD	12 (28)
Methotrexate (MTX)	21 (58)
Hydroxychloroquine (HCQ)	1 (1)
MTX + HCQ	4 (11)
Prednisolone	18 (50)
Comorbidity (n, %)	
Hypertension	4 (11)
Malignancy	1
Diabetes mellitus	2
Education	
No formal education	7 (19)
Incomplete primary school	4 (11)
Primary school	2 (6)
Completed O-levels	18 (44)
Completed tertiary education	7 (19)

Self-reported disease activity, medication adherence and Covid-19 symptoms: Overall, there were 33 interview respondents, an equivalent of 86% response rate of whom 30 (90%) were women. The findings from the interviews regarding self-reported disease activity, medication adherence and Covid-19 symptoms are summarised in Table 2. The majority of patients (91%) reported some level of pain in the joints while 52% reported swelling of at least one joint. Medication adherence was overall low (52%), and 45% reported difficulties obtaining funding for their medication (Table 2). Assessment of adherence at baseline showed it to be 58% in the same cohort of patients.

Table 2: Covid-19 phone interview response (n=33)

Response	No. (%)
Self-reported disease activity (n, %)	
Pain*	30 (91)
Swelling**	17 (52)
Disease activity	
Worse	9 (27)
Better	24 (73)
Self-reported medication adherence (n, %)	
Adherent	17 (52)
Difficulties obtaining medication (availability)	12 (36)
Difficulty acquiring funds for medication	15 (45)
Self-reported Covid-19 symptoms (n, %)	13 (39)

*Self-reported pain in any joint
** Self-reported swelling in any joint

Total household expenditure: Changes in household economy are presented in Table 3. Of the 33 participants, 13 reported a reduction in total household expenditure and the monthly household expenditure decreased from 668,700 to 502,900 Tanzanian shillings on average per month, equivalent to 288 and 216 US dollars, respectively. This was predominantly reported as a cutting down purchases on clothing and household items. Seven patients had a reduction in expenditure on food items from baseline mean of 408,600 to 287,500 Tanzanian shillings (USD 176-123) per month during the pandemic. Analysis of the change in expenditure showed the difference to be non-significant (P-value 0.08). Ten patients (30%) were unable to quantify their total household expenditure during the interview. This was either because they had moved during the pandemic to live with relatives or because they were not heads of the households.

Table 3: Change in total household expenditure during Covid-19 (n=33)

Expenditure	No. (%)
Household expenditure (n, %)	
No change	10 (30)
Increased	0
Decreased	13 (39)
Unable to quantify	10 (30)

Patient cases

Case 1

A patient in her 20s had been treated with methotrexate for RA in the last 10 years and her disease activity was low during that period. She was enrolled in this study in September 2019. Two months after enrolment, she switched to hydroxychloroquine (HCQ) therapy in preparation for pregnancy. During the pandemic, the drug was unavailable at all government hospital pharmacies and could only be purchased at a few privately owned pharmacies. It had been indicated that HCQ was a potential treatment for Covid-19 leading to subsequent massive over-the counter purchases of HCQ in Zanzibar and stockpiling by individuals, leading to stock outs at the pharmacies supplying it. Her income had not been affected.

The patient was advised to switch to sulfasalazine, which she could unfortunately not take because of an allergy to sulphur. She was then offered azathioprine as an alternative; however, this proved to be unattainable because of lack of availability. She was fortunate enough to receive HCQ as donation, but due to drug scarcity and the need to extend her supply, the patient took it once a day instead of her prescribed twice daily dose. This led to worsening disease activity to moderate. She was also taking prednisolone 5mg once daily sporadically during episodes of severe joint pains. Fortunately, over the remainder of her pregnancy, the patient has received further donations of hydroxychloroquine and has delivered a healthy baby boy. We hope she will continue receiving the drugs from well-wishers so that she will be able to continue breastfeeding her baby.

Case 2

This was a patient with symptoms of RA since 2004 and diagnosis was set in 2019 and methotrexate dose titrated to 25mg weekly. At baseline, disease activity score -28 (DAS28) was 3.56/ Clinical Disease Activity Index (CDAI) 16.5 indicating moderate disease activity. Resulting from dose adjustment she reached remission on follow-up. In late February 2020, she requested a switch to a pregnancy-safe drug due to plans of conception. She was therefore switched to HCQ and planned for routine follow up. Unfortunately, she presented in mid-March reporting a lack of availability of HCQ in the pharmacies for the same reasons as the patient in case 1. Sulfasalazine was prescribed as an alternative, but due to costs (0.30 USD/ 500mg tablet) it was not considered a feasible option for this patient. The patient is unemployed and depends on her brother for her health care expenses. She has been restarted on methotrexate and postponed conception until second line drugs are either available or affordable.

Case 3

A middle-aged patient was diagnosed with RA in 2018 after having had symptoms for 6 years. At the time of enrolment, she had moderate disease activity with severe joint deformity, especially of the hands, and was treated with both methotrexate and HCQ at doses of 25mg weekly and 200mg twice daily, respectively.

The patient sells snacks and sweets to schoolchildren to supplement her income (<200 USD/month) to purchase her medication. Upon school closure due to the Covid-19 outbreak her income was drastically reduced, and she was unable to afford both methotrexate and HCQ. When she presented to the hospital with these concerns, her disease activity was moderate. Fortunately, methotrexate is available at the government hospital pharmacy as an injectable and was provided to her. Hydroxychloroquine however was not. After two injections, she expressed the inconvenience of having to come to the hospital every week for her medication and opted to source methotrexate via her own means. She continues to take methotrexate as a single drug with low dose steroids for disease control. Patient is adherent to medication and has low disease activity.

Discussion

In this descriptive study the major findings were poor adherence to prescribed drug treatment and a reduction in total household expenditure during the Covid-19 pandemic. We found that more than 50% of patients interviewed were not adherent to the prescribed DMARDs, due to either loss of funding or availability of the drug. One expects that upon diagnosis and initiation of treatment patients would become more adherent especially with regular follow up. Although we cannot determine causality, it is likely that this is associated with the pandemic, as the cases illustrate.

Similarly, a study done in Egypt by Abualfadl *et al*[8] found disruptions among patients with RA in obtaining their medication. Adherence at baseline was 58%, but there is reason to believe it would be even higher after study-onset as the patients received information regarding the importance of drug treatment. Thus, the observed reduction during the pandemic is counter to what would be expected, and the most likely explanation is the pandemic.

A disruption or down-scaling of DMARD treatment will, in time, result in worsening of RA disease activity[15].

This was not seen in our study. In fact, the majority of patients reported improvement in disease activity. This self-reported improvement in disease activity is probably due to initiation or up-scaling of DMARD therapy during the original study. As the treatment effect of most DMARDs, and hydroxychloroquine in particular, is protracted, ranging from 3 to 6 months, possible adverse effects of disrupted treatment on disease activity could not be expected during the short time-span of this study and the pandemic.

There is significant out of pocket expenditure for healthcare among households in African countries[16]. The pandemic also led to disturbing reports on decline in total household expenditure[17] and is likely to be at least partly responsible for the reported difficulty in acquiring funds for medications, as reported by 45% of our patients. As the pandemic continues with resulting fall in national economies and resulting drop in household incomes, we fear that loss of follow-up and disruption or down-scaling of DMARDs will subsequently lead to increased disease activity.

Hydroxychloroquine and chloroquine in general have been banned for use in malaria in Tanzania since the development of resistance by malaria parasites in the year 2001[16]. Its use for RA is neither registered in the pharmacies nor is it in the Zanzibar treatment guidelines. It is however of significance, particularly in younger women, as it may be taken during pregnancy and lactation. With the announcement of hydroxychloroquine as a potential drug in the treatment of Covid-19, many individuals purchased the little that was available in the pharmacies for stockpiling, in the event that they or their families might require the drug. Attempts to re-purchase them resulted in a drastic hike of the price, making it non-feasible as a treatment option. These events rendered patients on hydroxychloroquine left with the option of sulfasalazine as a second line for those who could afford it. It is almost twice the price of HCQ. Leflunomide is not available on the island. The drastic shortage of HCQ that was seen in Zanzibar is similar to what was reported across several African countries by the African League Against Rheumatology (AFLAR) survey that found over 60% of rheumatologists experienced shortages of HCQ and almost a quarter had to switch from HCQ to other therapies[18].

Tanzania did not conduct community-wide testing for Covid 19. We assessed for Covid-19 infection using a symptoms questionnaire. In our study, 13 patients reported Covid-19 symptoms. Although there are multiple Covid-19 symptom questionnaires in use, no studies have verified their sensitivity and specificity for diagnosis. Furthermore, there is no study looking at the combination of symptoms and their sensitivity in predicting Covid-19 infection[19,20]. Therefore, even if a participant had symptoms, we have no way to verify whether they truly had Covid-19.

The study limitations included the insufficient sample size and subsequent lack of statistical power to evaluate the impact of Covid-19 in this patient group taking into consideration the challenges inflicted by the pandemic. The time span was also too short for the assessment of the effect of in-adherence to DMARD therapy. This report, describing three cases and a small study cohort, does, however, provide an illustration of the challenges inflicted on patients with inflammatory joint disease by Covid-19, in Zanzibar. Final results from the ongoing inflammatory arthritis study will be published in forthcoming articles.

Study strengths include the use of mixed methods on a prospective cohort in order to clearly highlight patient experiences during the pandemic.

Conclusion

Covid-19 has had a major impact on the global economy. On a more individual level, the majority of patients in this study were adversely affected with a drop in total household expenditure during the Covid-19 pandemic, probably reducing drug adherence. Because RA does not present as an acute and life-threatening medical need, patients may opt to skip medication and bear their pain to meet basic needs. This does not lead to catastrophic health expenditure but does in the long-term lead to adverse outcomes on morbidity and mortality. Patients who were on hydroxychloroquine therapy were also directly affected because of the lack of availability of medication and no cheaper alternative. Many will have to revert to monotherapy and steroid bridging until a sustainable solution is acquired, with subsequent expected side effects.

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Clinical and radiological features of neuropsychiatric systemic lupus erythematosus: case series from East Africa

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Abstract

Neurological and psychiatric manifestations of Systemic Lupus Erythematosus (NPSLE) are clinically diverse, may occur early in the disease, and can be the first manifesting symptom. A high index of suspicion is thus required in such cases to allow timely diagnosis and appropriate treatment in order to avoid irreversible damage of the brain. Magnetic Resonance Imaging (MRI) may offer a diagnostic clue, and several patterns have been described in the literature. We present here a series of cases of NPSLE with index neurological symptoms and uncommon MRI brain findings: diffuse white matter changes, optic tract signal change, slow dural venous sinus flow, and large non-dominant hemisphere stroke. The diagnosis of NPSLE was missed in the initial presentations, but was only made when the clinical picture, these MRI features and laboratory findings were put together for each case. Our case series highlight the broad spectrum of neurological manifestations and MRI brain scan findings in NPSLE.

Key words: Neuropsychiatric systemic lupus erythematosus, Magnetic resonance imaging, Stroke

Introduction

Systemic Lupus Erythematosus (SLE) is a classic multi-system autoimmune disease, more common in women and those of African origin[1]. Neuro-psychiatric presentations (NPSLE) occur in up to 75% of cases[2], and there are 13 recognised patterns of neurological syndromes encompassing both the central (CNS) and peripheral nervous system[3]. The commonest CNS symptoms are impaired cognition, seizures, headaches, and stroke[4], in addition to other diverse neurological symptoms[5], which pose a diagnostic challenge compounded by other mimicking insults such as SLE medications or concurrent infections[6]. NPSLE symptoms occur relatively early in the disease, correlate with disease activity levels, and are associated with higher SLE-related mortality and morbidity[7].

The pathophysiology leading to CNS damage in NPSLE is thought to be a combination of vascular insults, direct neuronal injury, precocious atherosclerosis and embolisms[8]. Magnetic Resonance Imaging (MRI) of the brain is the modality of choice for investigating CNS involvement in NPSLE, and MRI abnormalities correlate with clinical and immunological features[9], including on post-mortem examination[10]. Interestingly, up to 40% of NPSLE cases have normal MRI brain scans[11]. Abnormal brain MRI findings in NPSLE are largely classified into[12]:

(i) *Vascular:* Which includes small vessel disease, resulting in White Matter Hyperintensities (WMH) and cortical atrophy (both of which are the commonest abnormal findings on MRI in NPSLE[11] at 30-75% and 15-20% respectively), and large vessel disease causing strokes which are probably the most debilitating but occur less frequently at 10-15%[13].

(ii) *Inflammatory/demyelinating*: Characterised by ill-defined hyperintensities involving either grey or white matter and not conforming to vascular territories on T2 or Fluid-Attenuated Inversion Recovery (FLAIR) sequences, sometimes with contrast enhancement. These neuroradiological features are less frequent at around 7% of NPSLE cases[11], and demyelination is one of the rarer CNS manifestations of NPSLE[5].

NPSLE in Africa has been reported from the northern[14-16], western[17] and southern[18] regions of the continent; the study from South Africa focused on the neuroradiological correlates of the disease and interestingly MRI abnormalities were more common than other studies at 81.9% of NPSLE cases[18].

Materials and methods

We report here four cases of newly diagnosed NPSLE patients from East Africa who fulfil the international diagnostic criteria[3,19] managed at our regional tertiary referral centre, whose

MRI brain scans were conspicuously heterogeneous and not well described in the literature but were vital towards the eventual diagnosis and management in each case.

Case reports

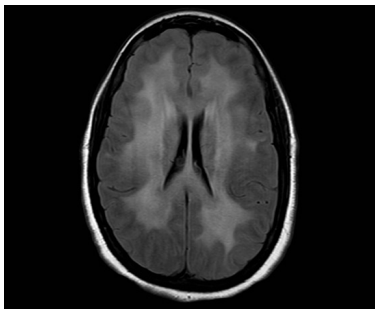
Case 1

A 41-year old female self-referred to our facility from Tanzania, having been evaluated in the interim in The Netherlands with no clear diagnosis. She presented with a six-month history of new-onset continuous migraine-sounding headaches with dizziness, unresponsive to standard therapies. Latterly, she experienced gait imbalance resulting in falls, and then intermittent painful swelling of her ankle, wrist and knee joints. Positive findings on physical examination were neck stiffness, nystagmus with broken pursuit of eye movements, brisk reflexes in the limbs, and inability to tandem walk; her joints had non-specific swelling. Laboratory investigations showed a normocytic anaemia with haemoglobin 8.4 g/dL (normal range, NR, 11.5 – 16.5), but otherwise normal kidney, thyroid, liver, and inflammatory marker profiles, with negative serum Angiotensin Converting Enzyme (ACE) levels and HIV serology testing. MRI brain scan [Figure 1(a) through (c)] revealed confluent bilateral symmetrical T2 and FLAIR white matter hyper-intensities extending to the brainstem, superior and inferior cerebellar peduncles, with patchy pachymeningeal and basal leptomeningeal but no parenchymal enhancement. Cerebrospinal Fluid (CSF) analysis revealed normal constituents including white cell count and protein, and was negative for Gram and Zeel-Neilsen (ZN) stains, Gene Xpert, adenosine deaminase levels, and viral PCR for Herpes Simplex, Epstein Barr and cytomegalovirus (HSV, EBV, and CMV). CT scan of the abdomen and chest revealed bilateral axillary and pelvic lymphadenopathy, and an ultrasound-guided biopsy of the axillary node showed non-specific inflammation. She was reviewed by a rheumatologist (author FOO), and a subsequent autoimmune panel revealed positive speckled Anti-Nuclear Antibodies (ANA), with a high titre at 1:640 (NR: negative), Low C3 complement at 0.85 g/L (NR 0.9 – 1.8) and positive Anti-smith antibody (NR: negative), as well as a strongly positive Anti-Phospholipid Antibody (APLA), all of which confirmed the diagnosis of SLE.

She was pulsed with methylprednisolone 1 gram daily for 3 days, followed by rituximab infusion and was thereafter discharged on mycophenolate mofetil, hydroxychloroquine, gabapentin and tapering doses of prednisone. She reported marked improvement over subsequent months, and her headaches resolved after 6 weeks. Follow up MRI brain scan done at six months and a year later [Figure 1(d) and (e)] revealed significant interval decrease in the extent of abnormal white matter T2/FLAIR hyperintense signals in the supra-tentorial and infra-tentorial brain, and no new abnormalities.

Figure 1: Magnetic Resonance Imaging (MRI) Fluid-Attenuated Inversion Recovery (FLAIR) sequences of the brain of Case 1. There is extensive confluent white matter hyperintensities on axial [images (a) and (d)], coronal [images (c) and (e)], and sagittal [image (b)] views, with improvement in respective images after >6 months of NPSLE treatment [images (d) and (e) when compared to (a) through (c)]

(a)



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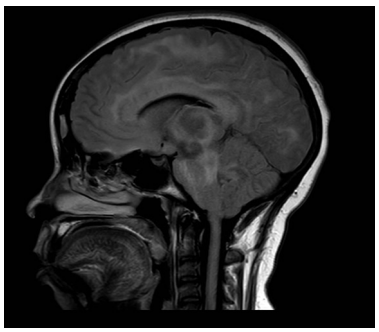

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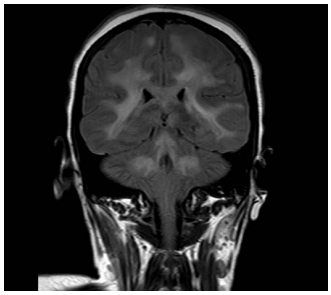

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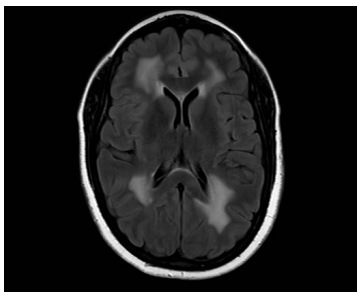
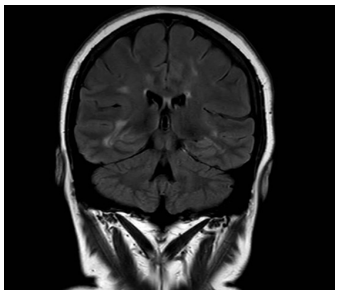


(e)



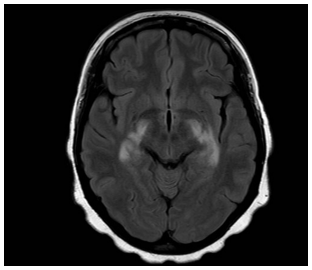
Case 2

A 47-year-old female presented to our rheumatology clinic with one month history of polyarthralgia, proximal upper limb myalgia and periorbital swelling, but no skin or mouth ulcers. Her examination revealed restricted shoulder movements, tenderness in the arm muscles, but no other stigmata of connective tissue disease. She was however noted to have a smooth, non-pulsatile goitre. She was due for further clinical work-up but got lost to follow up until she attended the endocrinology clinic with ongoing joint pains, worsening neck swelling and now additional visual obscuration, not accompanied with headaches. On examination by the ophthalmologist, she was found to have epiphora, mild periorbital oedema with conjunctival chemosis but no proptosis, and lid retraction with no impairment in extraocular muscle motility, and no abnormalities in the posterior segment. Blood tests revealed Thyroid Stimulating Hormone (TSH) 10.84 μIU/mL (NR 0.27 – 4.2); free T4 0.58 ng/dL (NR 0.89 – 1.52) and high titres of antibodies to thyroid-specific peroxidase at > 1000 IU/ml (NR 0 – 8); thyroid ultrasound showed heterogeneous enlarged thyroid gland so she was initiated on thyroxine replacement.

Her visual symptoms did not improve and an MRI scan of the orbits done at an external facility reported features of idiopathic orbital inflammatory disease rather than thyroid ophthalmopathy, so she was referred to a neurologist (author DSS) for further evaluation. MRI brain scan (Figure 2a) revealed non-enhancing, non-restricting bilateral symmetrical T2/FLAIR hyperintense signals within the optic chiasm and retro-chiasmatic optic tracts up to the level of the occipital lobes, with extension into the adjacent temporal lobes, posterior limbs of the internal capsule and peri-trigonal white matter. An auto-immune panel revealed positive speckled ANA (titre 1:320), positive Extracted Nuclear Antibodies (ENA) for SM/RNP and SSA/Ro, but negative anti-double-stranded DNA (dsDNA). These results confirmed NPSLE so after consultation with the rheumatologist she was started on mycophenolate mofetil, hydroxychloroquine and prednisone. She reported resolution of her joint pains two months later, and repeat MRI brain scan showed complete resolution of the abnormalities (Figure 2a).

Figure 2: MRI FLAIR sequences of the brain of Case 2 showing white matter hyperintensities along the optic chiasm to optic tracts on axial [images (a) and (d)], coronal [images (b) and (e)], and sagittal [image (c)] views, with improvement in respective images after 2 months of immunosuppression [images (d) and (e) when compared to (a) through (c)]

(a)



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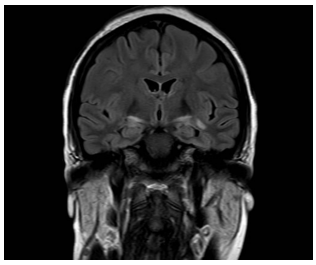

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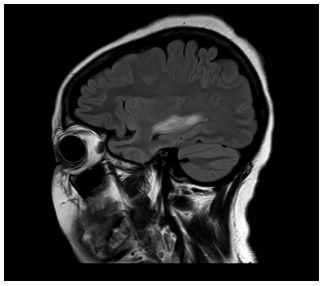

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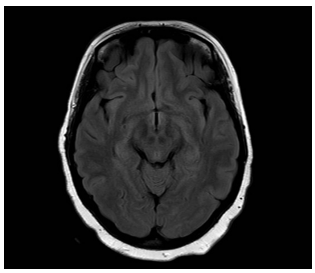

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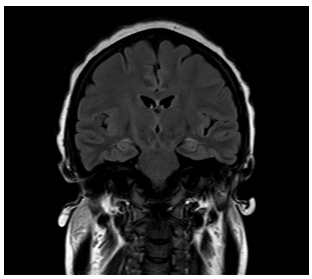


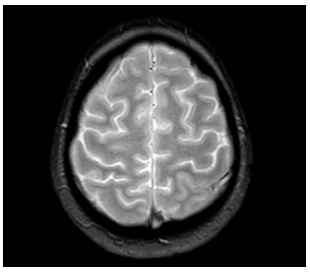
Case 3

A 16-year-old female was seen in the rheumatology clinic with unexplained chest pains, a facial rash and finger swelling for one month, and on clinical suspicion of a connective tissue disorder was treated with mycophenolate mofetil, hydroxychloroquine and prednisone. However, one month later she was admitted to our critical care unit because of new headaches, confusion, fevers and generalized weakness. MRI brain scan was normal except for high T2 and FLAIR signal in the left vein of Trolard with absence of blooming on gradient echo sequences, likely representing sluggish flow rather than thrombosis (Figure 3a). CSF studies were negative, and her laboratory tests from her rheumatology clinic were reviewed as she was found to have a positive ANA (positive speckled 1:640 titre), dsDNA and ENA (for Sm, Sm/RNP, SSA and SSB antibodies).

We therefore diagnosed NPSLE and she was pulsed with 1 gram intravenous methylprednisolone daily for five days with some improvement in her headaches, then three days later started having hallucinations, refusing oral medications and food, and catatonic posturing with hypersalivation. She received psychotropic medication but continued to have labile mood, abnormal mannerisms and episodes of confusion so we initiated intravenous cyclophosphamide and her symptoms gradually improved. She was discharged from the hospital one month later after the admission date, and continued outpatient cyclophosphamide for six doses and was thereafter continued on hydroxychloroquine, mycophenolate mofetil and a tapering dose of prednisone. She was able to resume school four months later and repeat scans showed resolution of the anomaly (Figure 3b), and to date she has had no flare up of her SLE.

Figure 3: Axial gradient echo (T2*) MRI sequences of Case 3 showing the blooming along the left vein of Trolard [image (a)] which resolved after 3 months of immunotherapy [image (b)]

(a)



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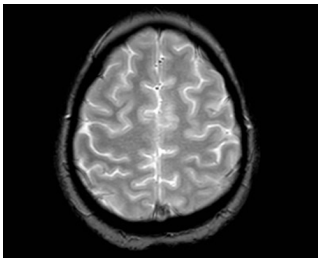


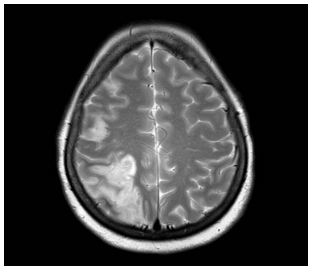
Case 4

A 31-year-old female initially presented with chest pain and progressive breathlessness found to be due to an unprovoked segmental Pulmonary Embolus (PE) with no known risk factors, and a thrombophilia screen was negative. She was managed by the haematology team and treated with rivaroxaban for 6 months, towards the end of which she began to suffer initially episodic then constant right-sided migraine-sounding headaches. Her husband then noted she was bumping into furniture on her left hand side and she was struggling to drive so she was admitted under our neurology service. On neurological examination she had a left homonymous hemianopia but no other neurological deficit. Neuro-imaging confirmed large sub-acute right hemisphere ischaemic strokes [Figure 4(a) and (b)], with normal venography and angiography.

As per our in-hospital stroke pathway, we requested a 'young-onset stroke' investigation panel including cardiac evaluation (24-hour holter monitor and trans-oesophageal echocardiogram) and laboratory tests which were all normal except for elevated Erythrocyte Sedimentation Rate (ESR) of 113 mm/hour (NR <30), and a positive connective tissue screen which was positive for anti-SSA and anti-RO52 antibodies, positive for ANA (anti-centromere titre 1:320) but negative for anti-dsDNA. She was switched to warfarin and commenced on prednisolone, mycophenolate mofetil and hydroxychloroquine. When reviewed in the neurology clinic one month later her visual fields were improving on clinical examination although she still had a significant homonymous hemianopia on Humphrey's Visual Field assessment [Figure 4(c)]. She had no further neurological complications, but later developed micro-albuminuria thought to be SLE-related, so her treatment regimen was appropriately modified.

Figure 4: Axial T2-weighted [image (a)] and diffusion-weighted [image (b)] MRI sequences revealing large right hemisphere acute ischaemic infarction, with corresponding left homonymous hemianopia on Humphrey's visual fields [image (c)]

(a)



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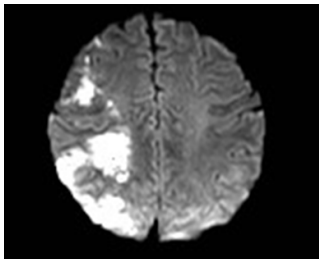

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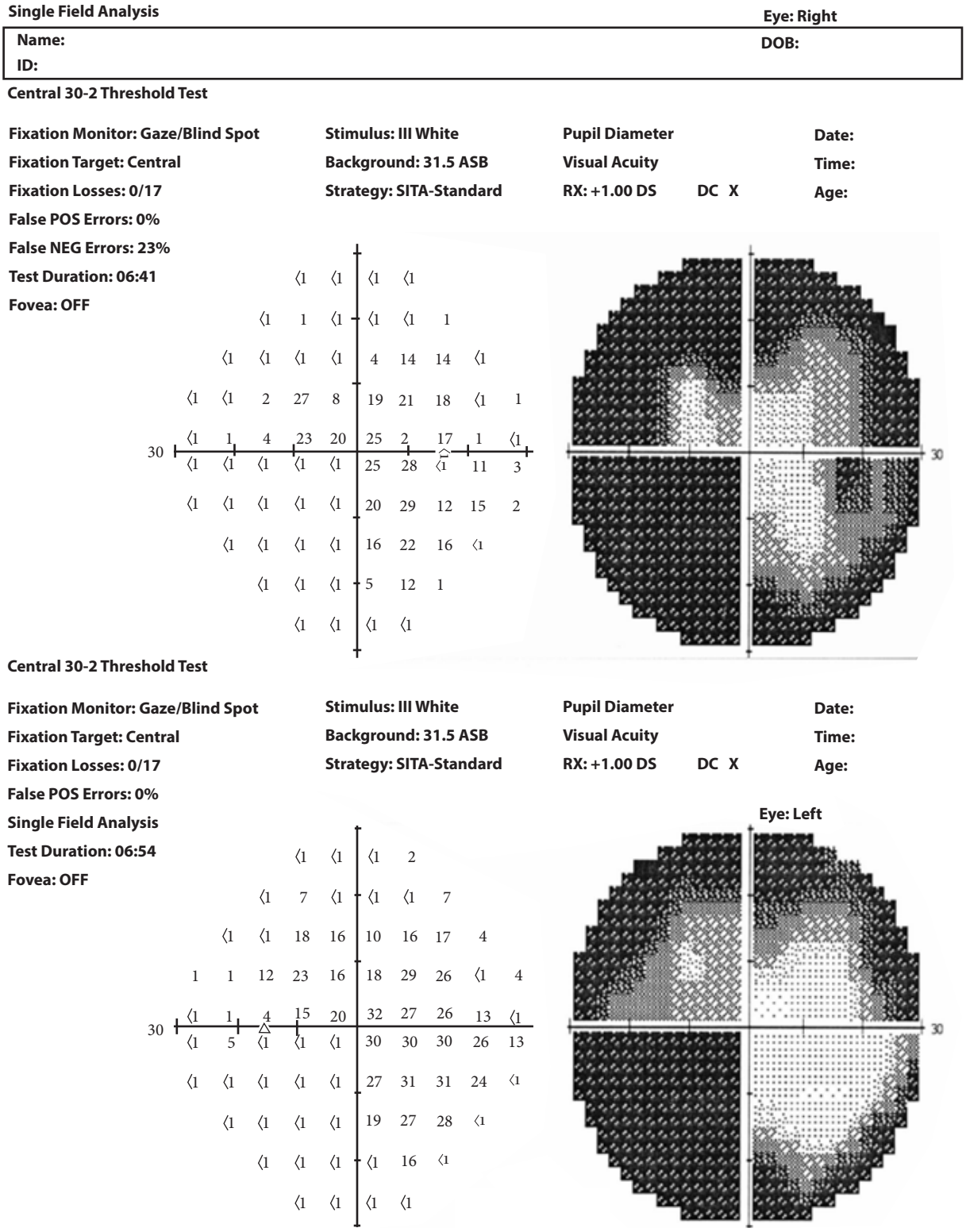

Discussion

All our patients were black African females, in whom SLE is known to be more prevalent[1], with the average age of our cohort being 34 years (range 16-47) which is also in keeping with other studies of NPSLE from Africa[17]. All patients fulfilled the 1982 criteria (with 1997 modification) international diagnostic criteria for SLE[19], but the average delay from initial presentation to diagnosis was 6.5 months (range 1-9), with Case 3 being diagnosed within 1 month as they presented acutely with neuropsychiatric features which tend to be more clinically urgent and more prevalent in younger patients with SLE[18]. This delay to diagnosis is significantly longer when compared to e.g. 2.9 months in European cohorts[20], but much less when compared to other parts of the developing world e.g. 23 months in a study from Israel[21]. A recent survey of physicians and specialists across Africa found that delays to diagnosis of SLE is due to a combination of lack of access to healthcare, low disease awareness in the population and in the primary health systems, inadequate specialist staffing, and lack of availability of diagnostic tools[22]. There is relatively easy availability of diagnostic services at our centre given it is a regional specialist referral hospital which may explain why we did not experience as much delay.

All our cases were treated with the appropriate immunosuppressive therapy[19] which may explain why they had good outcomes (except for Case 4 who then also developed lupus nephropathy), whereas NPSLE is usually associated with poorer outcomes[7].

Three of our cases presented with headaches, with one progressing to more florid neuropsychiatric features, which is in keeping with other studies from the continent where headache was the most common presenting feature in NPSLE[15,17]. However, interestingly none of our cases had seizures, which is similar to the NPSLE cohort reported from Egypt[15] (and in Tunisia only 6% presented with seizures[15]), but contrasts with Nigeria[17] and South Africa[18] where seizures were reported in 42.4% and 45.8% of NPSLE presentations respectively. The newer SLE classification place more weightage on seizures in the neuropsychiatric domain, more than delirium or psychosis[23]; other specific neurological syndromes as per the 1999 criteria do not appear. From our experience institutionally we have had NPSLE with more common MRI findings experiencing seizures as part of their presentation but have not reported them here.

The neuro-imaging of Case 1 illustrates the extreme end of the rarer demyelinating and inflammatory changes that can be seen in NPSLE, but have not been reported to be so extensive[11,12], which is probably why the diagnosis was not made initially. The patient also had positive APA which are known to be associated with more diffuse WMH on MRI in NPSLE[24]. This case would be the first with NPSLE coming from Tanzania, with only one previous published SLE report from Tanzania who presented with lupus nephritis[25].

The demyelinating/inflammatory changes seen in the imaging for Case 2 are quite unique. In the absence of uveitis and papillary involvement, the differential diagnosis included neoplastic causes such as optic nerve and tract glioma – which is more commonly described in children with neurofibromatosis type 1[26] – or inflammatory causes such a connective tissue disease. In comparison to the well described ocular SLE manifestations of uveitis and retinopathy, optic nerve and tract involvement are rarer entities in SLE[27], and to our knowledge such striking imaging findings such as in our case, which melted away on SLE treatment, have not been published in the literature. It is unlikely that her MRI findings were related to the thyroid disease, given they persisted despite thyroxine treatment for several months before she presented with visual disturbance, and the MRI of the orbits excluded thyroid ophthalmopathy.

Case 3 and 4 show MRI changes consistent with vascular pathology. Slow flow in the cerebrovasculature has been reported in NPSLE[28], physiology of which is not clear but is probably related to vasculopathy from SLE[8,9]. Complete venous sinus occlusion in the form of Cerebral Venous Sinus Thrombosis (CVST) is more frequently described in the literature reported, although SLE is deemed a very rare cause of CVST, approximately 1.3% of all predisposing conditions according to some studies[29].

Case 4 had an unprovoked PE heralded by pleuritic symptoms, but was not fully investigated for the underlying cause; SLE doubles the risk of PE compared to the general population, more so in females and the African-American race[30]. This explains why she then suffered a large-vessel stroke syndrome, though she was largely asymptomatic apart from headaches and the hemianopia as the non-dominant hemisphere was affected. In a large Swedish population-based study, individuals with SLE had over double the incidence of ischaemic stroke when compared with the general population, with the highest hazard ratios being in females and younger cases[31]. Acute ischaemic stroke can be the first manifestation of SLE, and tends to occur in younger females and in the posterior circulation[32]. The mechanism of stroke in SLE can be due to the presence of APA, Libman-Sacks endocarditis, Sneddon syndrome or CNS vasculitis[5], although our patient had none of these, which suggests a different mechanism that may also be attributed to her developing lupus nephritis later on. Large-vessel strokes affected 9.6% of the South African NPSLE cohort[18], and the global average is somewhere between 10-15%[13]. Case 4's stroke syndrome would have gone unnoticed had it not been for timely neuro-imaging; some propose routine MRI neuro-imaging, and even cardiac MRI, as pre-symptomatic biomarkers for all SLE cases[33,34].

Conclusions

NPSLE can be the presenting feature of the systemic disease, but the protean manifestations present a diagnostic challenge. Neuroradiological features, especially on MRI brain scans, can aid the diagnostic process. The few studies from sub-Saharan Africa on NPSLE describe some features that are unique to the continent. Our case series, the second such report on NPSLE brain imaging from Africa, highlight the diversity of MRI brain findings in NPSLE which fall into the two main pathophysiological categories: vascular, including small- and large-vessel disease as in Cases 3 and 4 respectively; and demyelinating, as in Cases 1 and 2. There was a delay to diagnosis of several months in most of our cases, as has been previously reported in NPSLE. Appreciation of the MRI features we have described can lead to earlier diagnosis and therefore timely initiation of appropriate treatment to reduce morbidity.

Data availability

The clinical history and imaging data used to support the findings of this study are included within the article.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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This case series did not receive any specific funding. The cases have been compiled as part of authors' current employment under the Aga Khan University Medical College of East Africa, Faculty of Health Sciences.

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Ethical Considerations

Our work has been conducted in accordance with the Declaration of Helsinki (1964). We have documented consent from all patients to use their images for publication. Case 1 and 2 have arisen as clinic mimics from a larger project that is collecting case of multiple sclerosis at our institution [approved by our Institutional Ethics and Research Committee (IERC) reference REC/2018-99]. Case 3 and 4 arise from a larger project on strokes presenting to our institution (IERC reference 2019-62). In line with our IERC guidelines, these case reports are exempted from full IERC review.

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A dual diagnosis of skeletal tuberculosis and sarcoidosis: case report

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Abstract

Tuberculosis (TB) is a common granulomatous infection in South Africa. The prevalence of TB and the extent of multi-system involvement have escalated since the advent of the HIV pandemic in the 1980's. The combination of TB and sarcoidosis is an uncommon concomitant diagnosis but has been described in the literature in multiple different contexts. We report the first known case of multisystem tuberculosis and sarcoidosis with multifocal skeletal lesions in a patient with complicated diabetes mellitus. We anticipate increasing the index of suspicion among clinicians of such a potential combination, especially in a population with impaired immunity such as in individuals with poorly controlled diabetes mellitus.

Key words: Sarcoidosis, Tuberculosis, Tubercular-sarcoidosis

Introduction

The clinical, histological and radiological differentiation of sarcoidosis from tuberculosis (TB) can be challenging owing to their multiple similarities. However, it is very important to differentiate the two since the therapeutic strategies to treat either one of them are completely different. The concomitant diagnosis of both conditions in the same patient can be even more challenging. We describe a rare case presentation of concomitant TB and sarcoidosis affecting the skeletal system in multiple sites in an immunocompromised host.

Case report

We report a case of multisystem tuberculosis TB and sarcoidosis in an HIV negative 39-year-old female with a medical background of hypertension and type 1 diabetes mellitus complicated by early retinopathy and advanced diabetic nephropathy with chronic renal failure and severe proteinuria.

The initial presentation to Tygerberg Hospital was in January 2016 with delirium secondary to non-PTH mediated severe hypercalcemia. An erythematous skin lesion suspicious for sarcoidosis was noted on the left shin and non- caseating granulomatous pathology with a negative Ziehl Nelson staining (ZN) was confirmed on biopsy (Table 1). Radiological features of hilar adenopathy and bilateral apical reticulo-nodular lung infiltrates (Figure 1*)* with restricted lung functions supported the diagnosis of sarcoidosis. A negative sputum GeneXpert made the diagnosis of pulmonary tuberculosis unlikely and the TB sputum culture detected no growth after 40 days. A diagnosis of multisystem sarcoidosis with restricted lung functions complicated by severe hypercalcemia was made, and she was treated with a combination of corticosteroids and bisphosphonate therapy.

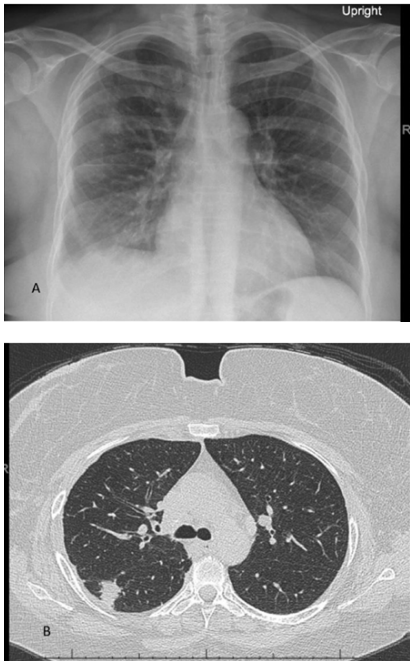
Table 1: Blood, urine, microbiology and histology results

Biochemical tests	2016		2017		2019		Range
Calcium							
● Serum (mmol/L)	3.82	3.69	2.60	2.44	2.48	2.54	2.15-2.50
● Urine (mmol/24hrs)	0.51				<0.20		2.5-7.5
S- PTH (pmol/L)	2.0	2.7					1.5-7.6
S- Vit D (nmol/L)	<10.5	23.7	31.1	74.89			>72.5
S- ALP (U/L)	400	168	99	129	209	169	42-98
S- ACE (U/L)	2	78			1		8-52
HBA1C (%)	8.9	9.9	7.5	8.9	8.0	8.6	<5.6
S- Urea (mmol/L)	9.3	12.9	14.8	10.5	12.5	17.5	2.1-7.1
S- Creat (umol/L)	123	127	206	164	183	268	49-90
Urine PCR (g/24hrs)					4.00	2.84	<0.3

	Microbiological and histopathological tests		
	2016	2017	2019
Sputum	GXP negative.		GXP positive. RIF sensitive.
Skin biopsy	Left shin region: Non-caseating granulomas seen. ZN stain negative for TB. Culture negative for TB on Bactec MGIT medium after 40 days.		Abdominal wall region: Non- caseating granulomas seen. Culture negative for TB on Bactec MGIT medium after 40 days.
Psoas muscle aspirate			Positive culture for TB on Bactec MGIT medium after 14 days. RIF and INH resistant.

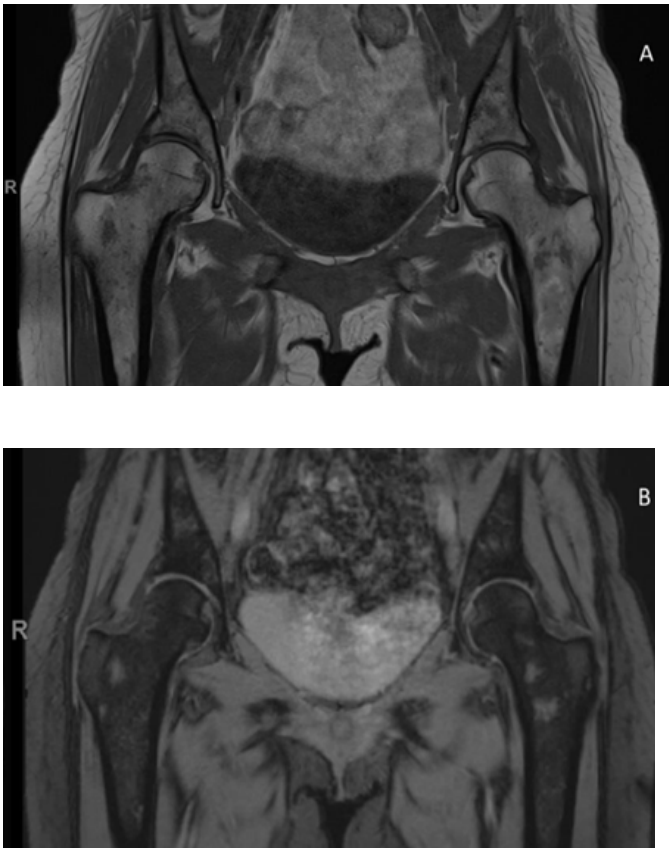
Abbreviations: S. (Serum); Ca (calcium); U. Ca (urine calcium); PTH (parathyroid hormone); Vit D (vitamin D); ALP (alkaline phosphatase) ; ACE (angiotensin converting enzyme); HBA1C (glycated hemoglobin); Creat (creatinine); UPCR (urine protein creatinine ratio); GXP (GeneXpert assay); ZN (Ziehl Neelsen); AFB (acid-fast bacilli); Bactec MGIT (Becton Dickinson and Company Mycobacterium Growth Indicator Tube); RIF (rifampicin); INH (isoniazid)

Figure 1: **A.** Plain chest radiograph demonstrating a reticulo-nodular infiltrative pattern. **B.** High resolution CT chest image demonstrating paraseptal and subpleural nodules compatible with stage II sarcoidosis



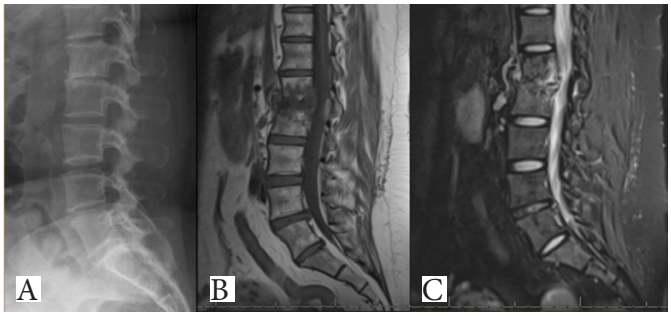
About two weeks into therapy, the patient developed severe left hip and buttock pain. No abnormalities were detected on plain radiograph films of the affected regions, but subsequent magnetic resonance imaging revealed extensive T2 hyper-intense and T1 hypo-intense focal lesions of the proximal femur, the pelvis and the sacrum. These lesions were suggestive of either skeletal or bone marrow sarcoid involvement (Figure 2). A bone marrow aspirate performed at the time showed morphological and immunohistochemical features suggestive of bone marrow infiltration by sarcoidosis. The ZN staining was negative. The immune-modulatory treatment was continued but modified after a few months to include the steroid sparing agent methotrexate due to severe cushingoid features and problematic glycemic control. Some regression of the observed skeletal lesions on MRI scan was confirmed 9 months later and the patient's symptoms also improved.

Figure 2: **A**. MRI T1 weighted image demonstrating multiple hypointense lesions of the pelvis and proximal femurs. **B.** MRI T2 weighted image demonstrating multiple hyperintense lesions of the pelvis and proximal femurs. Findings consistent with skeletal inflammatory lesions



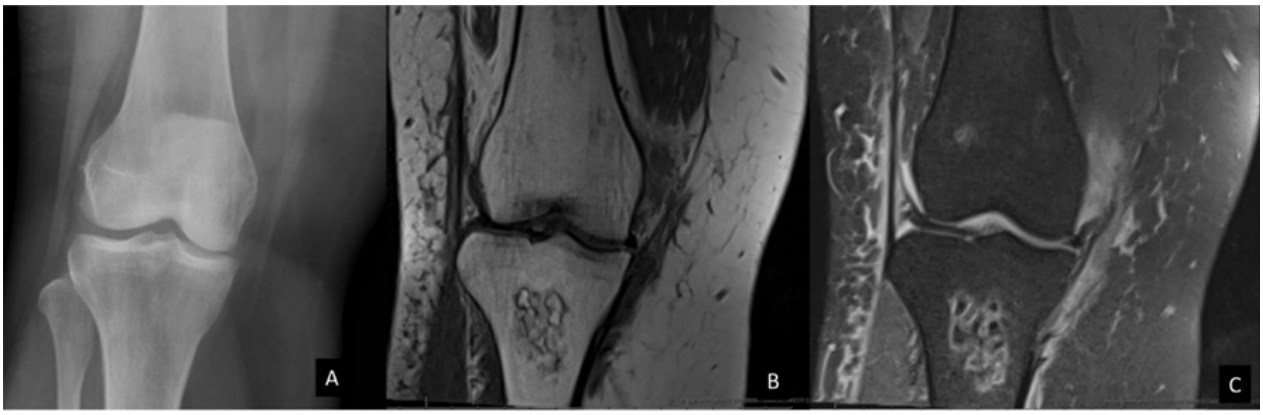
Three years after initial presentation, in February of 2019, the patient presented with new onset severe lower back pain of approximately one month's duration. In comparison to initial normal plain radiographs of the spine, L1- L2 intervertebral disc narrowing and adjacent vertebral sclerosis was now noted on conventional radiography suggestive of an infiltrative inflammatory process (Figure 3). MRI of the spine requested in response to the radiographic abnormality showed a spondylodiscitis at L1-L2 level with intervertebral disc space narrowing and both anterior and posterior sub-ligamentous abscess collection in keeping with a large left psoas abscess, findings very suggestive of TB of the spine and psoas muscle (Figure 3). Subsequent aspiration of the suspected psoas abscess confirmed the radiological suspicion of TB with a strongly positive aspirate for acid fast bacilli, and on culture was found to be resistant to both isoniazid and rifampicin. The sputum GeneXpert was also found to be positive for TB. A diagnosis of concomitant multisystem tuberculosis in a patient with known sarcoidosis of the skin, lungs and musculoskeletal systems was made.

Figure 3: A. Plain radiograph of lumbosacral spine showing L1-L2 intervertebral disc narrowing.
B & C. T1 & T2 weighted MRI lumbosacral images showing L1-L2 spondylodiscitis



Her immunosuppressive therapy was discontinued, and she was initiated on appropriate anti-tuberculous therapy with due consideration of the confirmed resistance of the organisms and the new musculoskeletal sites involvement. She later developed new skin lesions on the anterior abdominal wall, clinically suspicious for sarcoid and histologically confirmed as sarcoid when non-caseating granulomas were observed. These lesions were complicated by opportunistic fungal infection and ulceration resulting in significant distress to the patient. In addition, she developed a painful, tender right knee with inability to weight bear. A plain radiograph of the knee region appeared normal. Subsequent MRI revealed bone marrow edema, cortical bone lesions with sparing of the adjacent joint suggestive of bone sarcoidosis. Evident X-ray/MRI discrepancy was also in-keeping with sarcoidosis, and atypical for TB of the long bones (Figure 4).

Figure 4: **A**. Plain radiograph of the right knee with no significant findings. **B & C**. T1 & T2 weighted MRI images of the right knee showing proximal tibial lesions consistent with inflammatory lesions of bone



The patient was now acutely ill, metabolically difficult to control, bed-bound and with a high thrombo-embolic risk. The latter was addressed with prophylactic subcutaneous enoxaparin injections. Her clinical condition steadily declined. She suffered from new onset seizures, a focal lesion in keeping with either a tuberculoma or a vascular event was noted on CT scan of the brain and the patient unfortunately demised soon thereafter following a cerebrovascular event.

Discussion

The combination of tuberculosis and sarcoidosis in the same patient is a rare occurrence termed by some authors as "Tubercular Sarcoidosis"[1,2]. This term was later refuted owing to the lack of evidence [3]. The potential combination of these diagnoses has been described to occur in three different patterns which includes a patient with previous TB that later develops sarcoidosis, chronic sarcoidosis that later develops TB, or the co- existence of TB and sarcoidosis[1]. Our index case demonstrated features of the second pattern. Our index case was initially found to have sarcoidosis, and later demonstrated features of concurrent TB and sarcoidosis.

Sarcoidosis is an inflammatory granulomatous disease that rarely involves the skeletal system. Usually when the skeletal system is involved, it is limited to the phalanges of the hands and feet[4]. The incidence of sarcoidosis is said to be approximately 10 – 14 per 100 000 people per year, and the skeletal involvement is approximately 14% among all affected individuals[5]. Sarcoidosis and TB are closely related in many ways from pathophysiology, to clinical and radiological presentation, making it difficult to distinguish between the two, especially in a TB endemic region[6].

TB patients and in particular patients with extra-pulmonary TB, have an 8-fold higher risk of developing sarcoidosis when compared to non-TB individuals. On the other hand, sarcoidosis patients have a 2-fold risk of developing TB when compared with non-sarcoid individuals[7]. It has therefore been suggested that TB poses a bigger risk factor for subsequent sarcoidosis than vice versa[5]. A recent meta-analysis indicated the possibility of some insoluble mycobacterial antigens to be responsible for the type IV hypersensitivity immune response in the pathogenesis of sarcoidosis[8]; hence some authors believe that TB and sarcoidosis are possibly a spectrum of one disease[9].

Although these granulomatous diseases share some similarities in the pathophysiology, the therapeutic strategies are very different. It is therefore imperative to differentiate between these two conditions, especially in a TB endemic region since the immunosuppressive therapy used in sarcoidosis can predispose the host to TB infection[2]. Biopsies can differentiate between the two conditions, recognizing TB by its caseating granulomas while sarcoid lesions have non-caseating granulomas. At times this simple differentiation is not easy to ascertain, and in such a case *Mycobacterium* DNA detection with polymerase chain reaction (MTB-PCR) or the identification of acid-fast bacilli becomes the key in making the diagnosis of TB[10].

Molecular detection (PCR) of *Mycobacterium* species (16S RNA, IS6110, and rpoB sequences) on sarcoidosis tissue specimen in comparison with control tissue specimen revealed presence of *Mycobacterium* molecules. 16S RNA and rpoB sequences were amplified from 60% of all samples in a frequency of 48% and 24% of samples respectively (p=0.00002), and not amplified from any of the control specimens[11]. In this study, *Mycobacterium* other than TB (MOTT) were also identified including *M. gordonae*, and *M. kansasii*[11]. Evidently the clinical, histological and radiological differentiation of TB from sarcoidosis will remain a challenge since the overlap and co-existence of these entities extends to a molecular level.

There are no pathogmonic radiological features of musculoskeletal sarcoidosis described in literature, however there are some common radiological features described in various case reports. X-ray/MRI discrepant findings on large bones is described, whereby plain radiographs usually appear without any evidence of bone or soft tissue involvement, conversely on MRI bone lesions may resemble metastasis. Furthermore, bone marrow involvement and soft tissue lesions become evident on MRI[12]. Juxta-articular TB osteomyelitis is often associated with florid synovitis seen as low to intermediate T2 weighted signal intensity on MRI. Additional MRI features include bone marrow edema, cortical erosions, soft tissue swelling and abscess formation[13].

Conclusion

In a TB endemic region such as South Africa, making a diagnosis of TB is a daily routine in clinical practice. However, a diagnostic error of assuming that disseminated granulomatous lesions equates disseminated TB in immunocompromised hosts should be avoided. A combined diagnosis of skeletal TB and sarcoidosis should be considered in the differential diagnosis of uncertain cases.

Learning points

(i) Concomitant skeletal TB and sarcoidosis, although uncommon should be considered in immunocompromised patients with skeletal granulomatous lesions, and non-confirmatory investigations for TB.
(ii) Tissue biopsies can yield non-conclusive results in the attempt to differentiate between TB and sarcoidosis.
(iii) Skeletal MRI is a useful radiological diagnostic modality that can assist as an additional data point in differentiating between sarcoidosis and TB.

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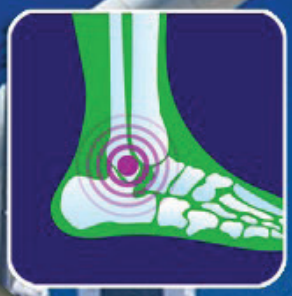

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