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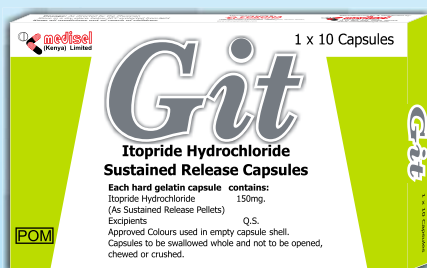
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During the last 20 years, Musculoskeletal Ultrasound (MSUS) practice knew great developments among rheumatologists, due to the improvement of the quality and the reduction in costs of the US machines, and the better understanding of the role of ultrasound in the diagnosis, follow-up and treatment of rheumatic conditions. In Europe and the USA, MSUS became a part of the daily practice of many rheumatologists, and in many countries, MSUS learning is systematically implemented during residency¹.

Among the reasons why MSUS practice is still growing, we can note the high costs and low access to Magnetic Resonance Imaging (MRI) in most countries, ionizing radiations with X-rays and computed tomography, the possibility to explore many anatomical regions at once with ultrasound and dynamically assess tendons and joints, the absence of contra-indications and being extremely patient-friendly. Ultrasound is even superior to MRI when dealing with superficial structures such as tendons and small joints of the hands and feet. Doppler is another advantage with MSUS as it allows direct visualization of micro-vascularization and thus gives an indirect idea on active inflammation. In Algeria, MSUS examination costs 20 times less than an MRI examination and 5 times less than a CT-scan and more than 100 rheumatologists in the country are equipped with US machines, making of it the first choice imaging modality in most of rheumatic situations.

Many studies have demonstrated the superiority of MSUS over clinical examination in assessing lesions such as synovitis, tenosynovitis and tendonitis² and the superiority over X-rays in terms of the detection of erosions and calcifications³. One of the most fascinating aspects of MSUS is the power to detect early flares in RA patients who are on perfect clinical remission⁴.

In RA, MSUS is superior to physical examination in detecting synovitis and tenosynovitis and predicting structural damage; it is also superior to X-rays in showing erosions, with 7 times more erosions in early RA than X-rays⁵.

It also helps in distinguishing between osteoarthritis and RA of the hand, between RA and polymyalgia rheumatica in the elderly and between RA and psoriatic arthritis of the hands and the feet⁶.

In Spondyloarthritis (SpA), MSUS is valuable in detecting enthesitis. Many scores have been developed to identify early SpA according to the presence and the features of enthesitis⁷. In psoriatic arthritis, dactylitis has a typical aspect on US, even in toes, for which clinical assessment is difficult.

In crystal-related diseases, the place of MSUS is being extensively studied during the last years. Many studies have shown a better visualization of gout and pseudogout lesions using MSUS than X-rays, especially in early disease. In gout, two elementary lesions are specific: the “double contour” sign and the tophus aggregates. More importantly, these lesions may decrease or even disappear under urate lowering therapy, making of US a good monitoring therapy⁸. In pseudogout, MSUS allows a direct visualization of intra-articular, ligament and meniscal calcifications with a pathognomonic aspect⁹.

MSUS seems a reliable technique in detecting inflammation in large-vessel vasculitis, particularly in giant cell arteritis. A typical “halo sign” is pathognomonic and may replace, in many cases, temporal artery biopsy¹⁰. However, training with a learning curve is required to perform such examinations and avoid false negative and false positive aspects as well as common pitfalls.

Osteoarthritis (OA) is a very frequent rheumatic condition. The ability of MSUS to assess inflammatory changes in OA (synovitis) as well as structural changes (osteophytes, cartilage thinning) has been recently investigated. Most studies reported a high prevalence of these changes, but some questions remained unanswered, such as the ability of MSUS to distinguish between symptomatic and asymptomatic OA, how to follow OA, and how to assess response to treatment¹¹.

In Fibromyalgia (FM), MSUS may help in distinguishing primary from secondary forms, linked to inflammatory

diseases. In muscle pathology, MSUS is very useful in detecting and grading muscle damage and monitoring lesions over time, as well as helping interventional procedures (haematoma puncture, injections)¹². Finally, in infections, US helps detect and aspirate fluid for further investigations.

Ultrasound is a great tool for helping the rheumatologist in his daily practice. Many certificates and diplomas are available in the African continent, especially in Egypt (EULAR introductory course), in Morocco (DU Rhumecho) and Algeria (DU Ecrin). Hundreds of physicians have been introduced to MSUS through these certificates and we hope that other African national societies will create such diplomas and integrate MSUS as part of the residency curriculum and continuing medical training in their countries. Ultrasound may be an excellent imaging modality in African countries because of the low cost of US procedures, making possible, more than ever, to concretize MSUS as the “Rheumatologist’s stethoscope”.

Conflicts of interests: The author declares no conflicts of interest with regard to the article.

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Prevalence and risk factors for hyperuricemia among patients with hypertension at Moi Teaching and Referral Hospital, Eldoret, Kenya

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Abstract

Objective: Uric acid, a mediator of high blood pressure, is an inexpensive easy-to-obtain indicator of cardiovascular risk (stroke, myocardial infarction and renal disease). This study was conducted to determine the prevalence and risk factors for hyperuricemia among patients with hypertension in western Kenya.

Methods: This cross-sectional study conducted at the Moi Teaching and Referral Hospital in western Kenya, enrolled randomly selected adults (≥ 18 years) with hypertension, attending medical outpatients' clinic. Clinical (age, gender, stroke history, Body Mass Index, antihypertensive drugs and duration of illness) and laboratory (fasting lipid profile, blood sugar, uric acid and serum creatinine) data were collected. Data were keyed into Microsoft excel database and analyzed using STATA© version 13. Descriptive statistics were summarized using means, frequencies and proportions. Risk factors for hyperuricemia were analysed using two-sample t-tests, two-sample Wilcoxon rank sum tests and Pearson's Chi Square tests.

Results: Of the 275 participants enrolled, 182 (66%) were female, mean age 54 (sd 12.5) years, mean Body Mass Index 28.9 (sd 4.9) and median duration of illness 6 months. Overall prevalence of hyperuricemia was 44%; with 37.6% and 47.3% in males and females respectively. Factors associated with hyperuricemia included high Body Mass Index ($p = 0.036$), low Glomerular Filtration Rate ($P < 0.0001$) and dyslipidemia ($p < 0.0001$).

Conclusion: There is a high prevalence of hyperuricemia among patients with hypertension in western Kenya. Risk factors associated with hyperuricemia include high Body Mass Index, dyslipidemia and low glomerular filtration rate. The use of losartan and calcium channel blockers is recommended in patients with hyperuricemia and

subsequent longitudinal studies to be done to determine utility of uric acid monitoring in blood pressure control.

Key words: Hypertension, Hyperuricemic Lipid Profile, Body Mass Index, Estimated Glomerular Filtration Rate (eGFR).

Introduction

Hypertension is currently the most common cardiovascular problem in Africa, affecting an estimated 20 million people. The prevalence of hypertension in Africa ranges from 25% to 35% in adults aged 25 to 64 years and increases with advancing age¹. In Kenya the prevalence of hypertension is 21%². In sub-Saharan Africa, hypertensive end organ damage including haemorrhagic and atherothrombotic strokes, hypertensive heart disease, hypertensive nephrosclerosis and coronary artery disease is a major cause of morbidity and mortality^{1,3}. There is a drastic shift from increase in communicable diseases to non-communicable diseases⁴.

Uric acid has been associated with development of hypertension in several reports.⁵⁻⁸. Studies have shown that hyperuricemia is closely associated with an increased risk for hypertension, impaired fasting glucose, Type II diabetes and the metabolic syndrome⁹⁻¹¹. In the Framingham Heart Study, each increase in serum uric acid levels by 1.3mg/dl was associated with the development of hypertension with an odd ratio of 1.17¹². In the First National Health and Nutrition Study (NHANES I) study, for every 1.01 mg/dl increase in the serum uric acid levels, the hazard ratio for total mortality and for cardiovascular mortality were 1.09 and 1.19 for men and 1.26 and 1.3 for women, respectively¹³.

Hyperuricemia is one of the important risk factors for coronary artery disease in patients with hypertension. It has been associated with end-organ damage for instance, left ventricular

hypertrophy, carotid atherosclerosis, microalbuminaemia, cardiovascular events and mortality in patients with hypertension^{14, 15}.

Uric acid has been considered a causative factor for hypertension and atherosclerosis¹⁶. Elevated serum uric acid lowers endothelial nitric oxide levels, reducing neuronal nitric oxide synthase in the macula densa of the kidney and stimulates the rennin-angiotensin system. This mechanism was demonstrated in animal studies where rats developed high blood pressure in about 3 to 5 weeks after raised uric acid levels was induced by the administration of oxonic acid which is an inhibitor of Uricase¹⁷.

Evidence from a number of studies suggests that uric acid be added to the list of conventional risk factors of hypertension like obesity, age, renal disease, and diabetes mellitus¹⁸⁻²¹. In Kenya, the current prevalence of hyperuricemia among patients with hypertension is unknown. Old data from Kenyatta National Hospital found a prevalence of hyperuricemia among untreated patients with essential hypertension to be 27.5% and among those on treatment to be 58%²². This study sought to determine the prevalence and associated risk factors for hyperuricemia among patients with hypertension at the Moi Teaching and Referral Hospital in western Kenya.

Materials and Methods

This study was conducted in the medical outpatient clinics of the Moi Teaching and Referral Hospital (MTRH). The hospital is located in Eldoret town, which is 350 Kilometers northwest of the Kenyan capital, Nairobi. MTRH is a tertiary (level 6) health facility serving as a teaching hospital for Moi University School of Medicine. It is the second referral hospital in Kenya and serves a catchment population of approximately 13 million people in western Kenya. The hospital has various specialist clinics, including medical outpatient clinics where patients with hypertension are seen twice weekly.

This was a cross-sectional descriptive study. The study enrolled adults (≥ 18 years) with hypertension for a period not exceeding 2 years since diagnosis. Hypertension was defined as a Systolic Blood Pressure (SBP) > 140 mmHg and/or a Diastolic Blood Pressure (DBP) > 90 mmHg on two occasions, or being on antihypertensive medications. Participants with malignancies, those on chemotherapy, who were critically ill and pregnant women, were excluded.

The sample size was computed using the Cochran formula (Cochran, 1963). In order to have 95% confidence interval of the proportion with hyperuricemia of 58%²² with a margin of error of 5%, a sample of 375 was required. However, after correcting for the finite population size of about 170 per month for 6 months, a sample size of 275 was computed.

Potential participants were identified through simple random sampling using computer generated

random numbers. The clinic booking register served as the sampling frame. Participants who met the study eligibility criteria were consented and then recruited. Those who were not fasted were rescheduled for another day. Patients' self-reported bio data and a comprehensive medical history of current and past illnesses, including but not limited to: duration of hypertension, history of diabetes, stroke, alcohol use and cigarette smoking as well as medication use including hypertension medication, drugs for diabetes, and lipid lowering agents being used was collected.

Body Mass Index (BMI) was computed in the standard manner and the degree of obesity was classified based on National Institute of Health (NIH) cut offs¹. Blood pressure measurement was done after a patient had rested for at least 5 minutes. Two readings were taken and the average was recorded in the questionnaire. Patients who reported history of diabetes, was verified from the records. The patients who were not known hypertensives but with BP readings of systolic above 140 mmHg and diastolic of more than 90 mmHg had their charts reviewed and if they had high blood pressure during their last visit they were considered hypertensive.

Fasting blood samples were drawn for lipid profile (total cholesterol, LDL, HDL and triglycerides); uric acid serum creatinine. The estimated Glomerular Filtration Rate (eGFR) was calculated using the Chronic Kidney Disease-Epidemiology Consortium (CKD-EPI) equation.

Data were collected between January and September 2015, using interviewer administered structured questionnaire. Medical records were also reviewed and relevant clinical and laboratory data were obtained and entered into the data collection form. The variables collected included demographic characteristics such as age, gender, history of smoking, alcohol use, diet and occupation. Medical and family history of hypertension, diabetes and kidney disease were also obtained. Other variables collected included; laboratory parameters (FBS, creatinine and lipid profile). The dependent/outcome variables are the levels of uric acid for the hypertensive patients. The data were de-identified, encrypted, double-entered into a Microsoft Excel© database and pass-word protected. All data were kept confidential in lockable cabinets.

Data were analyzed using STATA© version 13 special edition. Categorical variables were summarized as frequencies and corresponding percentages. Continuous variables that assumed Gaussian distribution were summarized as means and the corresponding Standard Deviation (SD). Continuous variable that violated the Gaussian assumptions were summarized as median and the corresponding Inter Quartile Range (IQR). Inferential statistics were used to draw conclusions about the population. Significance tests such as the two-sample t-test for comparison of two normally distributed continuous variables, two-sample Wilcoxon rank sum test (Mann Whitney U test) for non-Gaussian distributed continuous variables, and Pearson's Chi Square test for

categorical variables were used. Gaussian assumptions were assessed empirically using Shapiro Wilk test.

This study was carried out with the approval of the Institutional Research and Ethics Committee (IREC) of MTRH and Moi University School of Medicine and permission from MTRH management. A signed written informed consent was obtained for each participant who was included in this study. Confidentiality was maintained throughout the study by pass-word protecting database and limiting its access only to principal investigator and research assistants. Interviews were carried out in a consultation room to ensure privacy and convenience. All participants including those who declined consent received the same level of care awarded to all other patients irrespective of their participation. There were very minimal anticipated risks to the participants attributable to this study except the physical pain and discomfort associated with sample collection. Questionnaires will be shredded after three years of publication of the study findings. There was no conflict of interest in this study and no incentives were used to recruit patients. Patients were informed of their results and the same availed to their primary clinicians.

Results

Out of a total of 505 patients with hypertension screened at the medical outpatient clinics, 275 were enrolled as shown in Figure 1. Of the 275 who were enrolled 182(66%) were female. The mean age was 54.2 years (SD 14.3). More than two thirds, 215(78.2%) were un-employed. Thirty five (12.7%) had a history of smoking, 59(21.5%) had a history of alcohol use (Table 1). The median duration of illness after diagnosis was 6 months (IQR 2, 18). Twenty nine (10.6%) had a history of stroke and another 42(15.3%) had a history of diabetes. Treatment history showed that 40(14.6%) patients were on furosemide, 114(41.5%) were on hydrochlorothiazide, 29(10.6%) were on amlodipine, and 125(45.5%) were on nifedipine. Eighty four, 30.6%, were using enalapril while 10(3.6%) were on beta blockers (carvedilol-5 or propranolol-2 or atenolol-3). Twenty three 23(8.4%) were on atorvastatin for treatment of dyslipidemia (Table 2).

Figure 1: Enrollment Schema

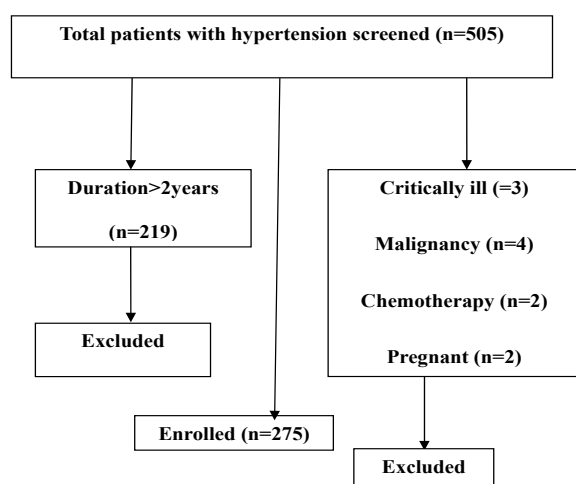


Table 1: Socio demographic characteristics

Variable	Normal uric acid (n=154)	Hyperuricemia (n=121)	p-value
Mean age (years)	55.0 (46.0, 61.0)	55.0 (45.0, 66.0)	0.739
Gender			
Male	58(37.7%)	35(28.9%)	0.128
Female	96(62.3%)	86(71.1%)	
History of smoking			
Yes	22(14.3%)	13(10.7%)	0.382
No	132(85.7%)	108(89.8%)	
Alcohol use			
Yes	32(20.8%)	27(22.3%)	0.758
No	122(79.2%)	94(77.7%)	

Table 2: Medical history of patients

Variable	Normal uric acid (n=154)	Hyperuricemia (n=121)	p-value
Reported history of stroke			
Yes	14(9.1%)	15(12.4%)	0.376
No	140(90.9%)	106(87.6%)	
Reported history of diabetes			
Yes	20(13.0%)	22(18.2%)	0.235
No	134(87.0%)	99(81.8%)	
Reported family history of hypertension			
Yes			0.668
No	74(48.1%) 80(51.9%)	55(45.5%) 45(54.5%)	
Reported family history of kidney disease			
Yes	6(3.9%)	9(7.4%)	0.199
No	148(96.1%)	112(92.6%)	
Hypertension control agents			
Hydrochlorothiazide	58(37.7%)	56(46.3%)	0.150
Furosemide	19(12.3%)	21(17.4%)	0.241
Amlodipine	14(9.2%)	15(12.4%)	0.376
Nifedipine	74(48.1%)	51(42.2%)	0.329
ACEI	47(30.5%)	37(30.6%)	0.992
ARB	29(18.8%)	21(17.4%)	0.753
Beta blockers	6(3.9%)	4(3.4%)	0.531 ^f
Diabetes control agents			
Yes	21(13.6%)	17(14.1%)	0.921
No	133(86.3%)	104(85.9%)	
Lipid lowering agents			
Yes	7(4.6%)	16(13.2%)	0.010
No	147(95.4%)	105(86.8%)	

The median BMI was 28.9 (IQR: 26.1, 33.4) kgs/m² with a median Systolic Blood Pressure (SBP), and Diastolic Blood Pressure (DBP) of 154.0 (IQR: 139.0, 166.0) mm Hg, and 94.0 (IQR: 85.0, 102.0) mm Hg respectively. More than 70% had SBP > 140 mm Hg, and more than half had DBP > 90 mm Hg. This gives the proportion of patients with uncontrolled blood pressure as 214 (77.8%). Other clinical characteristics are summarized in Table 3.

Table 3: Clinical characteristics

Variable	Normal uric acid (n=154)	Hyperuricemia (n=121)	p-value
Median duration of illness	6.0 (2.0, 12.0)	6.0 (2.0, 18.0)	0.402
Mean BMI (kg/m ²)	28.4 (25.6, 32.6)	30.2 (26.5, 33.9)	0.033
Mean SBP (mm/Hg)	156.0(141,164.0)	150.0(133, 169)	0.540
Mean DBP (mm/Hg)	93.5(87.0,102.0)	96.0(82.0,104.0)	0.943
Mean pulse rate (beats/min)	84.1±13.7	84.3±12.6	0.164
BMI			
Underweight (<18.5)	0(0%)	0(0%)	0.036
Normal (18.5-25)	34 (22.1%)	15 (12.4%)	
Overweight (25-30)	63 (40.9%)	45 (37.2%)	
Obese (>30)	57 (37.0%)	61 (50.4%)	
SBP			
>140mmHg	116 (75.3%)	83 (68.6%)	0.312 ^f
<140mmHg	38(24.7%)	17(31.4%)	
DBP			
>90mmHg	92 (59.7%)	67 (55.4%)	0.184
<90mmHg	62(40.3%)	54(44.6%)	

The median serum uric acid was 338.5 (IQR: 270.0, 415.0) mmol/l. The prevalence of hyperuricemia in this cohort was 44.0% (95% CI: 28.0%, 50.0%). The median total cholesterol, HDL, LDL, and triglycerides were 4.9 (IQR: 4.0, 5.7) mmol/l; 1.0 (IQR: 0.8, 1.3) mmol/l; 2.9 (IQR: 2.1, 3.7) mmol/l, and 1.3 (IQR: 1.1, 1.8) mmol/l respectively. There were 248(90.2%) participants with dyslipidemia; elevated total cholesterol, 114(41.5%); decreased HDL, 207 (75.3%), elevated LDL, 125(45.5%), and elevated triglycerides, 87(31.6%). The median creatinine was 66.0 (IQR: 53.0, 82.2) mmol/l, and median eGFR was 110.5 (IQR: 88.7, 122.7) ml/min per 1.73m² (Range 3.3-164.3 ml/min per 1.73m²). An estimated 24(8.7%) were in chronic kidney disease stage 3 or 4. Other clinical and laboratory characteristics are summarized in Table 4.

In the univariate model of factors associated with hyperuricemia, higher Body Mass Index (p=0.036); use of lipid lowering drugs (p=0.010); lower HDL (median 0.9 (IQR: 0.7, 1.2) vs. 1.1 (IQR: 0.9, 1.4) mmol/l, p=<0.0001) and elevated triglycerides 49(40.5%) vs. 38(24.7%), p=0.005) were positively associated with hyperuricemia. Dyslipidemia, defined as either elevated total cholesterol, Low-Density Lipoprotein (LDL), triglycerides or low levels of High-Density Lipoprotein (HDL), was associated with the presence of hyperuricemia, 118 (97.5%) vs. 130 (84.4%), p<0.0001. Lower eGFR levels were also associated with the presence of hyperuricemia (median eGFR: 103.4 (IQR: 74.5, 134.8) vs. 121.7 (108.0, 148.5), p<0.0001). Chronic kidney disease stage 3 or worse was associated with the presence of hyperuricemia, 20 (16.5%) vs. 1 (0.7%), p<0.0001. (Tables 3 and 4).

In the adjusted multivariate model, factors associated with increased risk of hyperuricemia included female gender (OR: 2.18 (95% CI: 1.15, 4.15); higher BMI (every 5 units higher) (OR: 1.50 (95% CI: 1.13, 1.99); dyslipidemia (OR: 4.40 (95% CI: 1.12, 17.19) and use of

Table 4: Laboratory characteristics

Variable	Normal uric acid (n=154)	Hyperuricemia (n=121)	p-value
Mean total cholesterol	4.9 (4.1, 5.6)	4.9 (3.8, 5.8)	0.919
Mean HDL	1.1 (0.9, 1.4)	0.9 (0.7, 1.2)	<0.0001
Median LDL	2.9 (2.3, 3.5)	2.9 (2.0, 3.8)	0.964
Median triglycerides	1.3 (1.1, 1.7)	1.4 (1.2, 2.1)	0.061
Median eGFR	116.6 (102.3, 127.4)	101.6 (73.9, 118.5)	<0.0001
LDL			
>2.50mmol/l	68(44.1%)	57 (47.1%)	0.626
<2.50mmol/l	86(55.84%)	64(52.9%)	
Total cholesterol			
>5.17mmol/l	59 (38.3%)	55 (45.5%)	0.233
<5.17mmol/l	95(61.7%)	66(54.5%)	
Triglycerides			
>1.8mmol/l	38 (24.7%)	49 (40.5%)	0.005
<1.8mmol/l	116(75.3%)	72(59.5%)	
HDL*			
Low	91 (59.1%)	99 (81.8%)	0.001
High	63(40.9%)	22(18.2%)	
Dyslipidemia	122 (79.2%)	116 (95.9%)	<0.0001
eGFR			
above 60	150(97.4%)	101(83.5%)	<0.0001 ^f
30-60	3(2%)	6(5%)	
15-30	0(0%)	5(4.1%)	
<15	1(0.7%)	9(7.4%)	
Stage 3 or worse CKD	4(2.6%)	20(16.5%)	<0.0001

Table 5: Factors associated with presence of hyperuricemia

Variable	Odds Ratio (95% CL)
Age (per 10 years increase)	0.71 (0.56, 0.90)
Female	2.18 (1.15, 4.15)
BMI (per 5 units increase)	1.50 (1.13, 1.99)
eGFR (per 30 units increase)	0.32 (0.22, 0.48)
Dyslipidemia	4.40 (1.12, 17.19)
Lipid drugs (ATOV)	4.63 (1.42, 15.13)
Drugs for diabetes mellitus	0.23 (0.06, 0.95)
Nifedipine	0.44 (0.24, 0.82)
ARB	0.39 (0.17, 0.92)
HCTZ	1.57 (0.88, 2.81)
Aspirin	3.01 (0.68, 13.32)
History of diabetes mellitus	2.75 (0.73, 10.35)

lipid lowering drugs (OR: 4.63 (95% CL: 1.42, 15.13). Factors associated with reduced risk of hyperuricemia included use of diabetes mellitus drugs (OR: 0.23 (95% CL: 0.06, 0.95); use of nifedipine (OR: 0.44 (95% CL: 0.24, 0.82); use of ARB (OR: 0.39 (95% CL: 0.11, 0.92); older age (every 10 years older) (OR: 0.71 (95% CL: 0.56, 0.90) and higher eGFR (every 30 units higher) (OR: 0.32 (95% CL: 0.22, 0.48) (Table 5).

Discussion

Nearly half (44%) of patients with hypertension in western Kenya have hyperuricemia, with prevalence of 37.6% and 47.3% among males and females respectively. In the last decade interest in uric acid has resurfaced after a long period of inertia, largely reflecting results from experimental studies that show detrimental effects of uric acid on blood pressure and kidney function.

Other reports have also found a high prevalence of hyperuricemia among patients with hypertension. For instance, an older study from Kenya found an incidence of 27.5% among untreated hypertensive patients and 58.3% among the treated hypertensive patients²³. Studies from West Africa including Nigeria, Cameroon and Mali documented prevalence of hyperuricemia ranging between 49% and 67%^{8,11,24}. Higher prevalence in these studies could be explained by the lower cutoff uric acid level ($> 5.5\text{mg/dl}$ for both sexes and in our study the cut off was $>5.7\text{mg/dl}$ for female patients and $>7\text{mg/dl}$ for the male patients)¹¹. In addition, those reporting the highest prevalence of hyperuricemia also had longer duration of hypertension (> 40 months) compared to ours which was 24 months¹¹. Studies have shown that hyperuricemia increases with duration of hypertension²⁵.

Studies from Asia and the US have also reported similarly high prevalence of hyperuricemia among patients with hypertension. For instance, in Taiwan a prevalence of 35% among male patients and 45% among female patients was reported²⁶. In the US a prevalence of 41.7% was reported²⁷. In another study, hyperuricemia was present in 25% of untreated hypertensive subjects, in 50% of subjects taking diuretics, and in $>75\%$ of subjects with malignant hypertension²⁸. These findings are generally comparable to our results.

The increase in serum uric acid in hypertension may be due to the decrease in renal blood flow that accompanies the hypertensive state, since a low renal blood flow will stimulate urate reabsorption²⁹. Hypertension also results in microvascular disease, and this can lead to local tissue ischemia³⁰. In addition to the release of lactate that blocks urate secretion in the proximal tubule, ischemia also results in increased uric acid synthesis. In ischemic conditions, ATP is degraded to adenine and xanthine, and there is also increased generation of xanthine oxidase. The increased availability of substrate (xanthine) and enzyme (xanthine oxidase) results in increased uric acid generation as well as oxidant (O_2^-) formation³¹.

In our study, factors associated with increased risk of hyperuricemia included higher BMI, dyslipidemia, use of lipid lowering drugs and female gender. A large study from China including 5235 hypertensive patients showed that with an increase of Body Mass Index (BMI), serum uric acid level increased significantly in both sexes [BMI < 25 , $>$ or $= 3032$]. An even larger study including 31,473 participants from the National Health and Nutrition Examination Survey from 1999–2012 in the US

demonstrated that the combined effect of hyperuricemia and overweight/obesity on the risk of hypertension is much stronger than any separate one³³.

Other factors associated with hyperuricemia from our study included low eGFR levels and chronic kidney disease stage 3 or worse. Other studies have reported similar findings^{8,23,24,34}. Since serum uric acid is eliminated principally by the kidneys its levels increase as the GFR falls. According to Froehlich and Susic demonstrated that an increasing serum uric acid level may be a useful biomarker of hypertension and its consequently deranged renal haemodynamics³³.

An estimated 90% of our participants had dyslipidemia, with only 8.4% being on statins. Other studies have shown a significant correlation between uric acid and dyslipidemia^{9,24,35,36}. Triglycerides have been linked to insulin resistance which promotes hypertension through renal tubular sodium re-absorption, augmentation of the sympathetic nervous system reactivity and activation of the renin-angiotensin system¹⁷. Given that uric acid can also induce the Renin-angiotensin system it is possible that they both have an additive effect on the blood pressure response.

Older age was associated with lower risk of hyperuricemia. This is in line with a study done in Cameroon by Nguedia *et al*²⁴ and Lin *et al*²⁶ where they found a significant negative correlation between uric acid and age. However, Teng *et al*³⁸ reported a contrary result wherein uric acid was associated with the risk of hypertension in the elderly. The differences with our study might be explained by differences in population characteristics.

Other risk factors for hyperuricemia reported in other studies include smoking, alcohol use and diuretic use^{24,38,39}. Our study did not show any significant association between hyperuricemia and alcohol or smoking probably due to under-reporting by patients in our study. In our study, diuretic (furosemide and hydrochlorothiazide) use was associated with hyperuricemia but did not reach statistical significance, this could be due to the fact that most patients $>95\%$ were on multiple antihypertensive agents, since none was on uricosuric drugs. Use of Calcium Channel Blockers (CCB) and Angiotensin Receptor Blockers (ARB) were associated with a 51% and 61% reduced risk of hyperuricemia respectively. This has been found in other studies as well. The hypouricemic effect of losartan may be due to losartan targeting the urate anion exchange and diminish urate reabsorption in the proximal convoluted tubule⁴⁰. ACE inhibitors and CCBs increase uric acid excretion but the effect is modest⁴¹.

Our study did not establish an association between blood pressure and hyperuricemia, despite the fact that majority (77.8%) of patients in our study had blood pressure of $>140/90$ mm/hg. This was a cross-sectional study, blood pressure was taken only once therefore some patients might have been misclassified due to white coat effect. This is similar to findings from other studies that

showed that serum uric acid at baseline did not predict the longitudinal changes in both SBP and DBP³⁴. This suggests that uric acid level does not influence response to pharmacotherapy for hypertension. Other studies have however found a significant independent association between uric acid with both systolic and diastolic blood pressure^{8,24}. An increase in both systolic and diastolic blood pressure was also marked by a corresponding increase in serum uric acid concentration. In the Framingham Heart Study including 3329 participants, it was found that serum uric acid levels was an independent predictor of hypertension incidence and longitudinal BP progression at short-term follow-up⁴².

Studies have shown that hyperuricemia independently predicts the risk of stroke^{12,13,42,43}. A systematic review and meta-analysis of 16 prospective cohort studies found that the elevated serum uric acid level in adults is associated with a modest but statistically significant increased risk of stroke incidence and mortality⁴⁴. In addition, higher serum urate levels predicted poor outcome at 90 days among patients with stroke independently of other prognostic factors⁴⁵. In patients with diabetes, elevated serum uric acid is thought to play a role, along with obesity, blood pressure, and insulin resistance, in the metabolic syndrome that may be responsible for endothelial dysfunction. We found a higher proportion of strokes among patients with hyperuricemia but the difference was not statistically significant.

One limitation of this study was that blood pressure was only measured during one visit. It is possible that some individuals were misclassified owing to the white coat effect. However, the study had a number of strengths, it was relatively easy and quick to conduct the study, data on all variables were collected at once, we were able to measure the prevalence of all factors under investigation and our findings can be analyzed to generate hypothesis for other in depth research.

In summary, there was a high prevalence (44%) of hyperuricemia among this population in western Kenya. Since there is a significant role of uric acid in development of hypertension and its complications, serum uric acid levels can be used as a marker of disease progression and existence of metabolic syndrome among these patients. Known risk factors for hyperuricemia such as higher BMI, dyslipidemia, female sex, and low eGFR were prevalent in this population. Therefore, we recommend the use of losartan and calcium channel blockers in patients with hyperuricemia and subsequent longitudinal studies to be done to determine utility of uric acid monitoring in blood pressure control.

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Abstract

Background: Vitamin D is classified as secosteroid. The main source of vitamin D is *de novo* synthesis in the skin. Although vitamin D is consumed in food, dietary intake alone is often insufficient, supplying only 20% of the body's requirement. The role of vitamin D in situations other than calcium homeostasis and bone health has become very topical. It is apparent that vitamin D has significant effects on the immune system and as such may contribute to the pathogenesis of autoimmune diseases.

Objective: To assess the frequency of vitamin D deficiency in our patients with autoimmune rheumatic diseases.

Methods: One hundred Libyan patients with rheumatic diseases who were registered in rheumatology outpatients' clinic, Tripoli Medical Center in the period between January 2017 and June 2017 were included in the study. Blood samples were extracted from these patients and sent for vitamin D (25-hydroxycholecalciferol) level.

Results: One hundred Libyan patients with different rheumatic diseases who were registered in rheumatology outpatients' clinic, Tripoli Medical Center, in the period from January 2017 to June 2017 were included in our study. The median age was 47 years (range from 18-58 years). Seventy (70%) patients were female and 30 (30%) patients were male. Ninety eight (98%) patients had vitamin D deficiency. Only 2 (2%) patients had normal vitamin D level. Sixty out of ninety eight (61%) of patients had vitamin D less than 10 ng/ml (ie severe deficiency).

Conclusion: Ninety eight per cent of our patients with different rheumatic diseases had vitamin D deficiency diseases.

Key words: Vitamin D, Autoimmune rheumatic diseases

Introduction

Vitamin D is classified as secosteroid. The main source of vitamin D is *de novo*

synthesis in the skin. Although vitamin D is consumed in food, dietary intake alone is often insufficient, supplying only 20% of the body's requirement¹.

The role of vitamin D in situations other than calcium homeostasis and bone health has become very topical. It is apparent that vitamin D has significant effects on the immune system and as such may contribute to the pathogenesis of autoimmune diseases². The net effect of the vitamin D endocrine system on the immune response is an enhancement of innate immunity coupled with multifaceted regulation of adaptive immunity³.

1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) the biologically active metabolite of vitamin D exerts immunomodulation via the nuclear Vitamin D Receptor (VDR) expressed in antigen presenting cells and activated T/B cells⁴. Epidemiological evidence indicates a significant association between vitamin D deficiency and an increased incidence of autoimmune diseases⁵.

Materials and Methods

One hundred Libyan patients with rheumatic diseases who were registered in rheumatology outpatients' clinic, Tripoli Medical Center in the period between January 2017 and June 2017 were included in the study. Blood samples were extracted from these patients and sent for vitamin D (25-hydroxycholecalciferol) level. Vitamin D level less than 30 ng/ml was considered as deficiency and levels between 0-10 ng/ml was considered as severe deficiency according to vitamin D council standard. The results were analysed statistically using the Statistical Package for Social Sciences version 11 computer package (SPSS Inc., Chicago, IL., USA).

Results

One hundred Libyan patients with different rheumatic diseases who were registered in rheumatology out patients' clinic, Tripoli Medical Center, in the

period from January 2017 to June 2017 were included in our study. Fifty (50%) patients had Rheumatoid Arthritis (RA), 30 (30%) patients had Systemic Lupus Erythematosus (SLE), 9 (9%) patients had systemic sclerosis, 7 (7%) patients had ankylosing spondylitis and 4 (4%) patients had polymyositis.

The median age was 47 years (range from 18-58 years). Seventy (70%) patients were female and 30 (30%) patients were male. Ninety eight (98%) patients had vitamin D deficiency. Fifty out of ninety eight (51%) patients had RA, 30/98 (30.6%) patients had SLE, 9/98 (9.2%) had systemic sclerosis, 7/98 (7.2%) had ankylosing spondylitis and 2/98 (2%) had polymyositis. Only 2 (2%) patients had normal vitamin D level. Sixty out of ninety eight (61%) of patients had vitamin D less than 10 ng/ml (ie severe deficiency).

Discussion

The vitamin D has direct and indirect effects which might be related to the risk of developing a rheumatic disease or the degree of disease activity⁶. We have three evidences which support the role of vitamin D in autoimmune diseases. The first is the presence of vitamin D receptor on extra-osseous cells, such as cartilage cells, sinoviocytes and muscle cells. The second evidence is the proven role of vitamin D in the control of transcription of genes involved in rheumatic diseases. The third evidence is that the activation of vitamin D not only presents in the kidneys, but also in monocyte-macrophage and lymphocytic cell lines⁶.

Most of our patients 98% with different rheumatic diseases had vitamin D deficiency with vitamin D less than 10 ng/ml (severe deficiency) in 60/98 (61%) patients. In Martin- martinez *et al*⁷ study which included a total of 2234 patients: 755 RA, 738 AS and 721PsA, in addition to 677 non-inflammatory individuals with OA, osteoporosis and low back pain. They found that the patients with inflammatory diseases had a more marked deficiency of vitamin D< 20 ng/ml, than the non-inflammatory diseases (40.5% in RA; 40% in AS; 41% in PsA; and 26.7% in the control group; (P<0.001).

With respect to RA, Cutolo *et al*⁸ point out the changes in the serum vitamin D concentration and the increase in the severity of joint symptoms in patients with this disease. Specifically they found that the lowest vitamin D concentration and the highest RA activity occur in winter. On the other hand, in susceptible populations high vitamin D intake lowers the risk of developing RA and, in individuals who already have the disease; it reduces RA activity.

Mok *et al*⁹ included 290 SLE patients. Two hundred and seventy seven (96%) had vitamin D< 30 ng/ml and 77 (27%) patients had vitamin deficiency<15 ng/ml. They found that, vitamin D levels correlated inversely

with SLE activity scores as physicians' global assessment (PGA) (β -0.20; P=0.003), total SLEDAI scores (β -0.19; P=0.003) and sub scores due to active renal, musculoskeletal and haematological diseases. Vitamin D supplementation is indicated in patients with SLE for the management of the changes related to bone mineral loss and, in the case of deficiency, can help to reduce the severity of the disease expression¹⁰.

Conclusion

Ninety eight per cent of our patients with different rheumatic diseases had vitamin D deficiency. As there are strong evidences which link vitamin D deficiency to autoimmune rheumatic diseases, this encourages us for more studies testing a therapeutic role of vitamin D in rheumatic diseases.

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Coexistence of gout and rheumatoid arthritis in Nairobi, Kenya

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Abstract

Background: There is a widespread belief that gout and RA rarely coexist in the same patient. Given that there is an excess burden of cardiovascular disease in patients with RA, this is compounded by hyperuricemia. The purpose of this study was to describe the clinical profiles of patients with coexistent gout and rheumatoid arthritis.

Methodology: This was a retrospective study to be carried out at the Nairobi Arthritis Clinic. The sample population comprised of all medical records of patients with RA and gout. The files were retrospectively reviewed from January 2009 to December 2017.

Results: The cohort included 13 patients with the diagnosis of rheumatoid arthritis and gout seen at the clinic between January 2009 and December 2017. Majority of the study participants were male (9/13) with a mean age of 60.8 years. The mean age of diagnosis of rheumatoid arthritis and gout was 55.25 years and 63 years respectively. The participants were obese with a mean of 31.4. Majority tested positive (10/13) for either or both rheumatoid factor and anti-citrullated peptide antibody. Urate acid crystals were identified in 10 of the 13 participants. All the participants had used glucocorticoids with a further 4 on diuretics which were later stopped.

Conclusions: Coexistence of rheumatoid arthritis and gout is still rare in Kenya. Being male and obese having either rheumatoid arthritis or gout increasing the chance of developing both diagnoses. A large number had tophi thus in patients with tophaceous gout not improving on standard therapy an alternative diagnosis could be rheumatoid arthritis.

Key words: Gout , Rheumatoid arthritis, Kenya

Background

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory disease of unknown cause. The annual incidence of

RA worldwide is approximately 3 cases per 10,000 populations. The prevalence rate is approximately 1% with majority affected between the ages of 35 and 50 years¹. The incidence of gout worldwide is 0.3 to 6 cases per 1000 person-years. The incidence of gout is 2- to 6-fold higher in men than in women and generally increases with age, leveling off after 70 years². There is a widespread belief that gout and RA rarely coexist in the same patient. Case reports of co-occurrence of gout and RA are rarely reported. The prevalence of gout has been noted to be lower in patients with RA than the general population in age and sex matched studies³. Reasons include it can also be difficult to clinically differentiate RA from polyarticular tophaceous gout especially when gout involves the hands. Women with RA have a decreased risk of gout as estrogens and progesterone cause better renal clearance of uric acid⁴. Glucocorticoids and NSAIDs used in RA can also potentially mask the clinical manifestations of gout. Urate crystals contribute to lower incidence of coexistent RA and gout through antioxidant and anti-phagocytic properties by blocking activation of T and B cells⁴. In addition, IL-6 in RA may reduce the likelihood of overt gout owing to its uricosuric properties⁵. These include a report of eight cases of coexisting RA and gout between 1994 and 2005 from Taiwan. This same report also records twenty-four other cases with similar diagnosis from other sources in English literature⁶. Given the excess burden of cardiovascular disease in patients with RA, the potential role of serum uric acid has not been well looked into. Research has found that hyperuricemia is an independent risk factor for hypertension, heart failure, coronary artery disease, and stroke^{7,8}. Uric acid contributes to pro-atherogenic processes including inflammation, endothelial dysfunction, and oxidative stress⁹. The purpose of this study was to describe the clinical profiles of patients with coexistent gout and rheumatoid arthritis.

Materials and Methods

This was a retrospective study carried out in the Nairobi Arthritis Clinic. The study site is situated in Nairobi, the capital city of Kenya and serves as a tertiary referral center. It not only serves the two million inhabitants of Nairobi but also patients from all over Kenya and the greater East and Central African Region. We reviewed the medical records of patients with RA and gout from January 2009 to December 2017. Rheumatoid arthritis was defined according to the 1987 ACR criteria. Gout was defined using the physician diagnosis along with typical mono-sodium urate crystal positivity in synovial fluid or the 1977 American Rheumatism Association clinical criteria for gout. We excluded calcium pyrophosphate-associated arthritis, hyperuricemia without gout, septic arthritis and traumatic arthritis.

Relevant parameters retrieved from patient records included clinical data (age, gender, primary diagnosis, comorbidities, presence of tophi, cigarette smoking) laboratory data (rheumatoid factor and anti-CCP status, uric acid levels at diagnosis, lipid profile, glycemic level, urate crystals in synovial fluid).

Results

The cohort included 13 patients with the diagnosis of rheumatoid arthritis and gout seen at the clinic between January 2009 and December 2017. Majority of the study participants were male (9/13) with a mean age of 60.8 years. The mean age of diagnosis of rheumatoid arthritis and gout was 55.25 years and 63 years respectively.

Table 1: Characteristics of 13 patients with rheumatoid arthritis and gout included in the study

Characteristics	Numbers
Mean age	60.8 years
Gender	Male (9) Female (4)
Seropositive (RF/CCP)	RF (8) CCP (4) Both (10)
Seronegative (RF/CCP)	3
Tophi	10
Mean BMI	31.4
Urate acid crystals	10
Alcohol	11
History of cigarette smoking	4
Glucocorticoid treatment	13

The participants were obese with a mean of 31.4. The mean uric acid levels were 392.6 $\mu\text{mol/L}$ with the normal reference for males at 200–430 $\mu\text{mol/L}$ and females at 140–360 $\mu\text{mol/L}$. Majority tested positive (10/13) for either or both rheumatoid factor and anti-citrullinated peptide antibody. Urate acid crystals were identified in 10 of the 13 participants. Ten of the participants had exposure to alcohol while four had smoked in the past.

All the participants had used glucocorticoids with a further 4 on diuretics which were later stopped (Table 1).

Discussion

There is paucity of documentation of co-existence of gout and rheumatoid arthritis in Africa let alone worldwide. There is a common belief that gout and RA do not, or rarely, coexist in the same patient. The presence of polyarticular tophaceous gout makes it more difficult for the clinician to differentiate gout from rheumatoid arthritis especially if the hands are involved. There has been less than 100 cases of coexisting rheumatoid arthritis and gout in English literature. They include a report from Taiwan of eight cases of coexisting RA and gout between 1994 and 2005; the authors also included the features of 24 previously reported similar cases in the English literature⁶. Olaru *et al*¹⁰ has documented case series of 13 patients also with dual diagnosis of gout and rheumatoid arthritis. Our case series had 13 patients of whom gout was the first diagnosis in 9 of the patients. They all had confirmed urate crystals in the synovial fluid. This corresponds to what has been reported in published literature^{6,11}. Jebakumar *et al*¹² had different findings in their case series where rheumatoid arthritis was diagnosed first. The cohort was predominately male, which was similar to Olaru *et al*¹⁰. However, it differed with Jebakumar's case series which was largely female though they had a slightly larger and younger population which could possibly explain the difference¹². Of the four with rheumatoid arthritis as the first diagnosis had hypertension and were on thiazide diuretics. We suspect this may have been the trigger of the gout in these cases. The patients in this cohort were obese with a mean BMI of 32.8 kg/m^2 . This is in keeping with similar studies on patients with co-diagnosis of rheumatoid arthritis and gout^{6,10,12}. The number of patients with tophi was higher than noted in other literature^{6,10,12}. The reasons could be that we being a tertiary center we see them after they have had the disease for a longer duration. A major limitation of our study is being a retrospective record-based in nature and a single center-based with a relatively small sample size.

Conclusion

This is the first study on patients with co-diagnosis of gout and rheumatoid arthritis done in Kenya and the greater east and central Africa. It shares similarities with other studies done across the world. Being male and obese having either rheumatoid arthritis or gout increasing the chance of developing both diseases. A large number had tophi thus in patients with tophaceous gout not improving on standard therapy an alternative diagnosis could be rheumatoid arthritis.

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Conflict of interest

The authors declare no conflict of interest.

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Systemic lupus erythematosus with acute inflammatory demyelinating polyneuropathy: a case report

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Abstract

We recently managed a case of acute inflammatory demyelinating polyneuropathy associated with SLE. A 20-year-old newly diagnosed SLE patient presented with a three-week history of acute bilateral ascending weakness associated with inability to walk. Physical examination revealed muscle strength in the legs with graded 2/5 proximally and 2/5 distally bilaterally and absence of deep tendon reflex in both knees and ankles. The muscle strength in upper limb was 3/5 proximally and 3/5 distally bilaterally. Paresthesia was observed in distal limbs with glove and stocking distribution. Cerebrospinal fluid analysis was normal. Electrophysiologic survey indicated asymmetrical mixed sensory motor demyelination and radiculopathy. The diagnosis of SLE was established based on her initial symptoms including fevers, fatigue, malar rash, myalgia, and positive ANA. Treatment with intravenous immunoglobulin and methylprednisolone resulted in clinical improvement.

Key words: Systemic lupus erythematosus, Acute inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, inflammatory, autoimmune disease characterized by multisystemic involvement with a myriad of clinical presentations. Neurologic complications are common and frequent in SLE. Central Nervous System (CNS) involvement is one of the more common complications that can occur at any stage of the SLE. These symptoms may precede the onset of SLE or can occur at any time during the course of SLE¹. Peripheral nervous system involvement occurs in 3–18%². Here we report a patient with AIDP that was associated with SLE.

Case report

A 20-year-old newly diagnosed SLE patient presented with a three-week history of acute bilateral ascending weakness for three weeks, fever, paraesthesias and inability to walk. She had a flu-like illness one month prior to the onset of neurological symptoms. She was diagnosed with SLE one month prior to the admission due to symptoms including fevers, fatigue, malar rash, myalgia, and positive ANA and double stranded DNA. Her vitals on admission were temperature of 36.2 degrees celsius, blood pressure of 110/62 mmHg, pulse of 78/minute and respiratory 22/minute. Physical examination revealed she was alert and oriented time, place and person, followed commands, and had no aphasia with intact comprehension and fluent speech. Cranial nerve exam was normal. Motor exam revealed 3/5 strength in the proximal upper extremities (abduction and flexion) and 5/5 in wrist flexion and extension. Hip flexion was 2/5 bilaterally. Knee extension and flexion, dorsiflexion, and plantar flexion were 4/5 bilaterally. Reflexes were equal and symmetric in upper extremities but diminished in lower extremities. Her cardiovascular, respiratory and abdominal were unremarkable.

Lab examination was as follows: haemoglobin 10.5mg/dl, white cell count 7.23×10^9 , platelet of 441×10^6 ; BUN-6.06mmol/l, Na-133mmol/l, K-4.1mmol/l, CL-101mmol/l, Cr-64.2umol/l; glucose-6.7 mmol/l, aspartate aminotransferase (AST)-8.9 U/l, alanine aminotransferase (ALT)-12.6 U/l, alkaline phosphatase (ALP)-107.8 U/l, total bilirubin-3.4umol/l, C-reactive protein-2.7mg/l. Cerebral spinal fluid revealed protein 26mg/dl, sugar 3.0mmol/l, LDH 269U/l, WBC 0-1/HPF. Serology for HIV, VDRL, Hepatitis B and C were negative. The b2microglobulin, antiphospholipid and lupus anti-coagulant anti-bodies tests were negative. MRI of the thoracolumbar spine showed L5/S1 annulus disc bulging narrowing the neural exit foramina. Electrophysiologic survey indicated asymmetrical mixed

sensory motor demyelination and radiculopathy. A pulse-dose methylprednisolone was initiated while hydroxychloroquine was continued while awaiting the CSF and EMG results. Guillain Barre' Syndrome (GBS) was diagnosed on the basis of clinical symptoms, EMG, and lumbar puncture. Further GBS workup, such as antiganglioside antibodies were not performed. The patient was started on intravenous immunoglobulins (IVIG) for 5 days. Motor strength and facial weakness improved during the course of therapy. From SLE standpoint, she was maintained on hydroxychloroquine and azathioprine and remained in clinical and serological remission.

Discussion

Neuropsychiatric lupus (NPSLE) is one of the least understood yet possibly could be one of the most prevalent manifestations of lupus. It can occur independently of active systemic disease and without serologic activity³. The numbers affected range from 14% to over 80% in adults and 22% to 95% in children⁴⁻⁶. The American College of Rheumatology established 19 specific neuropsychiatric syndromes case definitions from two broad categories: central and peripheral manifestations⁷. Common presentations include seizures, depression, and psychosis, headaches and cerebrovascular accidents. Peripheral neuropathy is an often-underestimated complication in SLE. The incidences range from 1.5% to 27.8%⁸⁻⁹. Guillain Barre Syndrome which is a manifestation peripheral neuropathy in SLE is rare with incidences reported to be 0.6-1.7%⁸⁻¹⁰.

Li *et al*¹¹ reported that GBS with SLE was more common in females (73.3%) than males (26.7%). Our patient was female. GBS manifested early in the course of lupus which was consistent with the previously reported case reports¹¹. We suspect the trigger for the GBS was the flu-like symptoms she had prior to the onset of the illness. This is consistent with what is reported in literature that up to two thirds of cases are preceded by symptoms of upper respiratory tract infection or diarrhoea. The most frequently associated infectious agent being *Campylobacter jejuni* (30%)¹². Others include cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, and *Mycoplasma pneumoniae*¹²⁻¹³. Autoantibody formation against gangliosides as part of immunological response in SLE can potentially elicit demyelinating polyneuropathy such as GBS. Elevated proinflammatory cytokines such as interleukin-6 and interleukin-8 have been found in patients with SLE with neurological symptoms¹⁴. We did not perform antiganglioside antibodies in our patient due to cost implications. The third potential trigger of GBS like response in SLE is vascular including vasculitis, microangiopathy, and premature atherosclerosis leading to ischemic demyelination¹⁵. The b2microglobulin, antiphospholipid and lupus anti-coagulant were negative in this case. The last triggers involve host specific factors such as genetics or ethnicity and environmental. Further research is required to elucidate the underlying reasons for GBS with SLE.

As GBS in SLE is rare controlled clinical trials are largely lacking which results in various non-standardized treatment regimens. The treatment options available for GBS with SLE, include corticosteroids, cyclophosphamide, plasmapheresis and immunoglobulin. Although clinical trials have demonstrated no benefits of corticosteroids in GBS, it's still the most frequent treatment option for neuropsychiatric manifestations of SLE¹⁶⁻¹⁷. This regime wasn't successful in our patient. Combination with cyclophosphamide may have had better results. This regime has been shown to have improved the overall outcome in patients with SLE where GBS was the initial presentation¹⁸⁻¹⁹. Due to her being in the reproductive age we opted for IVIG which has demonstrated efficacy against GBS and is the first line therapy along with plasmapheresis²⁰⁻²¹. The exact mechanism of action of IVIG in GBS is unknown. Its proposed mechanism involves antagonization of circulating pathological antibodies by anti-idiotypic antibodies, modulation of cell-mediated immunity and complement pathways²². The present patient received IVIG for treatment of GBS in the background of SLE and responded well.

Conclusion

There is a rare association between GBS with lupus probably due to an immunological aetiology. This may have an impact on both treatment and prognosis. This is strongly evidenced by reported literatures, which is translated into decisions for their management and impact on long-term outcomes. Our case suggests prompt diagnosis and treatment, early in the course of illness can result in a positive clinical outcome. It also supports corticosteroids alone does not alter the course of GBS and that IVIG should be considered as first line therapy for GBS associated with SLE.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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Abstract

For a diagnosis of polymyositis (PM) to be deemed probable or definite, affected patients must fulfil 3 or 4, respectively, of the Bohan & Peter 1975 diagnostic criteria (i.e. proximal muscle weakness, elevated muscle-specific enzyme levels, myopathic EMG and characteristic muscle histology)¹. We report here a patient who was initially misdiagnosed and treated as having PM, and whose diagnosis of sarcocystosis myopathy was only confirmed when specialist muscle histology was undertaken in a tertiary laboratory.

Introduction

Sarcocystosis, previously known as sarcosporidiosis, is a rare intracellular zoonotic protozoal parasitic infection of human beings caused by *Sarcocystis* spp, in the phylum Apicomplexa². *Sarcocystis* spp has a two-host life cycle of a sexual reproduction stage in a definite host (gametogony followed by sporogony) in the intestine of a carnivore or omnivore, and asexual multiplication stage (schizogony) in the tissue of an herbivore as an intermediate host. Human beings may serve as both intermediate and definitive hosts². Humans can be dead-end intermediate hosts for *S. nesbitti*, which is likely acquired via consumption of food or water contaminated with oocysts from snakes or monkeys³. This organism in humans will cause muscular sarcocystosis. Manifestations may be nonspecific and include fever, myalgia, and headache.

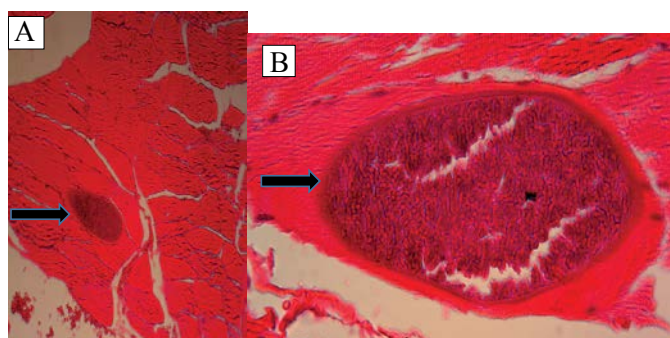
Case report

A 29-year-old previously well male labourer presented to a rural Kenyan clinic with myalgia and muscle weakness, in association with generalized malaise and fever. Examination revealed obvious proximal muscle weakness.

A presumptive diagnosis of PM was made, and he was commenced on prednisolone at daily doses ranging from 10-20mg. This gave no benefit even after five months of therapy. The patient discontinued the drug, and sought herbal medicines, again without benefit. After ten months of further continued symptoms, the patient thus journeyed to a specialist rheumatology clinic in Nairobi for a second opinion. Physical examination again revealed proximal weakness, but with no other signs of a connective tissue disease. Laboratory investigations revealed a white blood cell count of $12.6 \times 10^9/L$, and with an eosinophilia of 9%. It is unknown whether his eosinophil count was checked in the rural clinic. Muscle enzymes were also elevated: lactate dehydrogenase 270 U/L (NR 100-250) and aldolase 24.2 U/L (NR <7.5). Antinuclear factor was negative, and thyroid function tests normal. Neurophysiological examination was unavailable even in the Kenyatta National Hospital, University of Nairobi. As PM was still suspected muscle biopsies were obtained from the deltoid and quadriceps muscles, and corticosteroids were restarted. In view of the eosinophilia, and the possibility of a yet unproven infestation, albendazole was also recommenced, again with no improvement.

Muscle histology took a number of weeks, as the samples were sent to a tertiary laboratory in Italy, but eventually confirmed the diagnosis as one of sarcocystosis myopathy (Figure 1). The patient had meanwhile tested serologically negative for toxoplasmosis. As retreatment with steroids and albendazole was of no benefit, he was switched to high dose trimethoprim-sulfamethoxazole co-prescribed with steroids. He then recovered to normal within a matter of weeks, with normalisation of the muscle enzyme levels and resolution of the eosinophilia.

Figure 1: Cross-section of a sarcocyst in this patient's quadriceps muscle (arrow, H&E, x100) in A). The sarcocyst measures 320 μm x 180 μm and has a thin, oval, smooth cystic wall, and with numerous bradyzoites seen within the sarcocyst (arrow, H&E, x400) in B). Inflammatory cell infiltrations are conspicuously absent



Discussion

Sarcocystosis is a rare cause of human proximal myopathy, and is due to infestation by a coccidian parasite of the sarcocystis genus. It is spread by the faecal-oral route, from snakes and monkeys to pigs and cattle, and thence to man. Humans can be intermediate and/or end hosts, via accidental faecal/oral contamination by oocysts³. His initial diagnosis of PM was made in a rural clinic setting, but his chronic symptoms of fever, myalgia and proximal muscle weakness, in combination with an obvious chronic eosinophilia, widened the differential to include infectious and parasitic myopathies, including with viral infections (e.g coxsackie), trichinosis, cysticercosis, trypanosomiasis and HIV-associated myositis related to toxoplasma, cryptococcal or fungal infections. These myopathic diagnoses, and that due here to sarcocystosis, can currently be confirmed only by muscle histology, as serological testing is unavailable. Sarcocystosis has a worldwide distribution, and is generally harboured by livestock. Symptomatic and asymptomatic gastrointestinal infection occurs, with the highest prevalence actually being reported in Europe⁴. Most cases of human sarcocystosis are reported during outbreaks, e.g in Southeast Asia^{4,5}, and an autopsy study of 100 Southeast Asian patients dying of other causes reported a prevalence of 21%⁶. Sarcocystosis manifestations include myositis, myalgia, localized muscular swellings, low grade fevers, weakness, vasculitis and eosinophilia⁴. Serum muscle enzyme levels are usually elevated⁴. Sarcocystosis myopathy symptoms are due to secondary inflammatory cell infiltrations, and usually composed of lymphocytes and eosinophils⁸. The incubation period for muscular sarcocystosis is 9-13 days³, initial symptoms usually lasting for a median of 17 days. They may however persist for months, as occurred in our case, or even years³⁻⁵. Sarcocystosis may also have a brief, and self-limiting course with myalgia lasting less than a week³⁻⁵. The early clinical features of

muscular sarcocystosis are non-specific, so in an African setting raise the possibility of other tropical conditions, Sarcocystosis myopathy has no specific treatment, but trimethoprim-sulfamethoxazole, clindamycin and pyrimethamine have all been used with success^{4,5}. Corticosteroids and albendazole have also been used, but with limited success^{7,8}. A reported paucity of secondary inflammatory cell infiltrations in muscle sarcocystosis⁴ may explain the limited effectiveness of corticosteroids when used alone. Proper disposal of animal and human faeces, and careful animal husbandry, are prerequisites to avoid human sarcocystosis parasitism. Public health education regarding transmission, combined with proper diagnosis, are therefore vital. If a neurophysiological examination had been undertaken here, and had shown myopathic changes, it would have been possible to misdiagnose his case as “probable PM”, illustrating the crucial importance of undertaking diagnostic muscle biopsies in the African setting, to avoid missing this and other myositis mimics. Although rare, this diagnosis should clearly be considered in patients developing apparent PM after recent trips to rural Africa or Asia, and especially in the presence of an eosinophilia.

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More than skin colour: challenges of diagnosis and managing Raynaud's phenomenon in a Kenyan lady

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Abstract

We report the case of a 35-year-old female with Raynaud's associated with mixed connective tissue disease. The patient presented with a two-week history with pain, ulceration, and "darkening" of her fingers and feet. She had been diagnosed with mixed connective tissue disease two years earlier and had Raynaud's as one of the symptoms. She was subsequently lost to follow up due to financial constraints. Despite our efforts, we were not able to save her limbs from amputation.

Introduction

Raynaud phenomenon is defined as reversible spasms of the peripheral arteriole in response to cold temperature or emotional stress¹. The phenomenon manifests clinically by the sharp demarcation of colour changes of the skin of the digits. It is classified into primary Raynaud's phenomenon and secondary Raynaud's phenomenon according to the underlying aetiology such as systemic lupus erythematosus and systemic sclerosis. Abnormal vasoconstriction of digital arteries and cutaneous arterioles due to a local defect in normal vascular responses are thought to be the underlying cause of the primary form of this disorder². The goals of therapy are to improve quality of life and to prevent ischemic tissue injury. Severe cases of Raynaud's can lead to ulceration and gangrene of the affected extremities. We describe a case of severe secondary RP in a black African woman from a resource-limited setting, and the difficulties encountered in the diagnosis and management

Case report

A 35 year old female diagnosed with mixed connective tissue disease returns to the rheumatology clinic after 2 years with pain, ulceration, and "darkening" of her fingers and feet of two weeks duration. The pain had progressively worsened over the same duration with minimal relief from over the counter diclofenac.

She had initially been diagnosed with systemic lupus erythematosus based on Raynaud's, malar rash, oral ulcers, photosensitive dermatitis and positive dsDNA. She was initially put on aspirin, hydroxychloroquine, and prednisone. During subsequent follow up she developed worsening Raynaud's, arthritis, symptoms of proximal myopathy and skin tightening over the face, fingers and hands. Her lab tests showed elevated CRP and ESR with a negative antinuclear antibody, rheumatoid factor, and anti-citrullinated peptide. Due to finances, we were not able to do further investigations. Her diagnosis at this time was a probable mixed connective tissue disorder. She was added methotrexate and nifedipine. She did not return for a subsequent follow up at the rheumatology clinic partly due to financial constraints. The general examination revealed wasted patient, pedal edema and elevated blood pressure 151/113 mmHg. The right lower limb had dry gangrene over the right foot on all digits while the left foot had gangrene over digit 4 and 5 with intact pulses (Figure 1). The examination upper limbs revealed fixed flexion deformities on all fingers with gangrene on the left hand on digit 5 and right hand over digit 2,3 and 5 (Figure 2). She was admitted and put on nifedipine 40mg twice a day, methotrexate 10mg weekly, atorvastatin 40mg nocte, hydroxychloroquine 200mg twice a day, tramadol 100mg twice a day and sildenafil 25 mg twice a day. We pulsed with methylprednisone for 5 days when the gangrene did not improve despite the treatment as we have no access to iloprost. She had a normal arteriogram. With no improvement, she is due for amputation of the affected limbs and digits.

Figure 1: Gangrene in the lower limbs



Figure 2: Gangrene in the upper limbs



Discussion

Raynaud phenomenon presents as recurrent vasospasm of the fingers and toes and usually occurs in response to stress or cold exposure¹. It was first described by Maurice Raynaud, who, as a medical student, described a case in 1862 as “episodic, symmetric, acral vasospasm characterized by pallor, cyanosis, suffusion, and a sense of fullness or tautness, which may be painful². The prevalence of primary Raynaud phenomenon varies among different populations, from 4.9%-20.1% in women to 3.8%-13.5% in men¹. Raynaud’s is more common among young women, younger age groups, and family members of patients with the phenomenon^{1,2}. There’s no epidemiologic data on this phenomenon from Africa. Our patient had mixed connective disease. Other autoimmune causes of secondary Raynaud’s include scleroderma, systemic lupus erythematosus. Other causes include drugs (cisplatin, bleomycin, beta-blockers, amphetamines etc). Occupational and environmental causes such as vascular trauma (the use of vibrating tools, carpal tunnel syndrome, injury to the distal ulnar artery etc), hypothyroidism and haematologic abnormalities such as paraproteinemia and cryoglobulinemia³⁻⁵. It has been proposed that the pathogenesis of secondary Raynaud’s surrounds dysregulation of the neuro endothelial control mechanisms. There is evidence that suggests that it involves abnormalities in the blood vessel wall (endothelium and smooth muscle), neural control of vascular tone and a deficiency of vasodilatory mediators, including nitric oxide, has been implicated⁶.

Raynaud’s usually affects the fingers and toes but may rarely affect the nose, ears, nipples, or lips. This presents as either colour changes white (pallor), blue (cyanosis), and red (hyperemia) or numbness and pain in the affected area or areas. Primary Raynaud’s is usually benign. The attacks are usually symmetrical and lack evidence of peripheral vascular disease, tissues necrosis, ulceration, or gangrene⁷. Secondary Raynaud’s is characterized by tissue necrosis, ulceration, and gangrene-like our case⁷. The diagnosis of Raynaud’s in black skin still remains a challenge as it may be difficult to appreciate the typical

triphasic colour changes. Having a high index suspicion and identifying secondary aetiologies can be useful as some of the diagnostic tests, for example, ANA and anti-Scl 70 anti-bodies may be too expensive in a set up like in Kenya.

The goals of therapy are to improve quality of life and to prevent ischemic tissue injury. The efficacy of the treatment depends upon the severity of disease and upon the presence or absence of an underlying disorder. First line therapy for primary Raynaud’s consists of patient education, lifestyle measures like avoiding precipitating factors like keeping warm, cessation of smoking etc. Avoidance of sympathomimetic drugs (such as decongestants, amphetamines, diet pills and herbs especially those that contain ephedra) are usually recommended. However no trials have been performed to assessing the impact of over-the-counter preparations for example cold medications⁷. The Raynaud Condition Score (RCS) can be used to assess response to treatment. RCS is a validated tool that looks at the frequency of attacks, the duration of attacks, the disability caused, and the overall effect on daily quality of life^{8,9}. The RCS uses a visual scale of 0 to 100; a change of about 15 is the minimum change considered clinically important^{8,9}. Pharmacotherapy should be considered when nonpharmacologic treatment measures alone are insufficient to adequately reduce the frequency and severity of attacks. Calcium channel blockers that have proven effective for primary and secondary Raynaud phenomenon as the initial choice for drug therapy. Slow-release or long-acting preparations of the dihydropyridine calcium channel blockers, such as nifedipine or amlodipine are preferred¹⁰. Recommendations are to start at the lowest tolerated dose and titrate depending on response and tolerability. Those unable to tolerate alternative therapies include phosphodiesterase-5 inhibitors, angiotensin inhibitors, topical nitrates and local injection of botulinum toxin type A^{11,12}. For patients who experience persistent intense pain, ulceration, and gangrene combination of calcium channel blockers with phosphodiesterase-5 inhibitors, endothelin receptor antagonist (bosentan) and prostaglandin analog (iloprost, epoprostenol)^{11,12}. We think our patient may have benefited from prostaglandin analogs. These class of drugs are currently unavailable in Kenya. Multiple studies have examined the efficacy of treatment of severe refractory RP and ischemic digital ulcers with preparations of prostaglandin analog^{13,14}. Bosentan reduces the incidence of new digital ulcers⁷. Another option for our patient would have been sympathectomy. In patients with digital ulceration with critical ischemia, when oral and/or topical vasodilatory therapy does not quickly result in improvement in digital blood flow and when IV PG are not readily available, there is evidence that temporary chemical sympathectomy is performed with a digital or regional block¹⁵.

It’s unfortunate the patient presented late with gangrene affecting several digits. With the unavailable prostaglandin analogs and sympathectomy, the only other treatment available was amputation.

Conclusion

This was a case of Raynaud's with critical ischemia in a black African lady in a resource-limited set up in Nairobi. We have highlighted shortcomings and lessons learned from this case. This would have avoided the drastic option of amputation in a lady in her income-generating age. Diagnosis of Raynaud's in black African skin needs to be reviewed so as for enhancing early diagnosis and appropriate management, especially in a resource-limited setup.

Competing interests

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

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Abstract

This case report highlights the occurrence of neuropsychiatric lupus in a teenager with Systemic Lupus Erythematosus (SLE). The diagnosis of SLE was made based on the American College of Rheumatology (ACR) classification criteria. She presented with a history of fever, polyarthralgia, malar rash, pharyngitis, abdominal pain, discharging ears with reduced auditory function. She also had a history of fatigue, myalgia, weight loss, facial swelling, cough and hair loss. She had persistent headache, anxiety, confusion and generalized tonic clonic seizures. Essential findings on examination were those of distress on account of pain and difficulty with breathing, bilateral inguinal lymphadenopathy and a pulse rate of 118 beats/min.

Her laboratory results revealed a positive anti nuclear antibody (1:>5120) with a fine speckled pattern, positive anti double stranded DNA (>300 IU/ml), anaemia (Hb 7g/dl; PCV 21%), mean corpuscular volume of 66fl, white blood cell count of 3.5×10^9 , a normal platelet count, a negative rheumatoid factor, erythrocyte sedimentation rate of 123mm/HrWestergren. She had proteinuria (1+) with an essentially normal serum, electrolytes urea and creatinine.

Key words: Systemic lupus erythematosus, Neuropsychiatric, Anti nuclear antibody

Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disorder with multisystem involvement resulting in significant morbidity and mortality. Childhood-onset SLE (cSLE) is a rare disease with an incidence of 0.3-0.9 per 100,000 children-years and a prevalence of 3.3-8.8 per 100,000 children with a higher frequency reported in Asians, African Americans, Hispanics and native Americans¹⁻³. It represents 10-20% of all SLE cases, and is associated with higher disease severity than adult-onset SLE¹. Hiraki *et al*² noted that non-Caucasian

ethnicity is associated with increased childhood onset SLE disease prevalence and that non-Caucasian patients were significantly younger and more likely to have nephritis.

Most studies report a median age of onset of cSLE between 11-12 years. As in adult onset SLE, approximately 80% of patients with cSLE are females^{4,5}. As in adults the diagnosis is made based on the fulfillment of 4 or more of the American College of Rheumatology classification criteria for SLE⁶.

The clinical features in SLE are protean ranging from constitutional symptoms such as fever, anorexia, weight loss to neuropsychiatric involvement. Reports of childhood onset lupus from sub-Saharan Africa are scanty in spite of increasing reports of adult SLE⁷. In a study on juvenile SLE cases in Nigeria, 12 patients were seen over a 4 year period with all patients having haematological, constitutional symptoms and a positive anti nuclear antibody⁷. The only other report of juvenile SLE from Nigeria is a 2007 study of 11 children seen in a paediatric nephrology clinic⁸. Based on the rarity of this presentation we report a case of neuropsychiatric lupus occurring in a teenager.

Case report

The patient was a 13-year-old female student, who was apparently well until about a year prior to presentation when she developed high-grade fever, generalized joint pains and rash. Joint pains affected the wrist, knees, and the small joints of the hands with no associated swellings or stiffness. She observed a sudden appearance of non-pruritic rash on her face, sparing the nasal-labial area (malar-rash). The distribution of the skin lesions also involved the trunk and extremities. There was a history of pharyngitis, abdominal pains and bullous lesions appearing on the limbs. About two months prior to presentation, she developed bilateral, discharging ears which was initially painful. This has resulted in a decline in her auditory function.

Figure 1: Dyspigmented lesions on the face



Figure 2: Lupus hair with alopecia



She has had a history of fatigue, myalgia, weight loss, significant hair-loss, facial swelling and cough which is non productive and non pleuritic. She had been experiencing persistent headache which is dull in nature, acute confusion and anxiety. She had some episodes of generalized tonic-clonic seizures while on admission, sudden weakness of the upper and lower limbs a day prior to presentation and attained menarche on admission.

On general physical examination, she was chronically ill looking, in distress due to pain and difficulty with breathing and wide-spread dyspigmented lesions on the face and trunk. She was warm to touch (37.1°C), pale, anicteric, acyanosed, facial puffiness with bilateral inguinal lymphadenopathy. She was mildly dehydrated with bilateral pitting pedal edema.

Her pulse rate was 118 beats per minute; irregularly irregular with apex beat at the 4th left intercostal space, mid-clavicular line. Heart sounds S1, S2, S3 were heard with respiratory rate of 32 cycles per minute. Her breath sounds were broncho-vesicular with SPO₂ of 88%.

There was generalized abdominal tenderness. She was conscious and oriented in person but not in place and time.

Her laboratory results revealed a positive anti nuclear antibody (1:>5120) with a fine speckled pattern, positive anti double stranded DNA (>300 IU/ml), cardiolipin Ig M and IgG (1.7 NPL/ml, 3.0GPL/ml respectively), anaemia (Hb 7g/dl, PCV 21%), mean corpuscular volume of 66fL, white blood cell count of 3.5×10^9 , normal platelet count ($376 \times 10^9/L$), a negative rheumatoid factor (4.2 IU/ml), erythrocyte sedimentation rate of 123mm/HrWestergren, CRP<2.0mg/l. She had proteinuria (1+) with an essentially normal serum electrolytes, urea and creatinine. She was placed on pulse methyl prednisolone for 3 days and then oral prednisolone, hydroxychloroquine, azathioprine, phenytoin infusion and oral phenytoin thereafter. Other medications administered were; ceftriaxone, co-amoxiclav, omeprazole, lisinopril, and otomed ear drops. She was transfused with two units of blood. She was discharged on the nineteenth day on admission having improved remarkably.

Discussion

The reported case has SLE having had more than four (polyarthralgia, hair loss, anaemia, leucopenia, seizures, malar rash, a positive anti nuclear antibody and double stranded DNA) of the American College of Rheumatology classification criteria⁶. The exact aetiology is unknown but the interactions between immune complexes, autoantibodies, genetic, drugs and environmental factors do play a significant role in causing inflammation and eventually damage to the organs and systems⁹.

The age of the patient (13 years) is in keeping with most studies which have reported a median age of onset of cSLE between 11-12 years¹⁰. The female preponderance seen in other reports is highlighted in this case^{4,5}. Fevers, lymphadenopathy, rash, renal dysfunction, neurological and haematological disorders and polyarthralgias have been described¹¹.

She had constitutional symptoms which are frequently recounted in patients with childhood onset lupus⁸. She experienced some neuropsychiatric manifestations (seizures, headache, confusion and anxiety). The central and peripheral nervous systems can be involved with 19 distinct neuropsychiatric lupus (NPSLE) syndromes described¹². Up to 65% of childhood SLE patients develop NPSLE at any time during the disease course, and up to 85% of these patients will develop NPSLE within the first 2 years from diagnosis^{13,14}. Neuropsychiatric involvement with SLE is at least as common in children as it is in adults, with the former experiencing symptoms especially within a year after diagnosis with SLE (70% vs. 28%)¹⁶. Neuropsychiatric manifestations have been reported in 29-44% of paediatric patients with SLE¹⁷. Anaemia is not uncommon in childhood SLE as seen in this case. Cytopenias are common in cSLE, with more than 50% of patients presenting a decrease in at least one cell line^{4,16}.

Anti Nuclear Antibody (ANA) was positive with a significantly high titre. The commonest autoantibody is the ANA which is present in more than 95% of cSLE¹⁰. Anti-ds DNA antibodies are highly specific for SLE, and are present in about 61-93% children with active disease, especially active nephritis¹⁸. This serological marker was positive in the reported case with a significantly elevated titre as well as the presence of proteinuria. The use of corticosteroids and hydroxychloroquine have shown excellent results in control of the disease¹⁸ as in the reported case.

Conclusion

Systemic lupus erythematosus has protean manifestations. Neuropsychiatric lupus in children has been rarely reported in Nigeria. A high index of suspicion is imperative in making a diagnosis and the institution of effective aggressive therapy is rewarding.

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Abstract

Fever of Unknown Origin (FUO) is a syndrome defined by persistent fevers above 38.3°C that lasts for longer than 3 weeks with no obvious source. It usually poses a diagnostic challenge to the clinician.

We describe a case of FUO in a young male adult who was treated several times with antibiotics and anti-malarial with no resolution of symptoms. A diagnosis of Adult Onset Still's Disease (AOSD) was made after thorough investigation. A methylprednisolone pulse therapy relieved the fevers and maintenance therapy continued with methotrexate.

Adult Onset Still's Disease is a multi-systemic inflammatory disorder that can manifest as FUO and should be suspected if the fever does not respond to therapy.

Key words: Adult Onset Still's Disease, Fever of unknown origin

Introduction

Fever of Unknown Origin (FUO) is a syndrome defined by persistent fevers above 38.3°C and present for longer than 3 months¹. The differentials for FUO is vast and can be grouped as malignancies, infections and autoimmune conditions¹. It therefore requires an extensive laboratory and radiological work up. Adult Onset Still's Disease is a rare multi-systemic disorder that manifests in 5 to 10% of patients with FUO². Some of the diagnostic criteria's used are Yamaguchi, Cush, Calabro and Fautrel, however none has been validated in Africa. High ferritin levels has been associated with AOSD³. We describe a case of AOSD that manifested as FUO and did not fully fulfil the Yamaguchi criteria but had elevated ferritin levels.

Case report

A 16 year old school going African male presented with 1 episode of tonic clonic convulsions that lasted 5-7 minutes and a

3 month history of fever on and off that was relieved by paracetamol. There was positive history of 25kg weight loss in the past three months despite good appetite and food intake. He denied any history of diarrhoea, vomiting, cough, joint pains, rash and oral ulcers. There was no history of contact with person suffering from TB however he did come from a TB endemic zone. Systemic enquiry did not reveal anything significant.

Prior to presentation he had been seen at a peripheral clinic and completed a full course of anti-malarial as well as cefixime 2g bd. He was also started on iron supplementation for anaemia. His past medical and family social history were non-contributory. On physical examination he was febrile with a temperature of 38.8°C, pulse rate of 99 beats per min and a blood pressure of 106/62. He had no lymphadenopathy present. Abdominal exam revealed a hepatosplenomegaly. Cardiovascular, respiratory and neurological exam were normal.

His initial work up revealed a microcytic hypochromic anaemia (hb 12.2g/dl, MCV 74.4fl, MCH 24.8 pg), WBC 4.89 x 10⁹ with a neutrophils of 36%. His kidney function test was normal while transaminases were slightly elevated (ALT 50U/L, AST 65U/L, YGT 109 U/L). CRP was elevated at 41.6 mg/L, ESR elevated 27mm/hr and procalcitonin was normal at 0.83 ng/ml. Thorough screening for infection was negative (Salmonella typhi antigen, multiple blood and urine cultures, urinary lipoarabinomannan, VDRL, tropical fever PCR, HIV, CMV and EBV) TB Gold Quantiferon was indeterminate. Autoimmune screening tests were also negative (ANA, ENA panel, p-ANCA, c-ANCA, anti dsDNA and complement levels). Serum ferritin was elevated at 743 ng/ml.

Other tests included: sickling test negative, uric acid and LDH levels normal. Peripheral smear revealed a microcytic hypochromic picture. Radiological examinations were as follows: 2D ECHO, CXR, ECG and MRI brain were normal. Abdomino-pelvic ultrasound revealed

a hepatosplenomegaly and CT chest showed bilateral multiple pulmonary nodules with no hilar or mediastinal lymphadenopathy. Initially the patient received empirical antibiotics meropenem and azithromycin for 4 days with no improvement in symptoms and thus were stopped. Attempts to control fever with paracetamol were unsuccessful.

A rheumatologist review was done and a diagnosis of probable Adult Onset Still's Disease was made and recommended methylprednisolone pulse therapy of 500mg intravenous for 3 days. There was complete resolution of fevers after the first dose of methylprednisolone. Serum ferritin levels after the pulse therapy dropped to 207.9ng/ml. He was then initiated on oral prednisolone 15mg twice a day for 1 week with gradual tapering over 2 months. Steroid sparing therapy was initiated with methotrexate 10mg once a week and folic acid 5mg daily.

Discussion

Adult Onset Still's Disease (AOSD) is rare multi-systemic disorder of unknown aetiology². It affects 1–1.5 cases per 100, 000 people^{2,4}. Its prevalence in Africa is unknown with very little epidemiological data available. A few African case reports have been published from Nigeria⁴, Gabon⁵, Senegal⁶ and Kenya³, the patients age ranged from 12 to 48 years²⁻⁴. Some studies suggest a bimodal peak at ages 15-25 and 36-46 years⁷. It affects both genders but has a higher incidence in women⁸.

The exact pathogenesis is poorly understood. Studies suggest an association between AOSD and HLA antigens, viral and bacterial pathogens as well as environmental factors². Innate immune mechanism is activated with elevated levels of inflammatory markers such as IL-1, IL-18, IL-6 and TNF- α ^{2,4}.

The most common presentations are fever and arthralgia but other symptoms include rash, sore throat and myalgia². Rare presentations include lymphadenopathy, hepatosplenomegaly, pleurisy, pericarditis and abdominal pain^{2,9}. It could also manifest as fever of unknown origin without any other accompanying symptoms⁸, this was the case with our patient.

Neurological manifestations are rare, however, some cases have been reported of encephalitis and aseptic meningitis^{10,11}. Our patient presented with convulsions but we were unable to fully rule out central nervous system involvement without a consent for a lumbar puncture. Serum ferritin five times the upper limits of normal has 80% sensitivity and 46% specificity in diagnosing AOSD⁴. Glycosylated ferritin levels are decreased and combined with ferritin levels increases sensitivity and specificity compared to either test alone¹². In this case, the ferritin levels were elevated 1.5 times the normal upper limit. Glycosylated ferritin levels is unavailable in our facility as well as many parts of Africa. The Yamaguchi, Cush, Calabro and Fautrel are the diagnostic criteria used with the first being the most sensitive and commonly

used^{13,14}. These criteria have not been validated in Africa. The Yamaguchi criteria requires at least 5 to be fulfilled of which 2 must be major¹³.

Major criteria are as follows: Fever $\geq 39^{\circ}\text{C}$ for at least a week; Arthralgia or arthritis for at least 2 weeks; Non-pruritic salmon colored rash; Leukocytosis $\geq 10,000/\text{mm}^3$ with neutrophil predominance.

Minor criteria are as follows: Sore throat or pharyngitis; Lymphadenopathy; Hepatomegaly or splenomegaly; Abnormal liver function tests; Negative tests for RF and ANA.

Our patient fulfilled only 1 major and 3 minor criteria. Still's rash though part of a major criteria may not be present in all cases. A Kenyan study done by Oyoo *et al*¹⁵ only one of 68 children with JIA had the presence of still's rash. Salmon coloured rash may not be very visible on dark pigmented skin. The Fautrel's criteria requires glycosylated ferritin level¹¹ and its use is therefore limited in Africa due to availability of the test.

Non-Steroidal Anti Inflammatory have no role in AOSD with only 16% remission rates and higher incidence of adverse events¹⁶. Steroids are the mainstay of treatment and control symptoms in 60% of cases^{2,16}. New evidence supports the use of biologics in the early course of diseases e.g methotrexate, anakinra and tocilizumab¹⁶. Our patient received methylprednisolone pulse therapy with immediate resolution of fevers. Further treatment with tocilizumab as maintenance therapy was not possible due to financial constraints therefore methotrexate was the affordable steroid sparing option. The American College of Rheumatology recommends screening for latent tuberculosis before initiating treatment. During therapy continuous screening is recommended for high risk patients. Our patient came from a TB endemic zone and thus a clinical decision to start him on 3 months rifampin prophylaxis was made.

Conclusion

AOSD is rare and one should have a high index of suspicion when dealing with fevers of unknown origin in young adults.

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Rheumatology practice in Post Ebola Republic of Liberia, West Africa: Personal experience

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Dear Editor

The *African Journal of Rheumatology*, the foremost Rheumatology journal of the African continent, which has continued to showcase the myriads of terrain of practice of rheumatology in the continent, and also illustrates the various rheumatic conditions prevalent in the continent.

I would like to share with colleagues my brief experience of the practice of rheumatology in Post Ebola Republic of Liberia, situated in the West African sub region. I was contracted by the Liberia College of Physicians and Surgeons (LCPS) as one of the sub specialist consultants for a program that the college is anchoring, with funding being provided by the John Snow Incorporated (JSI); a US based NGO, to provide rheumatologic care to the Ebola survivors population as well as the general population and to also help with capacity building in rheumatology in the various health facilities chosen for the program. I came to Liberia in late July 2017, and the program is to last for 11 months (ending in May, 2018). I am writing this letter after spending 3 months in Liberia, practicing rheumatology in both the urban and rural Liberia, so as to share my little experience with colleagues, and probably suggest some ways in which to improve the current situation.

The rheumatology manpower: Like many countries in the sub-Saharan Africa, Liberia also has dearth of rheumatology manpower. As at the time of my arrival, there was no resident rheumatologist in the whole of the country. Other rheumatology support staffs were equally inadequate. No single rheumatology nurse or occupational therapist, but few physiotherapists, working in the bigger hospitals. The medical doctors, the Physician Assistants (PA's) and nurses have been the personnel taking care of people with rheumatic complaints in all health facilities in Liberia.

The rheumatology clinics: These were virtually non-existent in all the health facilities of Liberia for obvious reasons. Patients with rheumatic complaints are seen in the General Out Patients Clinics by the above mentioned categories of staff. This scenario is not peculiar to rheumatology patients though. With my arrival, I have started rheumatology clinics in Redemption Hospital and John F Kennedy Memorial Centre (located in Montserrado County), in Phebe Hospital (Bong County) and in Tellewoyan Memorial Hospital (Lofa County). These were all possible with much support from the LCPS, JSI and the individual management of the various health facilities.

The rheumatology laboratory support: As in many countries in the West African sub-region, laboratory support for evaluating rheumatic diseases is quite inadequate in Liberia. Rheumatologic investigations like Rheumatoid Factor, Anti CCP, HLA B27, ANA, ENA etc are not available in Government health facilities and when/where available in private facilities; they are too expensive, especially for the common patient. Other ancillary investigations (such as ESR, CRP, E/U/Cr, LFT's, etc) are equally not readily available in the Government health facilities. X-rays are readily available but other radio diagnostic facilities (such as CT scan, MRI, DEXA scan etc.) are lacking in many Government facilities.

The spectrum of rheumatology patients: In the past 3 months that I have consulted in at least 4 health facilities located in 3 counties (Montserrado, Bong and Lofa), the spectrum of cases I have seen are similar in the 3 counties. The degenerative arthritis predominates in all the facilities, with lumbar spondylosis being the commonest condition. Other degenerative conditions seen were knee osteoarthritis, hip OA and hand OA to a lesser extent. A couple of patients with

Rheumatoid Arthritis (RA) were also seen in all the 4 facilities visited; many thanks to the 2010 ACR/EULAR Classification Criteria¹ that made it possible for us to make definite diagnosis of RA in all the cases. Cases of gouty arthritis were equally seen, including tophaceous gout. We also had a suspected case of septic knee arthritis, but we could not have a culture support.

Other groups of rheumatologic conditions encountered are the soft tissue rheumatism; we saw a couple of patients with adhesive capsulitis, rotator cuff syndromes, lateral epicondylitis, medial epicondylitis, trigger finger, de quervain's tenosynovitis, anserine bursitis, popliteal cysts, plantar fasciitis etc. We are yet to encounter patients with connective tissue diseases, vasculitis and spondyloarhropathies, possibly because of the short duration of my report.

The rheumatology medications: This is another area where the healthcare system in Liberia is lacking for obvious reasons. There is paucity or unavailability of common rheumatologic medications across all the health facilities visited. The readily available drugs were paracetamol, ibuprofen, diclofenac, tramadol and prednisolone. Other NSAID's are not available, especially Cox-2 selective inhibitors. The Disease Modifying Anti Rheumatic Drugs (DMARD's) both traditional and the biologics are not available in the health facilities of Liberia. Few pharmaceutical outlets stock the traditional DMARD's like methotrexate, sulphasalazine and hydroxychloroquine, but the price is inhibiting to the patients. The biologics are completely not available in the country. Other drugs like allopurinol, colchicine, bisphosphonates, intra articular hyaluronan, and methyl

prednisolone are equally not available in the Government health facilities, and when available in the commercial pharmaceutical outlets, they are too expensive for the patients to afford.

Conclusion-A call for action: I hereby wish to make a passionate appeal to our regional body (AFLAR) to look into the situation of rheumatology practice in Liberia, particularly along the items enumerated above, and fashion out ways of remedying the problems, i.e. in the areas of manpower, diagnostics and medications. To my mentors and colleagues, I urge us to create time and leave our comfort zones so that we can come into this type of terrain and change the situation for good. I am very optimistic that in the nearest future, if similar visits are undertaken by colleagues, the story will surely be different. The Government of Liberia, the donor agencies and the People of Liberia are having the zeal to further strengthen rheumatology practice in the country, and this surely provides us with ample opportunity to capitalize on this will power.

Thank you very much for given me the opportunity to share my little experience practicing rheumatology in Liberia.

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