Research article

Clinical features of women with gouty arthritis in Cameroon, sub-Saharan Africa

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Abstract

Background: Limited data are available on the characteristics of women with gout in sub-Saharan Africa.

Objectives: To assess differences in clinical features of gouty arthritis between female and male patients in a Cameroonian population.

Methods: A cross-sectional study from January 2004 to December 2013 was conducted in the Rheumatology Unit of the General Hospital, Douala, Cameroon, including patients diagnosed with gout according to 1977 ACR criteria. A comparison between female and male patients with gout was made.

Results: We included 511 patients (96 women and 415 men). Women were older than men at the time of the diagnosis (62.56 ± 11.02 years *vs*. 54.45 ± 10.22 years; $p<0.001$). Gouty arthritis in Cameroonian women was characterized ($p<0.05$) by: (i) a late age at onset, mainly after menopause, with women older than men at the time of diagnosis; (ii) a higher frequency of hyperuricemia, but with uric acid levels lower compared to men; (iii) a lower frequency of structural joint damage; (iv) a greater frequency of comorbidities (particularly the metabolic syndrome components) and drugs intake like diuretics and low-dose aspirin. The distribution of joint damage was not different between the two sexes in our study. Women had globally fewer tophi than men ($p<0.05$), but they had more tophi at the proximal ($p=0.01$) and distal ($p=0.03$) interphalangeal joints than men.

Conclusion: Gout in women seems to present specific characteristics. Further studies with robust design are needed to understand these differences.

Key words: Gout, Women, Hyperuricemia, Cameroon, sub-Saharan Africa

Introduction

Gout is an ancient and common form of inflammatory arthritis. It is caused by an uncontrolled and chronic metabolic disorder, hyperuricemia, which leads to the deposition of monosodium urate crystals in tissues. Gout most often affects men and rarely women[1,2]. Although data are limited, studies show some differences between gout in women and men. Indeed, women with gout were older, had more significant comorbidities (chronic kidney diseases and some components of metabolic syndrome) often used diuretics and received appropriate surveillance of serum uric acid levels, but were less often treated with allopurinol[3-11]. Genetically, the two most prominent loci encode urate transporters *SLC2A9* and *ABCG2*, with sex-specific effects: *SLC2A9* is more potent in women, and *ABCG2* in men[2]. These data suggest that the factors leading to gout and treatment monitoring of are very different in women and men[3-11]. These features of gout in women were not found in all studies[12,13], despite similar tubular dysfunction for purine excretion in women and men in primary gout[14].

Data are scarce concerning the prevalence of gout in Africa. In a study from Sweden, the relative risk of incident gout was elevated in women born in Africa[1]. This data contradicted long-held beliefs that gout was rare in sub-Saharan Africa (SSA), particularly in women[15,16]. This may explain the scarcity of studies on the characteristics of gout in SSA[17,18]. In these studies, women were older than men at the time of diagnosis. The presenting feature was oligo- or polyarticular and tophaceous gout. Monoarthritis was rare and, if present, was found in joints other than the first metatarsophalangeal joint[17,18]. Women had more tophi, and the duration of the disease before the appearance of tophi was shorter. Comorbidities like hypertension, chronic kidney disease and dyslipidemia were common, with frequent diuretic use[16-18]. Since the publication of these works[16-18], no study to our knowledge with the same objective has been achieved in SSA. To overcome this unavailability of data, we performed this study intending to describe gout characteristics in Cameroonian women.

Materials and methods

Case ascertainment

We performed a cross-sectional study from January 2004 to December 2013 conducted at the Rheumatology Unit of the General Hospital, Douala, Cameroon, Central Africa. This study included all patients diagnosed with gout according to 1977 the American College of Rheumatology preliminary criteria[19]. Diagnosis is made if 6 of 12 clinical criteria are met or the presence of monosodium urate crystals in synovial fluid or in tophus. Clinical criteria included: more than one attack of acute arthritis, maximum inflammation developed within one day, oligoarthritis attack, redness observed over joints, first metatarsophalangeal joint painful or swollen, unilateral first metatarsophalangeal joint attack, unilateral tarsal joint attack, tophus, hyperuricemia, asymmetric swelling within a joint on X-ray, subcortical cyst without erosions on X-ray, complete termination of an attack[19]. The older 1977 criteria[19] were preferred instead of the more current 2015 gout classification criteria[20] because the patient recruitment period was before 2015 when these new criteria were published.

We categorized the patients included in this study into two groups according to gender, female and male. The main socio-demographic and clinical characteristics of both groups were compared.

Data collection

Data were collected on a standardized case-report form for each patient, including socio-demographic data, current and past medical history, clinical, laboratory and imaging data at the first consultation.

All affected joints were examined and recorded individually, except for the tarsometatarsal joints, collectively referred to as the Lisfranc/Chopart joint. We defined arthritis as a painful and/or swollen joint. Mono, oligo-, or polyarticular involvement was defined as involvement of 1, 2 to 3, or at least 4 joints respectively at the time of the first visit. Acute gout refers to a gout attack as an acute episode of inflammation (flare). Chronic gout or advanced gout was the existence of at least 3 gout attacks in the last 12 months, and/or chronic joint pain, and/or the presence of tophus, and/or the presence of structural joint damage as gout-related bone erosions on joint radiographs[2].

This study was performed per the ethical principles of the Declaration of Helsinki and approved by the institutional ethics committee (N° 027/AR/MINSANTE/HGD/DM/01/14). Informed consent from the patients was not needed as the study only involved file linkage and no actual handling of patients.

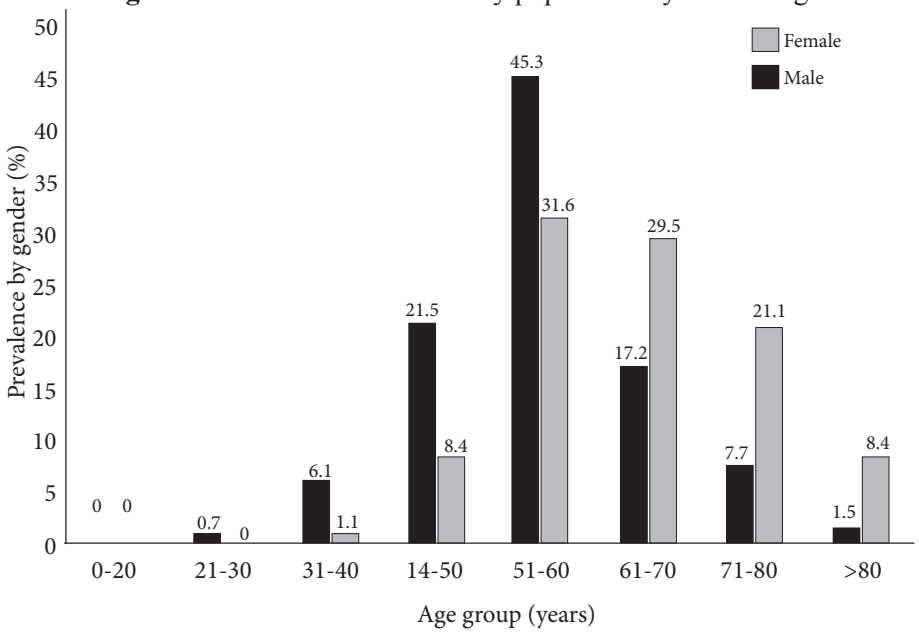
Statistical analysis

Data were analyzed using SPSS version 20.0 software (Chicago, IL, USA). Quantitative variables are presented as mean (standard deviation), qualitative variables are presented as numbers (%). Statistical comparisons were made with the Student's t-test for continuous variables and the Chi-square test for categorical variables. A *p-value* of less than 0.05 was considered statistically significant.

Results

Among the 511 patients included, 96 (18.8%) were women, and 415 (81.2%) were men. The female: male ratio was 1:4.32. The mean age was 55.97 ± 10.83 years. The women were significantly ($p < 0.001$) older than men at the time of diagnosis with the mean age at 62.56 ± 11.02 years (range: 43 to 86 years) for women vs. 54.45 ± 10.22 years (range: 26 to 84 years) for men. Gout occurs in 64 women (66.6%) after menopause, with a significant difference compared with those with the onset of gout before menopause ($p < 0.0001$). As shown in Figure 1, gout is more prevalent in women after 60 years than in men.

Figure 1: Distribution of the study population by sex and age



The mean serum uric acid was significantly lower in women compared to men (8.0 ± 2.71 *vs* 8.3 ± 1.08 mg/dL; $p = 0.001$). The following characteristics were also statistically significant ($p < 0.05$) in women: a high frequency of hyperuricemia, a greater frequency of comorbidities (hypertension, diabetes, dyslipidemia, and heart failure), a greater diuretics and low dose aspirin intake. Comparative socio-demographic data and clinical features for women and men patients with gout are summarized in Table 1. Regarding the joints affected (tender and/or stiffness), women seemed to have less upper limb involvement, but the difference was not significant ($p > 0.05$). Also, there was no gender difference in the number of joints affected (mono-, oligo-, or polyarticular) and the location of gout-related arthritis. These data are shown in Tables 1 and 2. In addition, women had fewer tophi than men, regardless of their location, but the difference was not significant ($p > 0.05$), except for the elbows [2 (2.1%) vs. 73 (17.6%); $p = < 0.001$)] which concerned more men (Table 3).

Table 1: Comparison of features of gout in women and men

Variables		Women (n=96)	Men (n=415)	P-value
Age (years), mean ± SD		62.56 ± 11.02	54.45 ± 10.22	0.001
BMI, n (%)	IMC normal	17 (17.7)	93 (22.4)	> 0.05
	Overweight	27 (28.1)	182 (43.8)	
	Obesity	52 (54.2)	140 (33.7)	
Alcohol intake, n (%)			52	
Place of residence, n (%)	Rural	15 (15.6)	34 (8.2)	> 0.05
	Urban	81 (84.4)	381 (91.8)	
Stages of gout, n* (%)	Acute gout	41 (42.7)	214 (51.5)	> 0.05
	Chronic gout	55 (57.3)	201 (48.5)	
Clinical presentation, n (%)	Monoarticular	41 (42.8)	214 (51.5)	> 0.05
	Oligoarticular	52 (54.1)	143 (34.5)	
	Polyarticular	3 (3.1)	58 (13.9)	
Serum uric acid, mean ± SD, mg/dL		8.0 ± 2.71	8.3 ± 1.08	0.001
Elevated uric acid levels, n (%)		56 (71.4)	329 (79.3)	0.001
Monosodium urate cristal (presence in synovial fluid)[†], n (%)		5 (50)	30 (51.7)	> 0.05
Inflammatory response, n (%)	Elevated CRP	32 (33.3)	132 (31.8)	> 0.05
	Elevated ESR	56 (58.3)	195 (46.9)	> 0.05
Arthritis, n (%)		95 (98.9)	413 (99.5)	> 0.05
Tophi, n (%)		10 (10.4)	193 (46.5)	0.001
Bone erosions in gout, n[‡] (%)		10 (10.4)	58 (13.9)	0.001
Current medical conditions, n (%)	Hypertension	53 (55.2)	155 (37.3)	0.001
	Diabetes	21 (21.8)	58 (13.9)	0,001
	Dyslipidemia	16 (16.6)	54 (13.0)	0,001
	Chronic kidney disease	3 (3.1)	39 (9.3)	> 0.05
	Heart failure	15 (15.6)	13 (3.1)	0.001
	Diuretics intake	15 (15.6)	36 (8.6)	0.01
	Low dose aspirin intake	2 (2.1)	4 (0.9)	0.03
Familial history of gout, n (%)		0 (0)	11 (100)	-

* Stages of gout: limited only on acute gouty arthritis and chronic gout; [†]Analysis of joint fluid was performed in 68 patients (10 women and 58 men) out of 87 patients with joint effusion; [‡]A radiography of the involved joint was done in 242 patients; SD, Standard deviation; CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

Table 2: Distribution of arthritis (tender and/or stiffness) according to gender

Variables		Women (n=96)	Men (n=415)	P-value
Shoulders		0 (0)	49 (11.8)	-
Elbows, n (%)		0 (0)	81 (19.5)	> 0.05
Wrists		11 (11.4)	82 (19.7)	> 0.05
Hands, n (%)	MCP*	0 (0)	53 (12.7)	-
	PIP†	7 (7.3)	49 (11.8)	> 0.05
	DIP‡	0 (0)	0 (0)	-
Knees, n (%)		64 (66.6)	236 (56.8)	> 0.05
Ankles, n (%)		27 (28.2)	160 (38.5)	0.055
Feet, n (%)	Lisfranc/Chopart joints	11 (11.4)	39 (9.4)	> 0.05
	1st MTP#	18 (18.7)	110 (26.5)	> 0.05
	Others MTP#	0 (0)	24 (5.7)	-

* MCP, metatarsophalangeal joints; †PIP, proximal interphalangeal joints; ‡DIP, distal interphalangeal joints; #MTP, metatarsophalangeal joints.

Table 3: Comparison of the location of tophi according to gender

Variables		Women (n=96)	Men (n=415)	P-value
Elbows, n (%)		2 (2.1)	73 (17.6)	< 0.001
Wrists		0 (0)	13 (3.1)	-
Hands, n (%)	DIP* joints	2 (2.1)	11 (2.6)	> 0.05
	PIP† joints	3 (3.1)	14 (3.4)	> 0.05
Knees, n (%)		0 (0)	11 (2.6)	-
Ankles, n (%)		0 (0)	12 (28.9)	-
Feet, n (%)	Lisfranc/Chopart joints	0 (0)	12 (28.9)	-
	MTP‡	2 (2.1)	27 (5.4)	> 0.05
Pinna, n (%)		1 (1.0)	20 (4.8)	> 0.05

* DIP, distal interphalangeal joints; PIP, proximal interphalangeal joints; MTP, metatarsophalangeal joints

X-rays of the involved joints were done in 242 patients. Among them, 61 patients had no lesion, 68 patients had gout-related bone erosions, and 113 patients had lesions related to osteoarthritis. Women had fewer gout-related bone erosions than men [10 (10.4%) women vs. 58 (13.9%) men; $p = 0.001$].

Discussion

The differences between women and men with gout are striking, as the women are about 7–12 years older, have more associated comorbidities like cardiovascular risk factors and are more likely to be on diuretics [3-11]. Because gout is known as "the disease of kings", and by extension the disease of men, gout is often misdiagnosed in women, and or the diagnosis is often delayed [1-8,21].

Studies performed on gout in women in Africa are scarce. The available data were collected in South Africa[16-18]. The primary purpose of our study was to describe the characteristics of women with gout and identify any differences between women and men with this diagnosis. The results of this study lead us to the conclusion that gouty arthritis in Cameroonian women is characterized by: (i) a late age at onset, mainly after menopause, with women older than men at the time of diagnosis; (ii) a higher frequency of hyperuricemia, but with uric acid levels lower compared to men; (iii) a lower frequency of structural joint damage; (iv) a greater frequency of comorbidities (particularly the metabolic syndrome components) and drugs intake like diuretics and low-dose aspirin; (v) and a lower frequency of tophi. The distribution of joint damage was not different between the two sexes in our study. This result had already been described by other authors[4;9-13]. Some peculiarities in the joint distribution in women described previously, such as a lower prevalence of podagra[13,22], more frequent

polyarticular involvement[18], a predominant upper limb[13] and ankle joint involvement[22] were not significant in our study.

We noted three main differences besides the similarities between our results and those previously reported[3-11,21]. Firstly, the presence of tophi differed in various studies according to gender[21]. However, men tend to have more tophi in the upper limbs than women[21]. In South Africa, tophi were more in women than men, but with the same distribution[18]. One surprising result of our study is the tendency for women to have more tophi in the hands (proximal and distal interphalangeal joints). Still, this difference was not significant when we considered all the upper limbs. Furthermore, tophaceous gout was similar in women and men, although the female gender was protective against the risk of developing tophi[13]. These findings require further confirmation. Secondly, although diuretics intake was highest among women, the frequencies are lowest in the already published data[3-18]. The missing data from our study could be an explanation. Still, we cannot formally rule out other risk factors such as genetic or environmental factors potentially implicated in the pathogenesis of gout in Cameroonian women. Thirdly, chronic kidney disease was associated with gouty arthritis in postmenopausal women, especially those with preexisting joint disease[5,12,17,18,21]. In our study, apart from chronic kidney disease, comorbidities were more frequent in women. Other authors also describe this greater frequency of comorbidities in South Africa[17,18], Taiwan[11,23], Turkey[24], and some Western countries[10,21]. However, in South Korea, there was no difference between women and men for comorbidities[12]. The design of the studies could explain these discrepancies.

On the other hand, gout in women is overwhelmingly postmenopausal[1-11, 18,21,22,24]. In our study, 66% of female patients had their first gouty attack after menopause. This rate is consistent with the literature data that find the onset of gout after menopause in more than two-thirds of the patients[3-8,18,21]. Likewise, data from the Third National Health and Nutrition Examination Survey show that menopause was associated with higher serum uric acid levels, and that postmenopausal hormone replacement therapy was associated with lower serum uric acid levels, suggesting that estrogen plays a key role in protecting women from hyporuricemia and gout[25]. Indeed, the fall in estrogen level during menopause is independently associated with higher serum uric acid levels, whereas postmenopausal hormone use is associated with lower uric acid levels[25], possibly owing to the uricosuric effects of estrogen[1]. Paradoxically, in a large nationwide population-based cohort study with the aim to determine whether there is an association between reproductive factors and the incidence of gout, the authors showed that shorter exposure to endogenous estrogens was associated with a higher risk of gout. Conversely, exposure to exogenous estrogens, such as oral contraceptives and hormone replacement therapy, was associated with an increased risk of gout[26]. In this sense, some authors have shown that the factors associated with gout in women are more related to aging than gender[4] or menopausal status[27]. Moreover, the prevalence of hyperuricemia sharply increases from the late menopausal transition stage in middle-aged women[28]. They recommended that sex can only be used to assess renal function in women with gout[4,28].

This study was conducted on a sample of 511 patients including 96 women, making it one of the largest populations of gouty patients described in SSA. This considerably reduces the impact of the three main limitations of this study. The first limitation is the unavailability of data on the lifestyle of our patients. Compared to men, women would have lower consumption of alcohol[5,9,29,30], and higher consumption of tobacco[30] seafood[29]. Moreover, consuming fructose-rich beverages increases the risk of incident gout in women[31], while consumption of coffee reduces this risk[32]. On the other hand, gout has a negative impact on women's identity and their relationships. Unrecognized by health professionals and women themselves, they will have a long delay in diagnosis compared to men and difficulties in finding relevant information about their disease as it is considered to be a male condition[33]. Concerning the quality of life, women seem to be more concerned about difficulty with footwear, dependency and joint deformity, while men seem to be more interested in interference with sexual activity[10,34]. Also, gout is associated with a modestly increased risk of hip fracture[35]. The second limitation of our study is the lack of data on the treatment of gout and lifestyle habits of women, related to the retrospective design of the study. Some studies have shown that women were more likely to receive febuxostat[5] and less likely to receive allopurinol[5,34]. In addition, febuxostat may be more effective than allopurinol in women[36], while no gender differences in response to uricosuric agents or xanthine oxidase inhibitors have been demonstrated[37]. Furthermore, in a Taiwanese study, women with gout had a higher risk of heart failure hospitalization than men and this risk was significantly higher in febuxostat users than in allopurinol users with low cardiovascular risk[11]. The last one was the hospital-based study and retrospective design which may limit the generalizability of the results. Population studies are then needed. We expect that they will determine the epidemiological characteristics of gout in the general population, confirm the specific features of gout in women, and, evaluate the place of lifestyle change and the management of associated comorbidities in the follow-up of gouty women in SSA.

In conclusion, gouty arthritis is common among Cameroonian women and has almost identical features in other countries. Late age at onset with a higher frequency after 60 years and a greater frequency of comorbidities are the main characteristics of gout in women in Cameroon. Moreover, a higher frequency of tophi in hands was observed. Further studies are needed, as far as

our country is concerned than in other African countries, to better understand these differences and sufficiently define the SSA profile of gouty arthritis in Women.

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