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Gout and sickle cell disease: not all pain is sickle cell pain

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Painful vaso-occlusive crises (VOC) are the hallmark of Sickle Cell Disease (SCD) and the most frequent reason for hospitalization. Aetiology and precipitating factors are complex and not completely elucidated. Gout is an inflammatory arthritis characterized by hyperuricaemia and deposition of monosodium urate crystals in articular or periarticular tissues (Rees *et al*, 2014), with a prevalence of 2·5–3·9% [males (4–6%) >> females (1–2%)] that increases with age (Zhu *et al*, 2011; Kuo *et al*, 2014). Hyperuricaemia is present in SCD (Gold *et al*, 1968), due to increased production of uric acid from ineffective erythropoiesis and decreased clearance (Ball & Sorensen, 1970; Diamond *et al*, 1979) from renal damage. There are case reports of gout in SCD, (Aquilina *et al*, 1958; Reynolds, 1983) but no larger-scale studies. We reviewed 13 consecutive cases of gout and SCD in order to identify predictors of gout and differentiate between VOCs and gout flares.

Electronic medical records of 90 adults with SCD who were enrolled in a Natural History protocol at the Clinical Center of National Institutes of Health from January 2006 to June 2014, (Clinicaltrials.gov identifier NCT00081523), were reviewed. Patients provided informed consent. We determined the date of onset of each patient's most recent gout flare. For patients that were hospitalized with VOC during this time frame, details of inpatient clinical course were reviewed. The most recent gout and/or VOC event and the preceding year were analysed. Diagnosis of gout was made by a rheumatologist based on polarized light microscopy for urate crystals from joint aspirate or clinically, if the patient met ≥6

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SG collected and analysed the data, cared for patients and wrote the manuscript; JY collected and analysed the data and wrote the manuscript; DX interpreted the data and collaborated to writing the manuscripts; CF collaborated in interpreting the data; CC collected and analysed the data; SS collected and analysed the data; AC collected data and cared for the patients; GJK interpreted the data and wrote the manuscript; CPM designed the study, interpreted the data and wrote the manuscript.

measures as per the 1977 American College of Rheumatology criteria (Wallace *et al*, 1977). Laboratory values over the one-year period before gout flare or VOC were sorted into three groups based on the clinical status of the patient: 'gout flare' includes values collected the first day of hospitalization for acute gout flare; 'VOC' refers to the first day of hospitalization for vaso-occlusive crisis; 'Steady state' is the mean values from three routine outpatient encounters. Values were compared using *t* test with R version 3.0.3 (http://cran.r-project.org/bin/windows/base/old/3.0.3/), and calculated p values with adjustment for age. Statistical significance was a two-sided $P < 0{\cdot}05$.

Thirteen patients had a diagnosis of acute gout flare during a hospitalization or had a history of gout. All were African-American, 12 had HbSS and 1 HbSC. Three patients had urate crystals in joint fluid aspirate, five had a history of gout from previous hospitalizations or primary care visits and joint aspiration was not performed. Four additional patients had insufficient amount of aspirate for crystal identification and one patient refused the procedure. Articulations mostly affected were: First metatarso-pharyngeal (podagra) > ankle> elbow >wrist. Mean age of first onset of gout: 40 years (range 23–77; males: 36; females 45). 46% were women, median body mas index: 23·4 (19·2–36·1). Baseline demographic characteristics of SCD patients with and without gout were similar, whereas laboratory values differed (Table I). Ten (77%) SCD patients with gout were on hydroxycarbamide therapy compared to 52 (67·5%) of non-gout. One patient each had hyperlipidaemia, diabetes or a positive family history of gout. Patients had no significant alcohol intake (73% abstainees). Among other risk factors for gout, 61·5% of patients with gout had hypertension, compared to 39% without gout ($P = 0{\cdot}143$). No patients had preceding trauma or surgery to the affected joints. Table II provides details of the 13 patients with SCD and gout.

At steady state, sickle cell patients with gout had higher creatinine ($P = <0{\cdot}001$) and serum uric acid ($P = <0{\cdot}001$) than patients without gout. Haemoglobin was lower ($P = 0{\cdot}024$), while total bilirubin and reticulocyte count were not ($P = 0{\cdot}141$ and $0{\cdot}441$), suggesting decreased red cell production, possibly because of renal insufficiency. The higher serum lactate dehydrogenase (LDH) in patients with gout ($P = 0{\cdot}043$) could be attributed to renal insufficiency, end organ damage and/or haemolysis, indicating complexity of the gout phenotype. In those patients that experienced both VOC and gout, we compared the laboratory values obtained at the onset of these episodes to each other and to the VOCs that occurred in the 77 patients without gout. Uric acid and serum creatinine did not change significantly whether patients were experiencing a gout exacerbation or VOC, and were significantly higher during either type of painful crisis in gout patients than in patients without gout ($P < 0{\cdot}001$ for both). White blood cell count (WBC) and LDH were higher during VOC crisis than gout flares, but did not reach statistical significance, probably because of small sample size. All patients received parenteral opioids for pain, and oral colchicine was added after gout was diagnosed: Seven (~50%) responded well; two received oral prednisone, which led to severe VOC within 24 h; two received intra-articular methylprednisolone without complications. Two additional patients continued to have refractory gout on colchicine and received subcutaneous anakinra (an interleukin-1 inhibitor) for three days with improvement. Patients switched to allopurinol (100 mg to 300

mg/day) for maintenance therapy. One patient with poor renal function (glomerular filtration rate: ~60 ml/min) continued to have gout flares and received febuxostat (a non-purine xanthine oxidase inhibitor), with improvement.

This retrospective review found an earlier presentation (~40 years) and a higher incidence of gout in patients with SCD, compared to the general population (18% vs. 4%), without male predominance. Sickle cell disease patients with gout had few classical risk factors for gout. Our data suggests that patients with HbSS phenotype, high uric acid, low haemoglobin and poor renal function are at high risk for gout and should elicit suspicion when presenting with acute monoarticular joint pain, especially if they don't respond to their usual regimen. A rheumatology consultation should be requested. In the typically milder HbSC phenotype, gout onset was delayed until 77 years of age, similar to the occurrence in the general population. Acute pain episodes complicated by gout can be differentiated from uncomplicated VOC on the basis of the lack of the increase in WBC and LDH (Buchanan & Glader, 1978), while uric acid does not change significantly from steady state in either a gouty flare or a VOC, and remains elevated in patients with gout (Table II).

Therapy of acute gout consists of non-steroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 inhibitors, colchicine and/or corticosteroids. In SCD we use NSAIDs cautiously due to potential for nephrotoxicity, and avoid systemic corticosteroids because of the risk of severe vaso-occlusive crises, while allowing intra-articular steroids. Our data supports the use of colchicine, as well as febuxostat and anakinra. Limitations of our study are its retrospective nature and that the diagnosis of gout was often clinical, with the possibility of underrepresenting clinical events.

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Table I

Clinical and laboratory characteristics of SCD patients comparing patients with gout and without gout.

	All	Gout (*N* = 13)	Non-Gout (*N* = 77)	*P*-value
Age, years; mean (range)	42·7 ± 13·1 (22–82)	48 ± 14·4 (30–81)	41·8 ± 12·7 (22–82)	0·16
Female Sex, *N* (%)	52 (57·8%)	6 (46·2%)	46 (59·7%)	0·38
African-American, *N* (%)	87 (96·7%)	13 (100%)	74 (96·1%)	>0·99
SC Genotype, *N* (%)	7 (7·8%)	1 (7·7%)	6 (7·8%)	>0·99
Number of VOCs, mean ± SD (range)	1·4 ± 1·6 (0–7)	0·9 ± 1·3 (0–4)	1·5 ± 1·6 (0–7)	0·17
Hydroxycarbamide, *N* (%)	62 (68·9%)	10 (76·9%)	52 (67·5%)	0·75
Diabetes, *N* (%)	4 (4·4%)	1 (7·7%)	3 (3·9%)	0·47
Hypertension, *N* (%)	38 (42·2%)	8 (61·5%)	30 (39%)	0·14
Body mass index, median ± SD (range)	25 ± 5·7 (16–43·6)	23·4 ± 4·9 (19·2–36·1)	25 ± 5·9 (16–43·6)	0·98

	Gout (*N* = 13)	Non-Gout (*N* = 77)	*P*-value	*P*-value*
Uric acid, μmol/l, mean ± SD (range)				
Steady state	795·6 ± 185·6 (477·4–1149·2)	512·7 ± 176·8 (159·1–981·2)	<0·001	<0·001
VOC	786·7 ± 194·5 (539·2–1016·6)	442·0 ± 159·1 (132·6–848·6)	0·001	<0·001
Gout flare	689·5 ± 238·7 (397·8–1131·5)			
White blood cell count, × 10^9/l, mean ± SD (range)				
Steady state	8·8 ± 3·9 (4·1–17·6)	7·7 ± 2·9 (3·1–17·7)	0·337	0·078
VOC	11·2 ± 8·4 (2·4–29·1)	11·1 ± 4·7 (3·6–26·8)	0·973	0·718
Gout flare	7·3 ± 4·1 (0·6–16·4)			
Haemoglobin, g/l, mean ± SD (range)				
Steady state	78 ± 9 (61–90)	88 ± 15 (58–123)	0·002	0·024
VOC	80 ± 12 (61–93)	92 ± 44 (55–396)	0·111	0·335
Gout flare	80 ± 14 (57–98)			
Platelet count, × 10^9/l, mean ± SD (range)				
Steady state	317·9 ± 129 (171·5–499·8	313·4 ± 103·5 (49–542)	0·908	0·571
VOC	287·2 ± 135·1 (108·6–444·2	318 ± 112·8 (63–572)	0·554	0·72
Gout flare	279·5 ± 154·7 (58			
LDH, u/l, mean ± SD (range)				
Steady state	571·6 ± 470·8 (188·8–1609)	423·2 ± 183·2 (143·5–1209)	0·283	0·043

	Gout (*N* = 13)	Non-Gout (*N* = 77)	*P*-value	*P*-value*
VOC	532·2 ± 361·6 (269–1286)	527·4 ± 216·5 (232–1268)	0·974	0·984
Gout flare	487·1 ± 360·3 (204–1449)			
Creatinine, μmol/l, mean ± SD (range)				
Steady state	185·6 ± 150·3 (53·0–565·8)	70·7 ± 35·4 (35·4–194·5)	0·047	<0·001
VOC	247·5 ± 203·3 (88·4–574·6)	61·9 ± 26·5 (26·5–185·6)	0·073	<0·001
Gout flare	203·3 ± 229·8 (53·0–813·3)			
Total bilirubin, μmol/l, mean ± SD (range)				
Steady state	123·8 ± 53·0 (35·4–229·8)	185·6 ± 106·1 (17·7–477·4)	0·003	0·141
VOC	114·9 ± 70·7 (26·5–256·4)	229·8 ± 123·8 (35·4–548·1)	0·001	0·019
Gout Flare	97·2 ± 53·0 (17·7–194·5)			
Reticulocyte Absolute, × 10^9/l, mean ± SD (range)				
Steady state	175·6 ± 134·6 (53–503·9)	220·5 ± 109·6 (27·7–515·6)	0·272	0·441
VOC	165·4 ± 166·6 (7·3–443·7)	237·2 ± 115·3 (0·9–545·1)	0·273	0·21
Gout flare	112·6 ± 85·5 (4·2–318·1)			

VOC, vaso-occlusive crisis; LDH, lactate dehydrogenase; SD, standard deviation.

*Adjusted for age.

Table II

Details of individual SCD patients with gout.

	Age at onset (years)	Sex	SC/SS	Hydroxycarbamide	HTN	BMI	Fam Hx	Joints involved	Serum UA (μmol/l)	UA crystals in joint
1	56	M	SS	No	No	36·1	No	R ankle	406·6–998·9	IA
2	24	M	SS	Yes	Yes	20·3	No	L 1st MTP	671·8–813·3	Yes
3	51	F	SS	Yes	Yes	31	Yes	L ankle	786·8–972·4	ND
4	47	F	SS	Yes	Yes	25·9	No	R 3rd MTP	831·0–919·4	ND
5	31	F	SS	Yes	No	25·1	No	R ankle, R and L 1st MTP	875·2–1034·3	IA
6	49	M	SS	Yes	Yes	23·4	No	L 1st MTP	583·4–663·0	Refused
7	27	M	SS	No	Yes	22·2	No	R wrist, R 3rd PIP	1131·5–1149·2	Yes
8	77	F	SC	Yes	Yes	30·2	No	R 1st MTP, L 1st MTP	477·4–742·6	ND
9	30	M	SS	Yes	No	20·2	No	R wrist	610·0–689·5	IA
10	23	F	SS	Yes	No	25·5	No	R 1st MTP, R ankle	397·8–477·4	ND
11	24	M	SS	No	Yes	23·2	No	R elbow, R 3rd PIP and DIP, R 4th MCP	530·4-663·0	Yes
12	40	F	SS	Yes	Yes	19·2	No	R 1st MTP	468·5–645·3	ND
13	40	M	SS	Yes	No	22·5	No	R Knee	857·5–1016·6	IA

M, male; F, female; DM, diabetes; HTN, hypertension; BMI, body mass index; Fam Hx, family history; R, right; L, left; MTP, metatarsophalangeal joint; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; DIP, distal interphalangeal joint; ND, not done; IA, insufficient amount of aspirate for crystal analysis; UA, uric acid.