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Hospitalization increases the risk of acute arthritic flares in patients with gout: a population based study over two decades

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Abstract

Objective—Assess in-hospital gout flares in patients with gout.

Methods—Hospitalizations were evaluated for gout flare in a cohort of Olmsted County, Minnesota residents with incident gout in 1989–1992 or 2009–2010.

Results—429 patients were followed up to 5 years. 169 patients experienced 454 hospitalizations. Hospitalization rate increased without reaching statistical significance from 1989–1992 to 2009–2010 (rate ratio[RR]:1.19; 95% CI:0.98–1.45). The gout flare rate increased significantly during hospitalization (RR:10.2; 95% CI:6.8–14.5). In-hospital gout flare increased average hospital stay by 1.8 days ($p<0.001$).

Conclusion—Hospitalization increased the risk of gout flares by 10-fold. In-hospital gout flares were associated with longer hospitalization.

Keywords

gout; hyperuricemia; hospitalization; healthcare utilization

Introduction

Gout is the most common inflammatory arthritis in the US. The prevalence of gout and its burden in healthcare cost has increased over recent decades.(1–5) Gout is associated with several comorbidities but independently predicts increased health resource utilization, including hospitalization.(6, 7)

It is unclear how the increased risk for hospitalization among patients with gout may affect the risk of arthritic flares or length of hospital stay. A previous study suggested significantly increased risk of a gout attack during hospitalization in patients with established gout.(8) Factors such as temporary discontinuation of gout medications and fluid shifts may influence urate hemostasis and risk of gout flare during hospitalization.

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This study aimed to examine factors associated with gout flare during hospitalization, if hospital admission increased the risk of gout flares, and whether hospitalization rates for patients with gout have changed over time.

Materials and Methods

Patients

Patients with incident gout in the Olmsted County, Minnesota population were identified using the resources of the Rochester Epidemiology Project (REP).(9) The REP enables complete capture of all inpatient and outpatient medical records and virtually complete ascertainment of all clinically recognized cases of gout. Using the REP, adult (age 18 years) Olmsted County residents with a potential diagnosis of gout were retrieved using diagnostic codes (International Classification of Diseases Version 9: code 274.x) during two different time periods (January 1st 1989–December 31st 1992) and (January 1st 2009–December 31st 2010).(9) Case definition was met when one of three proposed gout criteria (1977 American Rheumatism Association, Rome, New York) were fulfilled.(10–12) All potential cases were manually reviewed to ascertain fulfilment of criteria as previously described.(13) All patients were followed from the date of gout diagnosis to the earliest of: 5 years after gout diagnosis, death or migration from Olmsted County. This study was approved by the Institutional Review Boards of the Mayo Clinic (#12-007239) and the Olmsted Medical Center (#018-OMC-15). Informed consent waived for this minimal risk study.

All hospitalizations for patients with a diagnosis of gout were reviewed. Data collection included admission and discharge dates, primary reason for admission, comorbidities, body mass index (BMI) and kidney function at time of admission. Medication use was captured for diuretics, statins, uric acid lowering therapy and anti-inflammatory medications (non-steroidal anti-inflammatory drugs [NSAIDs], colchicine and glucocorticoids, as was in-hospital use of intravenous fluids, diuretics and intravenous contrast.

In-hospital flare of gouty arthritis was defined as a new onset inflammatory arthritis during hospitalization attributed to “gout” by the treating providers and not attributed to an alternative cause. Only one flare per hospitalization was considered. Outpatient flares were defined similarly.

Statistical Analysis

Descriptive statistics (means, percentages, etc.) were used to summarize data. Person-year methods were used to calculate the rate of flares of gouty arthritis during hospitalizations and out-of-hospital. The rate of inpatient flares was calculated by dividing the number of hospitalizations with flare by the total number of days in hospital to obtain the rate of flares per 100 inpatient person-years (py). Generalized estimating equation regression models with binary outcomes and random effects (accounting for multiple hospitalizations per subject) were used to explore risk factors of in-hospital gout flares and to compare log-transformed in-hospital length of stay with and without gout flare. Cumulative incidence methods adjusting for the competing risk of death were used to estimate the percentage of patients

with a hospitalization after gout diagnosis. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 429 patients with incident gout were identified (158 patients in 1989–1992 and 271 patients in 2009–2010). The demographic characteristics at gout diagnosis were similar between the two cohorts, including mean age (59.3 years in 1989–1992 versus 60.0 years in 2009–2010), and male predominance (73% in 1989–1992 versus 72% in 2009–2010; table 1). BMI increased over the study period (mean 28.6 kg/m² in 1989–1992 versus 32.0 kg/m² in 2009–2010). Kidney disease also increased (11% in the early period versus 32% in the late period). The median length of follow-up was 5.0 years in the early period and 4.7 years in the late period with only 17% of the early and 11% of the late with less than 4 years of follow-up.

There were 454 hospitalizations in the two cohorts during the 5 year follow-up. By 5 years after gout diagnosis, at least one hospitalization occurred for 39.1% of patients in the early cohort and 43.1% of patients in the later cohort ($p=0.56$; figure 1). Accounting for multiple hospitalizations per patient, the overall rate of hospitalizations increased marginally from a rate of 2.26 per 10 py (95% CI: 1.91–2.65) in the early cohort to 2.69 per 10 py (95% CI: 2.40–3.01) in the later cohort (rate ratio [RR]: 1.19; 95% confidence interval [CI]: 0.98–1.45).

Cardiovascular disease was the most common reason for admission in both time periods (23% in the 1989–1992 cohort and 28% in the 2009–2010 cohort). Other reasons for admissions in the 1989–1992 and 2009–2010 cohorts, respectively, included infection (7% and 28%), gastrointestinal diseases (11% and 19%), pulmonary disease (4% and 6%), renal disease (3% and 6%), trauma (5% and 8%) and other reasons (65% and 37%).

Gout flare occurred in 28 of these 454 hospitalizations; 23 patients had a gout flare during hospitalization, as individual patients could have multiple hospitalizations with gout flares. The relative risk of a gout flare during hospitalization was 10.2 (95% CI: 6.8–14.5) with a rate of 85 flares per 100 inpatient py compared to 8.5 per 100 py of outpatient follow-up (554 outpatient flares during 1784 py of follow-up). In addition, the rate of in-hospital flares increased marginally over time (6.3 per 10 py in 1989–1992 vs 11.7 per 10 py in 2009–2010; RR: 1.85; 95% CI: 0.89–4.00).

Variables evaluated as possible predictors of inpatient gout flares included discontinuation of urate lowering therapy (ULT), recent start of ULT within 3 months prior to the hospitalization, diuretic use, intravenous fluids, and intensive care unit stay during the hospitalization, as well as sex, age and number of prior outpatient flares. Several variables including recent start of ULT were associated with increased risk of gout flare but did not reach statistical significance. (Table 2).

Hospitalizations complicated by gout flares were associated with an average length of stay that was 1.8 days longer than hospitalizations without gout flares ($p<0.001$ adjusted for age,

sex and cohort). Unadjusted median lengths of stay were 3 days (interquartile range [IQR]: 2–6) for hospitalizations without flare and 6 days (IQR: 2–11.5) for hospitalizations with flare.

Discussion

This study adds to the evidence that hospitalization is associated with an increased risk of acute gout attacks in patients with pre-existing gout. The risk of acute arthritic flare during hospitalization was 10-fold higher in patients with preexisting gout.

A study reported a 4-fold increased risk for hospitalization occurring in a 2-day risk window prior to an acute gout attack.(14) Methodological differences may account for the higher estimate in our study. This study was population-based and captured precisely the hospitalization length, enabling accurate calculation of in- versus out-of-hospital events per patient-years of follow-up. In-hospital gout flares were associated with significantly longer hospital stays. (8)

Factors that may increase the risk of gout flares during hospitalization include volume depletion, acidosis, fluid shifts, discontinuation of gout medications, diuretic use and obesity.(15, 16, 17, 18) Similar to a previous report, there were no statistically significant associations between these and other factors with gout flares.(14) This may be due to the limited power in both studies.

There was a marginally increased rate of hospitalization for patients diagnosed with gout in 2009–2010 compared with those diagnosed in 1989–1992. This finding is in contrast to secular trends of overall decreasing hospitalization rates in the US.(19) This could be partly explained by the increased comorbidities among patients with gout.(13)

Methodological strengths of this study include the population-based approach eliminating selection bias that may affect studies based on convenience samples and data registries without confirmation of diagnosis or reason for hospitalization.(7, 9, 14) Comprehensive data on hospitalizations were available. Criteria defining gout diagnosis were applied to all patients, thus limiting problems associated with a code or physician diagnosis based case definition.(9)

Limitations of this study are those inherent to its retrospective design. Flares in the outpatient setting may be underascertained if patients did not seek clinic visit nor report the event to the provider. The validity of retrospective ascertainment of inpatient flares is unknown. The majority of the Olmsted County population is of Northern European descent, which may limit generalizability to more diverse populations.(4, 8, 9, 20) The study was completed prior to the publication of the updated 2015 American College of Rheumatology classification criteria for gout; it is unclear how, if at all, these might affect the study results. (20)

Hospitalization is strongly associated with acute flares in patients with pre-existing gout. The significantly prolonged hospitalization in patients who experience gout flare after

admission warrant further studies to identify strategies to mitigate this risk and possibly reduce attendant costs.

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Figure 1. Cumulative incidence of first hospitalization following a diagnosis of gout in 1989–1992 (dashed line) and 2009–2010 (solid line).

Table 1

Characteristics at diagnosis of Olmsted County, Minnesota residents with incident gout in 1989–1992 and 2009–2010

Characteristic	1989–1992 (N=158)	2009–2010 (N=271)
Age at diagnosis, years	59.3 (±17.9)	60.0 (±17.0)
Sex, male	116 (73%)	196 (72%)
Length of follow-up, years	4.1 (1.6)	4.2 (1.2)
Serum uric acid level, mg/dL	8.0 (1.8)	8.2 (2.0)
Body mass index, kg/m ²	28.6 (±5.3)	32.0 (±6.8)
Kidney disease	18 (11%)	86 (32%)

Values in table are n (%) or mean (±standard deviation)

Table 2

Potential predictors of in hospital gout flares

Predictors	Value*	Odds Ratio (95% CI)
Diagnosis year 2009 2010 (vs. 1989 1992)	306 (56%)	1.47 (0.65, 3.35)
Age at gout diagnosis (per 10 year increase)	59.7 ($\pm$ 17.3)	1.15 (0.86, 1.55)
Male sex	312 (73%)	1.08 (0.46, 2.56)
Time since most recent flare prior to hospitalization (per 1year increase)	3.4 ($\pm$ 4.0)	0.87 (0.74, 1.02)
Number of flares prior to hospitalization	2.7 ($\pm$ 2.2)	1.04 (0.88, 1.23)
More than 1 joint affect at gout diagnosis	861 (12%)	1.75 (0.60, 5.06)
Joint other than 1st MTP joint affected at gout diagnosis	253 (36%)	1.31 (0.57, 3.03)
On uric acid lowering therapy at hospital admission	211 (30%)	0.36 (0.11, 1.01)
Started uric acid lowering therapy within 3 months prior to hospitalization	27 (8%)	2.82 (0.71, 11.25)
Uric acid lowering therapy discontinued at/during hospitalization	18 (4%)	0.86 (0.11, 6.83)
ICU stay during hospitalization	61 (13%)	1.24 (0.45, 3.42)
Patient on diuretics during hospitalization	248 (55%)	1.46 (0.64, 3.30)
Kidney disease	325 (46%)	0.91 (0.40, 2.06)
Serum uric acid level at gout diagnosis, mg/dL	8.7 ($\pm$ 1.9)	1.40 (1.11, 1.77)
BMI at hospital admission, kg/m ²	29.2 ($\pm$ 7.8)	0.99 (0.94, 1.05)
Obesity at hospital admission (BMI $\geq$ 30 kg/m ²)	244 (37%)	0.80 (0.33, 1.96)
Obesity at hospital admission (BMI $\geq$ 35 kg/m ²)	120 (18%)	1.43 (0.52, 3.90)
Morbid obesity at hospital admission (BMI $\geq$ 40 kg/m ²)	63 (10%)	1.97 (0.61, 6.39)

* Values are n (%) or mean ($\pm$ standard deviation) based on number of hospitalizations, not number of unique patients.

CI, confidence interval; ICU, intensive care unit; MTP, metatarsophalangeal joint; BMI, body mass index