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Original Article

Gout, allopurinol intake and clinical outcomes in the hospitalized multimorbid elderly

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ABSTRACT

Background: Increased serum uric acid has been considered a cardiovascular risk factor but no study has assessed its relation with hospital mortality or length of stay. On the basis of data obtained from a prospective registry, the prevalence of gout/hyperuricemia and its association with these and other clinical parameters was evaluated in an Italian cohort of elderly patients acutely admitted to internal medicine or geriatric wards.
Methods: While the prevalence of gout was calculated by counting patients with this diagnosis hyperuricemia was inferred in patients taking allopurinol at hospital admission or discharge, on the assumption that this drug was only prescribed owing to the finding of high serum levels of uric acid. A series of clinical and demographic variables were evaluated for their association with gout/hyperuricemia.
Results: Of 1380 patients, 139 (10%) had a diagnosis of gout or were prescribed allopurinol. They had more co-morbidities (7.0 vs 5.6; $P < 0.0001$) and consumed more drugs (6.8 vs 5.0; $P < 0.0001$). The CIRS (co-morbidity index) was worse in these patients (OR 1.28 95% CI 1.15–1.41). Multivariable regression analysis showed that only renal and heart failures were independently associated with gout/allopurinol intake. Moreover, this combined event was associated with an increased risk of adverse events during hospitalization (OR 1.66, 95% CI 1.16–2.36), but not with the risk of re-hospitalization, length of hospital stay or death.
Conclusions: Gout/allopurinol intake has a high prevalence in elderly patients acutely admitted to hospital and are associated with renal and cardiovascular diseases, an increased rate of adverse events and a high degree of drug consumption. In contrast, this finding did not affect the length of hospitalization nor hospital mortality.

1. Introduction

Gout is a clinical manifestation of hyperuricemia that leads to the deposition of urate crystals into joints, causing local reactions with typical signs and symptoms of inflammation. The clinical picture of gout may develop in subjects predisposed to produce high amounts of uric acid. More commonly, given that uric acid is eliminated through the kidney, patients with decreased glomerular filtration rate have elevated serum concentrations. Gout prevalence has been increasing in recent years and is currently one of the most common causes of inflammatory arthritis [1]. This disease impacts on healthcare institutions in terms of health costs and utilization of healthcare services [2]. For instance, Robinson et al. reported an increasing trend in hospital admission due to gout from 1999 to 2009 [3]. In-hospital gout represents a significant patient and health care burden, with patients staying 6–7 days longer in hospital [4].

Gout is typically an age-associated disease, because uric acid deposition progressively increases over the years and gout flares are correlated with older age [5]. With this background, the aim of this study was to estimate the prevalence of gout and/or hyperuricemia prompting the prescription of allopurinol in an Italian population of patients aged 65 years or older acutely admitted to internal medicine or geriatric wards, during four different weeks representing the

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4 seasons over one year. Furthermore, secondary aims were to investigate whether or not gout/allopurinol intake in the elderly was associated with other demographic or clinical variables, in a particular length of hospital stay and mortality.

2. Methods

2.1. Study setting and design

This study was conducted in 66 hospital wards (representative of the Italian internal and geriatric medicine wards), participating during 2010 in the 'Registro Politerapie SIMI' (REPOSI). REPOSI is a collaborative and independent registry run by the Italian Society of Internal Medicine (SIMI), the Mario Negri Institute of Pharmacological Research and the IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation in Milan. The detailed design of REPOSI is described elsewhere [6,7]. In brief, patients aged 65 years or more consecutively admitted to hospital during a period of four weeks, three months apart from each other, were enrolled in the registry. A standardized web-based case report form was filled in by the attending physicians, including socio-demographic factors, clinical parameters, diagnoses and medications prescribed both at hospital admission and discharge, adverse events (AEs) during hospitalization, co-morbidities according to the Cumulative Illness Rating Scale (CIRS) [8], performance in basic activities of daily living according to the Barthel Index scale [9], cognitive status according to the Short Blessed Test (SBT) [10] and presence of depression according to the Geriatric Depression Scale (GDS) [11]. All these data were collected and checked for consistency and accuracy, with possible contacts of the external contributors, by a central monitoring institution (the Mario Negri Institute for Pharmacological Research, Milan).

2.2. Cohort composition

All patients 65 years or older with a diagnosis of gout (International Classification of Disease 9th Edition (ICD-9): 274.xx) made at hospital admission or during hospital stay or in therapy with allopurinol (Anatomic Therapeutic Classification (ATC): M04AA01) were included in the study. Because serum levels of uric acid were not reported in the case report form, it was assumed that the prescription of allopurinol unrelated to the diagnosis of gout was triggered by the finding of high uric acid serum levels. Patients taking allopurinol for chemotherapy or chronic renal failure were excluded (n = 12). Co-morbidities were recorded according to the Cumulative Illness Rating Scale (CIRS). The CIRS co-morbidity index was computed by counting the number of items for which moderate to severe illness was reported (scores of 3, 4 or 5), while overall illness severity was represented by the mean of the 13 CIRS items [8]. The study was approved by the Ethical Committees of the IRCCS Cà Granda Maggiore Policlinico Hospital Foundation, Milan, and of all participating hospitals.

2.3. Statistical analysis

Univariable analyses were applied to compare patients with gout or treated with allopurinol versus those without these features, and data were described using means and standard deviations (SD) for numeric variables or number and percentages for categorical variables, compared applying univariate logistic regression and reported as odds ratios (OR) and 95% confidence intervals (95% CI). Multivariable logistic regression analyses assessed the association between gout/allopurinol intake and presence of other diseases. Selection of variables to be included in the multivariate model was based on statistical and clinical significance. The analysis was repeated using two different approaches for co-morbidity: first it was adjusted by sex, age, CIRS co-morbidity index and adverse events, then relevant concomitant diseases replaced the co-morbidity index. Further analyses were directed to assess whether or not gout/allopurinol intake were predictors of adverse events, mortality at discharge, increased length of hospital stay and readmission. All statistical calculations were performed with the software JMP Pro 10 (SAS Institute Inc.).

3. Results

Of 1380 enrolled patients, 1368 (99%) were included in the study: 139 (10%) had a diagnosis of gout or were taking allopurinol (exposed group), whereas the remaining 1229 represented the non-exposed group (Table 1). Table 1 also shows the socio-demographic and clinical characteristics of the exposed and non-exposed patients and factors associated with gout diagnosis or allopurinol intake. Even though 65 years was the limit for admission to the study, the average patient age was much higher, with no statistically significant difference between the two groups even though the exposed patients tended to be older.

By univariable analysis, the exposed group showed the following statistically significant differences in comparison with the non-exposed group. Patients with gout/allopurinol intake were more often males (61% vs 48%; $P = 0.003$) and their body mass index (BMI) was higher than that of the remaining patients (27.7 vs 25.8%; $P = 0.0004$). Patients with gout/allopurinol intake was also characterized by a higher number of concomitant diagnoses at hospital admission (mean: 6.8 vs 5.6; $P < 0.0001$) and consumed more drugs other than allopurinol (6.8 vs 5.0; $P < 0.0001$): more sulfonamides (73%), proton pump inhibitors (52%), statins (32%), vitamin K antagonists (27%), nitrates (26%), beta blocking agents (25%) and angiotensin-II antagonists (23%). At admission the CIRS co-morbidity index (3.6 vs 2.8; $P < 0.001$) and the severity index (1.8 vs 1.6, $P < 0.001$) were worse in patients with gout/allopurinol intake. The diagnoses more frequently associated to gout/allopurinol intake were hypertension (85% vs 76%, $P = 0.011$), chronic renal failure (45% vs 14%, $P < 0.0001$), diabetes (37% vs 26%, $P = 0.005$), heart failure (37% vs 14%, $P < 0.0001$) and coronary artery disease (30% vs 21%, $P = 0.025$).

On the other hand, there was no difference between the two groups for the rates of atrial fibrillation, COPD, cerebrovascular disease and malignancy. Moreover, there was no significant difference pertaining to smoking and alcohol intake, Barthel Index, SBT and GDS at admission, nor for duration of hospital stay and mortality. After adjustment for variables statistically significant at univariable analysis, the multivariable regression analyses (Table 2) restricted the number of significantly different variables only to chronic renal failure (OR 3.56, 95% CI 2.39–5.31) and heart failure (OR 2.63, 95% CI 1.75–3.92).

Table 2 also shows that having a diagnosis of gout or taking allopurinol was also associated to an increased risk to have adverse events (AEs) during hospitalization (OR 1.66, 95% IC 1.16–2.36), but not with the risk of re-hospitalization, length of hospital stay or in-hospital mortality. The most frequent AEs were urinary tract infections (10.1%), hypokalemia (3.6%), anemia (3.6%), pneumonia (3.6%), heart failure (3.6%), respiratory tract infections (2.8%), atrial fibrillation (2.1%), fever (1.4%), renal failure (1.4%) and bacteremia (1.4%).

4. Discussion

This study shows that gout and/or allopurinol intake presumably due to hyperuricemia is very frequent diagnoses in elderly patients admitted to internal medicine or geriatric wards, because they were reported in about 10% of people acutely admitted to the hospital because of different causes and diagnoses. This prevalence is high, especially considering that the prevalence of gout is 0.46% in the Italian general population [12], similar to that of other Mediterranean countries [13]. It must be considered that prevalence of gout and hyperuricemia are rapidly growing and that the population analyzed was at high risk, being old and hospitalized. Only cardiac and renal failures

Table 1
Sociodemographic and clinical characteristics of patients with or without gout/allopurinol intake (univariable analysis).

Socio-demographic and clinical characteristics				
Variables	Allopurinol intake or gout			
	Yes (N = 139)	No (N = 1229)	Odds ratio (95% CI)	P value
Age, mean (SD)	80.0 (7.1)	78.8 (7.3)	1.02 (1.00–1.04)	0.058
Risk factors, N (%)				
Smoker	14 (10.0)	109 (8.8)	1.15 (0.63–2.06)	0.65
Heavy alcohol drinker	70 (50.3)	510 (41.6)	1.42 (1.00–2.01)	0.051
Number of patients at admission with 5 or more diagnoses, mean (SD)	91 (65.4)	588 (47.9)	2.06 (1.42–2.97)	<.0001
Number of patient at admission taking 5 or more drugs, N (%)	113 (81.2)	675 (54.9)	3.57 (2.33–5.65)	<.0001
Severity index at admission, mean (SD)	1.8 (0.3)	1.6 (0.3)	5.13 (3.02–8.71)	<.0001
CIRS comorbidity index at admission, mean (SD)	3.6 (1.6)	2.8 (1.7)	1.28 (1.15–1.41)	<.0001
Barthel at admission, mean (SD)	77.6 (32.4)	77.4 (30.3)	1.00 (1.00–1.00)	0.101
Short blessed test, mean (SD)	10.9 (8.8)	9.7 (8.0)	1.02 (0.99–1.04)	0.141
Geriatric depression scale, mean (SD)	1.5 (1.2)	1.4 (1.2)	1.13 (0.98–1.30)	0.107
Duration of hospital stay, mean (SD)	10.9 (8.9)	10.7 (8.1)	1.00 (0.98–1.02)	0.787
Adverse clinical events during hospitalization, N (%)	63 (45.3)	410 (33.3)	1.65 (1.16–2.36)	0.006
Hospital mortality, N (%)	8 (5.8)	40 (3.3)	1.81 (0.83–3.95)	0.160

were significantly associated with gout/allopurinol intake. These associations can be attributed to the well established risk to develop cardiovascular complication in patients with urate overproduction/decreased elimination [14,15]. Another hypothesis is that many patients with gout or hyperuricemia share with those with cardiovascular or renal diseases some frequent risk factors such as overweight, hypertension, coronary artery disease and diabetes [16,17].

Another finding of this study was that patients with gout/allopurinol intake experienced during hospitalization a higher number of AEs that were often severe, including bacterial infections, heart and renal failure and arrhythmias. Accordingly, particular care and attention should be devoted when elderly patients with gout or allopurinol therapy are hospitalized pertaining to the functions of the cardiovascular system and the kidney. Prevention of these complications might be obtained by avoiding excessive diuretic medications in patients with increased serum creatinine according to the definition of acute kidney injury (an increase of 50% above the basal value or of 0.3 mg/dl within 48 h) and, on the other hand, by reducing or stopping fluid infusion in those with early signs of impending cardiac failure. Another very important recommendation is to implement any possible effort to reduce the burden of infectious agents in the environment.

Table 2
Association of gout and/or allopurinol intake with the incidence of adverse events during hospitalization (univariable and multivariable analysis).

Variables	OR (95% CI)	P value
1. Univariable analysis		
Patients with gout/allopurinol intake	1.66 (1.16–2.36)	0.006
2. Multivariable analysis adjusted for age, sex, AEs and CIRS comorbidity index.		
Patients with gout/allopurinol intake	1.52 (1.06–2.19)	0.024
Sex (female)	0.93 (0.74–1.18)	0.557
Age groups		
65–75	1.0	0.0005
75–84	1.29 (0.99–1.69)	
> = 85	1.89 (1.37–2.60)	
CIRS comorbidity index	1.07 (1.00–1.15)	0.036
3. Multivariable analysis adjusted for age, sex and associated diseases.		
Patients with gout/allopurinol intake	1.48 (1.02–2.16)	0.041
Sex (female)	0.92 (0.73–1.16)	0.493
Age groups		
65–75	1	0.0004
75–84	1.30 (1.00–1.71)	
> = 85	1.91 (1.38–2.64)	
Hypertension	0.89 (0.69–1.16)	0.380
Chronic renal insufficiency	1.27 (0.93–1.73)	0.138
Diabetes mellitus	0.89 (0.68–1.16)	0.390
Heart failure	1.13 (0.83–1.53)	0.431
Ischemic heart disease	0.94 (0.71–1.24)	0.659

Our study did not show a relationship between gout/allopurinol intake and an increased risk of re-hospitalization, length of hospital stay or in-hospital mortality. In contrast, a previous study [4] showed that hospitalized patients with acute gout stayed 6 days longer than controls, perhaps because gout was a complicating factor for hospitalization owing to other reasons. Moreover, Robinson et al. showed that patients with hospital admissions secondarily complicated by gout had a poorer survival compared with those admitted primarily for gout [3].

In general, the in-hospital management of elderly patients should take into account the frequent association with co-morbidities. The BMI of our cohort was indeed significantly higher in these patients, consistently with knowledge that overweight or obesity is a well established risk factor for abnormal glucose and lipid metabolisms. Unfortunately, the data collected in the REPOSI registry did not include also the serum levels of glucose, cholesterol and tryglicerides. However, patients with gout/allopurinol intake often took medications such as statins, which are prescribed in order to decrease serum lipid concentrations. Furthermore, at univariate analysis, gout/allopurinol intake was associated with the diagnosis of diabetes, suggesting once more that similar pathogenic mechanisms exist for gout, hyperuricemia, diabetes and dyslipidemia. Indeed, studies in elderly people with pre-diabetes suggested that high uric acid levels raise a personal chance to become diabetic [18].

The present study has also shown that patients with gout and/or allopurinol intake took a greater number of drugs to treat the frequent multiple concomitant diseases. This prescription behavior raises the issue of the usefulness of basing drug prescription solely on the simple sum of different diagnoses, because in the elderly the effects of many drugs may be magnified or reduced due to pharmacodynamic changes and/or important interactions between the many prescribed medications. Accordingly, an individually tailored therapy should take into account the risk of interactions with concurrent medications. In particular, drugs with an excretion pathway common to that of uric acid should be prescribed with caution, because in these instances side effects could be early and severe.

The present study has limitations. The main weakness was that the diagnosis of high serum concentrations of uric acid was not based on the direct dosage of this moiety in patient serum, but mainly inferred from the finding of allopurinol intake. This assumption was based on the belief that it is unlikely that a drug not free of adverse events such as allopurinol is prescribed in the presence of normal serum levels of uric acid, even though we are also cognizant that not all patients with hyperuricemia benefit from allopurinol intake. By contrast, there are also some strength that are mainly related to the prospective data

collection and the participation of more than 70 wards of general hospitals, making the study representative of a wide area in Southern Europe.

5. Learning points

- Gout and/or hyperuricemia is frequent in elderly patients admitted to internal medicine wards.
- Only cardiac and renal failures were significantly associated with gout/allopurinol intake.
- Gout or taking allopurinol was associated to an increased risk of hospital adverse events.
- Gout or allopurinol intake should prompt to look for cardiovascular or renal diseases, drug interactions and clinical risks.

Disclosure statement

All authors have no conflicts of interests to disclose

Appendix A. Investigators and co-authors of the REPOSI (REgistro POliterapie SIMI, Società Italiana di Medicina Interna) Study Group are as follows:

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