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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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[1] REPOSI denotes Registry of Polytherapies SIMI (Società Italiana di Medicina Interna).

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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