

Original article

Generalized pain hypersensitivity and associated factors in gout

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Abstract

Objectives. Previous studies have indicated that a sizeable proportion of patients with inflammatory arthritis present with features characteristic of central pain sensitization. However, this has not yet been examined in patients with gout. The objective of this study was to explore the presence of generalized pain hypersensitivity and associated factors in patients with diagnosed gout.

Methods. A cross-sectional survey was performed in outpatients with crystal proven gout using the generalized pain questionnaire (GPQ) to screen for the presence of generalized pain hypersensitivity. Additional self-reported socio-demographic and medical information was collected and several patient-reported outcome measures were completed. Univariable logistic regressions and multivariable LASSO regression analysis with 10-fold cross-validation was used to explore relationships with patient characteristics, clinical features and PROMs.

Results. Of the 97 included patients (84.5% male; mean (s.d.) age: 68.9 ± 11.9 years), 20 patients (20.6%, 95% CI: 13.0, 30.0) reported possible generalized pain hypersensitivity defined as a GPQ score ≥ 11 (range: 0–28; mean (s.d.) GPQ: 6.3 ± 5.3). Lower age, concomitant fibromyalgia and more experienced difficulties in performing their social role were independently associated with generalized pain hypersensitivity. Notably, use of urate lowering therapy was significantly lower in those with generalized pain hypersensitivity.

Conclusions. Generalized pain hypersensitivity appears to be quite common in gout, despite its more intermittent nature compared with other inflammatory arthritides. As this kind of pain does not respond well to regular treatment, screening for non-inflammatory pain may be important for improving pain management in gout.

Key words: gout, central sensitization, pain, pain mechanisms

Rheumatology key messages

- Generalized pain hypersensitivity may be present in up to one of five patients with gout.
- Generalized pain hypersensitivity was associated with both patient and clinical characteristics and medication use.
- Screening for generalized pain hypersensitivity may improve pain management in gout.

Introduction

Gout is one of the most common forms of inflammatory arthritis, especially in men, and is characterized by an intense inflammatory reaction triggered by the deposition of monosodium urate crystals in and around the joints [1–3]. Acute gout flares are usually extremely painful and self-limiting, with resolution within several days [1, 2, 4]. The pain is most often directly related to the

inflammation and typically also resolves completely. However, gouty arthritis may also result in chronic pain between gout flares due to gouty bone erosions and deformities [3, 5].

Although gout pain is generally assumed to be either inflammatory or nociceptive in nature, it remains unclear whether other pain mechanisms, including central sensitization, may also play a role in gout. Several studies have indicated that different types of inflammatory

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arthritis are associated with an altered state of central pain processing, referred to as central sensitization [5–11]. Central sensitization typically manifests as general hypersensitivity of the pain system, including allodynia, (secondary) hyperalgesia and aftersensations [12]. Previous studies have suggested that up to 40–45% of patients with inflammatory arthritides display signs of central sensitization, which is generally not associated with objective parameters of inflammation or disease activity [7, 8, 13].

As pain due to central sensitization does not respond well to traditional anti-inflammatory medications such as those typically used in gout treatment and may have a serious negative impact on functionality and quality of life [13, 14], it is important to examine if and to what extent central pain processing may also play a role in gout. To date, the characteristics of non-inflammatory pain and potential pain sensitization have not yet been investigated in gout [5]. Therefore, the objectives of this study were to explore the presence of generalized pain hypersensitivity in patients with gout in daily clinical practice and to investigate possible associated factors.

Methods

Study population and data collection

Patients for this cross-sectional survey study were recruited from the rheumatology outpatient department of the Medisch Spectrum Twente (MST) hospital in Enschede, the Netherlands. Adult patients with a diagnosis of crystal proven gout (established before or in 2018 through polarized light microscopy of synovial fluid in which monosodium urate crystals were proven) and that had visited the outpatient clinic in 2018 were selected from the patient record system. Random selections of 100 patients were sent an invitation letter and paper survey by postal mail in 2019. After four batches of 100 patients were invited, 97 patients had returned a completed survey.

The study was reviewed by the Medical Ethical Assessment Committee (METC) Twente (K19-08). The METC concluded that this study was not subject to the Medical Research Involving Human Subjects Act and was exempt from full ethical review. Nonetheless, patients were fully informed about the nature of the study and all patients provided written informed consent before completing and returning the survey.

Measures

Besides four standardized patient-reported outcome measures (PROMs), all patients provided self-reported demographic and clinical information. This consisted of socio-demographic factors (e.g. age, gender, smoking, usage of alcohol), use of drug therapy, number of gout flares over the last year and the existence of (rheumatic) comorbidities.

PROMs

The generalized pain questionnaire (GPQ) was used to measure and classify generalized pain hypersensitivity. The GPQ was recently developed and validated among patients with RA or fibromyalgia. It asks for the severity of seven symptoms typical of generalized pain, using recognizable examples of manifestations of symptoms identified in the literature, including allodynia, (secondary) hyperalgesia and aftersensations. All items are answered on a 5-point response scale from 'never' (0) to 'very strongly' (4). Total scores range from 0 to 28, with a score ≥ 11 being indicative of likely generalized pain hypersensitivity [15]. Cronbach's alpha of the GPQ was good in the current study ($\alpha = 0.85$).

Patients additionally completed the SF-12 Health Survey (SF-12v2) to measure their physical and mental health-related quality of life [16]. Two orthogonal summary scores can be computed, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), with higher scores indicating better health status. Both scores are standardized and normed with a mean of 50 and a s.d. of 10 using the 1998 US general population data [17]. Internal consistency was good for the PCS items ($\alpha = 0.84$) and excellent for the MCS items ($\alpha = 0.91$).

Functional disability was additionally measured with the HAQ Disability Index (HAQ-DI) [18]. The HAQ-DI asks about difficulties in performing 20 specific activities over the past week in eight categories of daily living. Items are scored from 0 (without any difficulty) to 3 (unable to do). A total score is calculated by averaging the highest score in each category (corrected for the use of aids and devices) if at least six categories are completed. Internal consistency was excellent for the HAQ-DI ($\alpha = 0.94$).

Social role participation was measured with the shortened Social Role Participation Questionnaire (s-SRPQ) [19]. The s-SRPQ assesses participation across six social roles (e.g. intimate relationships, employment) along two dimensions (experienced physical difficulty and satisfaction with performance) on a 5-point scale. Higher total scores indicate more experienced difficulty and higher satisfaction on the two subscales, respectively. Internal consistency was good for the experienced difficulties subscale ($\alpha = 0.87$) and excellent for the satisfaction subscale ($\alpha = 0.94$).

Finally, patients completed 0–10 numerical ratings scales (NRSs) for current pain severity and for worst pain and average pain in the past 4 weeks with higher scores indicating more pain. NRS average pain scores ≥ 4 were considered indicative of clinically important, or unacceptable, pain severity [20].

Statistical analysis

All analyses were conducted in R version 3.5.3. Missing data (total 3.9%, ranging from 0% to 17.5% for individual independent variables) were imputed using random forest imputation with the MissForest package [21]. The

prevalence of possible generalized pain hypersensitivity (GPQ >10) was computed with exact 95% binomial CIs.

Univariable logistic regression analyses were performed to explore simple associations with generalized pain hypersensitivity. The following variables were considered potentially associated with presence of generalized pain hypersensitivity: gender, age, current smoking, alcohol use, concomitant rheumatic diagnoses (OA, RA, fibromyalgia), current medication (allopurinol, colchicine, paracetamol, NSAIDs, opioids), pain severity, HAQ-DI disability, SF-12v2 psychical and mental component summaries, and s-SRPQ difficulties and satisfaction scores. Given the very high intercorrelations between the three pain NRSs (r 's >0.80), only average pain severity was used. Smoking, alcohol use, diagnoses and current medications were each separately dummy coded as present =1 or absent =0. The use of antiepileptics and antidepressants was not considered as an independent variable due to very low use. The self-reported number of gout flares was dichotomized into 0 or 1 or more, as it was strongly zero-inflated.

Next, logistic LASSO (least absolute shrinkage and selection operator) regression was used to perform model selection with the glmnet package [22]. LASSO regression is a regression method that regularizes (or shrinks) the coefficients of a model towards zero. Similar to ordinary regression analyses, LASSO regression minimizes the prediction error, but additionally includes a shrinkage penalty (λ) that has the effect of shrinking some of the estimates exactly to zero. This allows the use of LASSO regression to select variables and create a parsimonious model from a larger set of variables. The optimal value for λ (i.e. the strength of the penalty parameter at which the prediction error is minimized) was determined by using 10-cross-validation [23]. Finally, the variables that were not shrunken to zero were used to perform a parsimonious multivariable logistic regression model with 10-fold cross-validation using the caret package [24]. The overall fit of the final model was examined using the area under the receiver operating characteristic curve (AUC). As a general rule of thumb, an AUC of 0.7–0.8 is considered to indicate adequate discriminative ability and between 0.8 and 0.9 excellent discriminative ability [25]. Odds ratios (ORs) with 95% profile likelihood CIs were computed for independent variables in all logistic regression analyses.

Results

Patient characteristics

Approximately 88% of the 97 included patients were male and the average age was 69 years (Table 1). Almost half of the patients (48.5%) self-reported an additional rheumatic condition, most frequently OA. Around half of the patients reported no gout flares (31.6%) or only one gout flare (17.3%) in the previous year. The vast majority currently used urate lowering therapy (ULT). Average pain severity was relatively low, but still

TABLE 1 Patient characteristics ($n = 97$)

Male, n (%)	83 (87.4)
Age, mean (s.d.)	68.9 (11.9)
Currently smoking, n (%)	6 (6.1%)
Current use of alcohol, n (%)	67 (68.4%)
Rheumatic comorbidities, n (%)	
OA	33 (33.7%)
RA	20 (20.4%)
Fibromyalgia	6 (6.1%)
Gouty flares over the last year, median (IQR)	1 (0–2.5)
Current medication, n (%)	
ULT (allopurinol)	85 (86.7%)
Colchicine	55 (56.1)
Paracetamol	44 (44.9)
NSAIDs	18 (18.4)
Corticosteroids	12 (12.2)
Opioids	5 (5.1)
Antidepressants	1 (1.0)
Antiepileptics	1 (1.0%)
GPQ, mean (s.d.)	6.3 (5.3)
NRS average pain, mean (s.d.)	2.4 (2.6)
HAQ-DI, mean (s.d.)	0.9 (0.7)
SF-12v2, mean (s.d.)	
PCS	41.9 (10.1)
MCS	52.0 (9.8)
s-SRPQ, mean (s.d.)	
Difficulties	11.1 (5.8)
Satisfaction	19.6 (7.1)

GPQ: generalized pain questionnaire; HAQ-DI: HAQ Disability Index; MCS: Mental Component Summary; NRS: numerical rating scale; PCS: Physical Component Summary; SF-12v2: SF-12 Health Survey version 2; s-SRPQ: shortened Social Role Participation Questionnaire; ULT: urate lowering therapy.

35.6% of the patients reported clinically relevant pain severity in the past 4 weeks (NRS ≥ 4). Additionally, the sample scored approximately one s.d. lower than the general population norm on physical health-related quality of life.

Prevalence of generalized pain hypersensitivity

Twenty patients (20.6%, 95% exact binomial CI: 13.1, 30.0) reported possible generalized pain hypersensitivity according to the GPQ. Three of the six patients with concomitant FM were also included in these twenty patients.

Univariable associations with generalized pain hypersensitivity

Gout patients with and without possible generalized pain hypersensitivity did not significantly differ in socio-demographic characteristics, although current smoking did tend to be associated with higher odds of generalized pain hypersensitivity (Table 2). As expected, having concurrent FM also tended to be associated with generalized pain hypersensitivity. Interestingly, using ULT was associated with a 5-fold decreased odds of generalized

TABLE 2 Univariable associations with generalized pain hypersensitivity

	OR (95% CI)	P
Male sex	0.846 (0.228, 4.074)	0.814
Age	0.983 (0.944, 1.025)	0.404
Current smoking	4.353 (0.750, 25.372)	0.087
Current alcohol use	0.639 (0.232, 1.822)	0.389
OA	1.472 (0.517, 4.040)	0.456
RA	0.953 (0.247, 3.042)	0.939
FM	4.353 (0.750, 25.372)	0.087
Gout flare in previous year	1.09 (0.956, 1.252)	0.181
ULT	0.162 (0.041, 0.606)	0.007
Colchicine	2.775 (0.968, 9.219)	0.071
Paracetamol	1.265 (0.468, 3.425)	0.640
NSAIDs	1.806 (0.512, 5.718)	0.328
Corticosteroids	3.333 (0.885, 11.940)	0.064
NRS average pain	1.525 (1.241, 1.938)	<0.001
HAQ-DI	2.593 (1.331, 5.326)	0.006
SF-12v2 PCS	0.938 (0.887, 0.988)	0.018
SF-12v2 MCS	0.889 (0.832, 0.941)	<0.001
s-SRPQ Difficulties	3.904 (2.103, 8.184)	<0.001
s-SRPQ Satisfaction	0.411 (0.235, 0.672)	<0.001

FM: fibromyalgia; HAQ-DI: HAQ Disability Index; MCS: Mental Component Summary; NRS: numerical rating scale; PCS: Physical Component Summary; SF-12v2: SF-12 Health Survey version 2; s-SRPQ: shortened Social Role Participation Questionnaire; ULT: urate lowering therapy.

pain hypersensitivity, while using colchicine and using corticosteroids both tended to be associated with a 3-fold increased odds. For all other PROMs, worse scores were also significantly associated with higher odds of generalized pain hypersensitivity.

Multivariable associations with generalized pain hypersensitivity

In the multivariable LASSO selected model, one socio-demographic, three clinical and three PROM variables were not shrunken to zero (Table 3). Overall, the multivariable model showed excellent ability to discriminate between patients with and without generalized pain hypersensitivity (AUC =0.823).

Younger age, not using ULT and more perceived difficulties in social role participation were significantly independently associated with higher odds of generalized pain hypersensitivity. Using corticosteroids, higher average pain severity and worse mental health-related quality of life remained in the reduced model, but were no longer significantly associated with generalized pain hypersensitivity.

Discussion

The current study explored the existence of generalized pain hypersensitivity and associated factors in a cross-sectional sample of 97 patients with crystal proven gout. Around 20% reported possible generalized pain

TABLE 3 Multivariable LASSO reduced model of correlates of general pain hypersensitivity

	OR (95% CI)	P
Age	0.910 (0.840, 0.971)	0.009
FM	11.146 (1.151, 121.227)	0.037
ULT	0.086 (0.006, 0.812)	0.042
Corticosteroids	3.130 (0.457, 23.726)	0.246
NRS average pain	1.289 (0.954, 1.811)	0.114
SF-12v2 MCS	0.974 (0.887, 1.067)	0.562
s-SRPQ Difficulties	4.766 (1.715, 16.261)	0.005

FM: fibromyalgia; MCS: Mental Component Summary; NRS: numerical rating scale; SF-12v2: SF-12 Health Survey version 2; s-SRPQ: shortened Social Role Participation Questionnaire; ULT: urate lowering therapy.

hypersensitivity as classified by the GPQ. Lower age, self-reported concomitant fibromyalgia, non-use of urate lowering therapy, and more experienced physical disabilities in performing their social role were all independently associated with generalized pain hypersensitivity.

Around three-quarters of the patients reported at most two gout flares in the previous year. Nonetheless, >35% of the patients reported clinically significant pain, defined as an average NRS pain score in the past month ≥ 4 [20], suggesting that there is room for improvement in pain management control in gout. On the one hand, these clinically significant pain ratings may be associated with other unmeasured gout manifestations relevant for disease activity, including the presence of tophi and gouty bone erosions. However, this could also suggest that (acute) inflammation may not be the only factor contributing to pain in gout and that central sensitization may also play a role in some patients. The findings of this study suggest that the pain of a relevant number of gout patients may be due to central sensitization, as has also been shown in other rheumatic conditions. Nonetheless, this prevalence appears to be somewhat lower than those reported for other inflammatory diseases with a generally more continuous disease course. For instance, in spondyloarthritis, psoriatic arthritis or RA, self-reported prevalences between 30–45% have been reported for central sensitization [7, 8, 13]. There are several possible explanations for this apparent lower prevalence of generalized pain hypersensitivity in gout in the current study. First of all, conditions causing continuous or highly repetitive stimulation of the nociceptive system may be more likely to cause the progressive increase in pain perception known as the wind-up phenomenon, which possibly contributes to the development of generalized pain hypersensitivity. Furthermore, gout flares can generally be controlled quite easily, whereas more difficult to manage pain conditions may more likely induce negative experiences, beliefs and expectations and the neurobiology of stress that is associated with generalized pain hypersensitivity. However, gouty arthritis with persistent low-grade inflammation caused by crystal deposits in the intercritical

period could still contribute the nociceptive stimuli leading to central pain sensitization. Finally, it should be noted that all of the previous studies in inflammatory arthritis that relied on self-reported instruments only to classify central sensitization used the Central Sensitization Inventory (CSI) [26]. However, the CSI measures the concept of central sensitization in general from a biopsychosocial perspective, and as such also measures sensitization features such as fatigue and gastrointestinal problems that may share a common aetiology. The GPQ used in the current study only measures specific typical symptoms for generalized pain hypersensitivity described in the literature [15], and may thus provide a more specific identification of central pain sensitization.

Generalized pain hypersensitivity was independently associated with younger age and the presence of a concomitant FM diagnosis. This supports the notion of fibromyalgia as a prototypical central pain syndrome [27], and confirms previous findings that generalized pain hypersensitivity is associated with both fibromyalgia and younger age [15]. The finding that average pain severity did not remain a significant independent predictor of generalized pain hypersensitivity in the reduced multivariable model confirms the unique nature of central pain experiences, which are not simply a reflection of more pain severity only [12, 28].

Univariable regressions also confirmed previous findings that central sensitization is associated with decreased functional ability and health-related quality of life [13, 14]. The current study also examined associations with social role participation [19], which is increasingly recognized as an important outcome from the patient perspective, but which is rarely specifically measured in pain research [29]. Interestingly, in the multivariable model only experienced difficulties in performing social roles remained independently associated with generalized pain hypersensitivity, while functional disability and physical and mental health-related quality of life did not remain associated. This underscores both the specific impact that central sensitization may have on the patients' personally relevant social roles and the distinctiveness of the social participation construct from for instance activities of daily living [29] such as those measured with the HAQ-DI.

Notably, gout patients with and without generalized pain hypersensitivity appeared to differ in their prescribed drug therapy with significantly lower use of ULT in those with generalized pain hypersensitivity. ULT is the cornerstone of gout management by reducing urate deposition and thus preventing gout flares and reducing kidney damage. On the other hand, patients with generalized pain hypersensitivity tended to more frequently use colchicine and corticosteroids. Acute gout flares are often treated with anti-inflammatory drugs (e.g. NSAIDs, colchicine or corticosteroids) [30]. Thus, patients with higher generalized pain tended to use less preventive gout therapy and more flare-specific therapy. As the current study did not collect serum urate levels at the

specific time of the survey, it cannot be exactly ascertained which patients were at target serum urate levels. However, when patients still report pain symptoms or flares despite ULT treatment, physicians often decide to switch to a more symptom-driven therapy. However, the patient's perspective on the presence of an actual gout flare can be different from the physician's perspective, with the main drivers of disagreement being lower pain scores at rest and less presence of joint swelling or joint warmth [31]. If patient-reported pain symptoms or flares are due to generalized pain hypersensitivity, these are not likely to respond to anti-inflammatory drugs and therefore patients with generalized pain hypersensitivity may report more pain even after progressing in their therapy plan. This underlines the importance of screening for pain mechanisms other than inflammatory-mediated or nociceptive pain in gout patients with chronic pain complaints. The GPQ used in this study may provide a feasible option to quickly screen for generalized pain hypersensitivity in gout patients in daily clinical practice.

This is the first study that explored the presence and associated factors of generalized pain hypersensitivity in real-world gout patients whose characteristics appear representative for a typical gout population seen by rheumatologists. However, some limitations of the study should be considered. First of all, the study had a modest sample size resulting in a fairly large uncertainty around the prevalence estimate and reduced power to detect more trivial associations with sociodemographic and clinical characteristics. Additionally, the cross-sectional nature does not allow any conclusions on the direction of associations. Also, although the occurrence of generalized pain hypersensitivity is both assumed, and often demonstrated, to be related to the disease duration, information about disease duration was not available in the current sample. Finally, all data in the current study, including the presence of generalized pain hypersensitivity, were based on patients' self-reports. As there is no absolute gold standard for central pain sensitization, future studies should additionally use more objective assessment methods, such as quantitative sensory testing for allodynia, hyperalgesia and after-sensations. Although the internal consistency reliability and construct validity of the self-report GPQ were promising in patients with RA or fibromyalgia [15], its test-retest reliability and validity against quantitative pain sensitivity measurements of generalized pain hypersensitivity are still under study (Netherlands Trial Register, trial ID NL8760).

In conclusion, generalized pain hypersensitivity may also be present in gout, despite its more intermittent nature compared with other inflammatory rheumatic diseases. As centralized pain does not respond well to regular treatment, screening for non-inflammatory pain may be important for improving pain management in gout. Future studies could specifically focus on gout patients who appear to be in remission, but continue to report chronic pain despite the absence of clinical features of crystal arthritis over a sustained period of time.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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