Patterns and Predictors of Acute Calcium Pyrophosphate Crystal Arthritis (Pseudogout) Flares

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Scholarly Report Title: Patterns and Predictors of Acute Calcium Pyrophosphate Crystal Arthritis (Pseudogout) Flares

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Abstract

Title: Patterns and predictors of acute calcium pyrophosphate crystal arthritis (pseudogout) flares

Objective: Pseudogout is a crystalline arthritis that causes episodes of joint inflammation, and is the most dramatic manifestation of calcium pyrophosphate deposition disease (CPPD). The rate at which pseudogout flares occur has not been well-described. We characterized pseudogout flares in detail and determined the rate and predictors of pseudogout flares in an academic medical center cohort.

Methods: We performed a retrospective cohort study among a random sample of pseudogout patients identified in the Partners HealthCare electronic medical record (EMR), 1990-2017. Pseudogout was defined by synovitis, plus synovial fluid calcium pyrophosphate crystals and/or x-ray chondrocalcinosis. For each pseudogout patient we reviewed the EMR from the date of first episode (index date) through the last clinical note in the EMR for evidence of a recurrent flare. Subjects with no follow-up after the index date were excluded. For the first episode and each documented flare of pseudogout we collected data on the affected joint(s), treatments, and clinical data from the preceding 30 days. We calculated flare rate overall and separately in men and women. We compared characteristics of patients that did and did not have >1 recurrent pseudogout flare using Fisher's exact and t-tests. We estimated hazard ratios (HR) and 95% confidence intervals (CI) for pseudogout flare for baseline and time-varying covariates using multivariable Cox regression models that accounted for clustered data.

Results: We identified 70 pseudogout patients with a total of 111 pseudogout episodes. Recurrent flares of pseudogout occurred in 24% of patients with 7% of patients experiencing at least 5 total flares. The median interval between flares was 5.7 months (range 0.4-110.5 months). Approximately half of recurrent flares occurred in a previously unaffected joint and most were in the hands, wrists, and

knees. Flare rate was 11.4 (95% CI 11.3-11.5) per 100 person-years overall, 14.2 (95% CI 14.0-14.3) per 100 person-years in women, and 7.1 (95% CI 6.9-7.2) per 100 person-years in men. Patients with >1 recurrent flare were more likely to have received no treatment during the index episode compared to those that did not flare (23.5% vs. 5.3%, p=0.04). The risk of pseudogout flare was increased in patients with cancer (HR 2.98, 95% CI 1.33-6.68) and chronic kidney disease (HR 2.92, 95% CI 1.10-7.76).

Conclusion: Pseudogout flares occurred in approximately one-fourth of patients in this tertiary care cohort, and often occurred in previously unaffected joints. The flare rate was similar to prior reports in gout; in contrast to gout, the flare rate was twice a high in women compared to men.

Glossary of Abbreviations

Coronary artery disease (CAD)

Chronic kidney disease (CKD)

Calcium pyrophosphate (CPP)

Calcium pyrophosphate disease (CPPD)

Electronic medical record (EMR)

Monosodium urate (MSU)

Scholarly Question

What are the characteristics of pseudogout flares, including flare rates and predictors of flares?

Student Contributions

Dr. Sara Tedeschi and colleagues used an algorithm from previous work to identify patients from the Partners HealthCare electronic medical record with a potential diagnosis of pseudogout. Dr. Tedeschi and I reviewed the EMR for a random sample of 1000 patients identified by the algorithm to determine if the patient fulfilled the study definition of definite or probable pseudogout. Based on a literature review and with guidance from Dr. Tedeschi, I developed a list of covariates to collect from the EMR and developed a data collection form. I conducted an in-depth chart review for all 70 patients identified to have at least one flare of pseudogout, including medical history, treatments, distribution of affected joints, and laboratory abnormalities. I preformed the initial analysis and interpretation of the data. Dr. Tedeschi performed the statistical analysis with input from Dr. Yoshida and assisted with the interpretation of the data. I draft the tables and the initial manuscript, which were subsequently critically edited by Dr. Tedeschi. I am first-author on our manuscript, which we plan to submit to *Rheumatology*.

The data that we collected for the random sample of 1000 patients is also being used to develop an algorithm for identifying pseudogout in the Partners HealthCare EMR. I will be a co-author on the pseudogout algorithm manuscript.

Patterns and predictors of acute calcium pyrophosphate crystal arthritis (pseudogout) flares

INTRODUCTION

Acute calcium pyrophosphate (CPP) crystal arthritis, often referred to as pseudogout, is a common manifestation of calcium pyrophosphate deposition (CPPD) disease. Pseudogout typically presents as an acute mono or oligoarticular inflammatory arthritis with warmth, erythema, and swelling in and around the affected joint.[1]

The natural history of pseudogout, including the frequency at which it flares, is not well characterized. Only one study to our knowledge has evaluated risk factors for pseudogout recurrence using a clinic-based pseudogout cohort.[2] Baseline proton pump inhibitor use, warfarin use, and chemotherapy were associated with acute CPP crystal arthritis recurrence. Whether time-varying risk factors prior to each flare, including specific joints or pattern of joint involvement over time, interval between flares, or treatments used in management are associated with the risk of future flare has not been evaluated.

In a population-based study of patients with a prior diagnosis of gout, the recurrent flare rate has been reported as 13.7 per 100 person-years.[3] The rate of gout flares was slightly higher in men than women.[3] Pseudogout is thought to be more common in women than men, but a sex-specific flare rate has yet to be investigated.[2,4]

We aimed to estimate the rate of pseudogout recurrence, determine predictors of recurrence, and describe specific features of each flare.

METHODS

Study population and pseudogout identification

We performed a retrospective cohort study among a randomly selected sample of pseudogout patients from the Partners HealthCare electronic medical record (EMR).

Because a validated algorithm for pseudogout does not yet exist, we selected a random sample of 1000 patients with at least one ICD-9 code for chondrocalcinosis (712.1*, 712.2*, 712.3*) or calcium metabolism disorder (275.49) or with a positive text search of notes for at least one of the following terms: "pseudogout," "CPPD," "calcium pyrophosphate," or "chondrocalcinosis", as in prior work.[5]

Two authors (KAY and SKT) reviewed the EMR to determine if the patient fulfilled the study definition of definite or probable pseudogout (Table 1). The study definition was developed based on historical diagnostic criteria for CPPD as well as input from senior clinicians, as classification criteria for research do not yet exist.[6] For each patient, we searched clinical notes for each of the four terms mentioned above ("pseudogout", etc.) using an electronic text search tool available in the Partners HealthCare EMR. If a term was present, we reviewed the notes in which it appeared. If none of the terms were present, we searched radiology reports for the term "chondrocalcinosis". We then reviewed clinical notes around the time of the radiology reports in which chondrocalcinosis was documented. A board certified-rheumatologist (SKT) confirmed that all subjects fulfilled the study definition of pseudogout.

In order to identity recurrent flares of pseudogout among subjects in the cohort, we reviewed all notes in which any of the four terms ("pseudogout", etc.) appeared and determined if they were addressing a new flare or referencing a previous flare. We also searched the EMR for the term "swelling" for each subject and reviewed the notes in which it appeared to determine if the swelling was due to a flare of pseudogout.

Baseline and follow-up time

The date of the visit at which pseudogout was first diagnosed was labeled as the index date. Follow-up time was defined as the time from the index date to a recurrent flare or the last note in the EMR from a health care professional prior to 12/31/2018. We required a baseline period of >=30 days before the index episode

and a follow-up period >=30 days following the index episode. Dates of recurrent flares were recorded; we did not require a minimum interval between flares. To establish whether flares that were <30d apart were truly separate flares and not a one episode that was insufficiently treated, we required documentation that the pain and swelling had resolved before reoccurring. Recurrent flares were excluded if the last EMR note occurred <30 days after the flare.

Covariates

For the index episode and each recurrent flare, we collected data on anatomic site, number of sites involved, whether the flare fulfilled the study definition of definite or probable pseudogout, the presence of chondrocalcinosis on imaging, whether aspiration was attempted and the results of the synovial fluid analysis if conducted, and the treatment of the flare. Treatments were categorized in a hierarchical manner, such that patients were classified according to the most potent treatment used (no treatment; NSAID only; colchicine with or without NSAID; oral or intra-articular steroid with or without colchicine or NSAID).

Age, sex, and race were recorded at index date. Baseline comorbidities were identified by reviewing the EMR prior to and through the index date. We used the text search function of the electronic medical record to manually search for each comorbidity of interest based on past reports of pseudogout risk factors[4,7] and reviewed the pertinent notes to confirm presence of the condition. Comorbidities included cancer (active or in remission), coronary artery disease (CAD), stroke, hypothyroidism, hyperparathyroidism, chronic kidney disease (CKD), hemochromatosis, osteoarthritis, gout, rheumatoid arthritis, and osteoporosis.

Acute medical events documented in the 30 days prior to index date or recurrent flare date were recorded, such as acute illness, hospitalization, trauma to the affected joint, or surgery. Acute illness was defined as a sickness with an abrupt onset such as influenza, bronchitis, or pneumonia. We reviewed the medication list within the 30 days prior to index date or flare date for bisphosphonates, calcium

supplements, thiazides, loop diuretics, proton pump inhibitors, warfarin, and chemotherapy based on prior literature associating these with increased risk for pseudogout.[2,4,7]

Statistical Analysis

We compared baseline characteristics of patients with no recurrent flare to those with >=1 recurrent flare using Fisher's exact and t-tests. We calculated flare rate and 95% confidence intervals (CI) overall and separately in men and women. To estimate the risk for recurrent flare, we developed a series of univariate Cox models accounting for within-person correlated data using PROC GLM. We assigned characteristics of the prior pseudogout episode to the subsequent episode using a lag function. We estimated hazard ratios (HR) and 95% CI for baseline comorbidities, time-varying medications 30 days before flare, time-varying acute medical events 30 days before flare, and characteristics of the prior flare using univariate Cox models. We then developed multivariate Cox models including each univariate predictor with $p<0.20$, to estimate adjusted HRs for pseudogout flare. For multivariate models, the level of significance was set at $p<0.05$. Analyses were preformed using SAS v9.4 (SAS Institute, Cary, NC).

Results

We identified 70 patients with definite or probable pseudogout with a total of 111 pseudogout episodes. Seventeen (24%) patients had >=1 recurrent flare, for a total of 41 recurrent flares. Table 2 shows the baseline clinical characteristics in patients with and without recurrent pseudogout flares. Treatment of the initial pseudogout episode significantly differed between patients who experienced >=1 recurrent flare and those who did not have a recurrent flare ($p=0.04$). NSAID monotherapy was more common among patients that did not have a recurrent flare (35.9%) compared to patients that had a recurrent flare (11.8%). Steroid treatment and no treatment were each more common among patients that did have >=1 recurrent flare (58.8% and 23.5%) compared to those without recurrent flare (51.4% and 8.6%). Thirteen patients had a history of gout, in addition to fulfilling the study definition of

pseudogout. Of these, 1 had MSU crystals documented on a different occasion in a joint other than the joint affected by pseudogout; 1 had simultaneous observation of MSU and CPP crystals in the same joint; 7 had a history of podagra; and 4 had been diagnosed with gout based on elevated uric acid and synovitis in a joint other than the joint affected by pseudogout.

Recurrent flare characteristics

Of the 17 patients who experienced subsequent flares of pseudogout, 7 patients experienced one recurrence, 5 patients experienced two recurrences and 5 patients experienced four or more recurrences. Table 3 shows the joints affected in the index pseudogout flare as well as joints involved in recurrent flares. Of the 41 recurrent flares, 21 involved previously unaffected joints. Hands, wrists, knees and ankles were the most common joints affected by recurrent pseudogout flares. The vast majority of recurrent flares (82.9%) were diagnosed through the combination of synovitis and chondrocalcinosis on imaging without an attempted aspiration.

Incidence and interval between recurrent flares

The flare rate was 11.4 (95% CI 11.3-11.5) per 100 person-years among all subjects. The flare rate in women (14.2 [95% CI 14.0-14.3] per 100 person-years) was twice a high as the rate in men (7.1 [95% CI 6.9-7.2] per 100 person-years). The median interval between recurrent flares was 5.7 months (range 0.4-110.5 months).

Predictors of pseudogout recurrence

Several baseline characteristics and features of the initial pseudogout episode were associated with time to pseudogout recurrence in univariate Cox models. Patients with cancer and those with CKD had three times the risk for pseudogout recurrence compared to subjects without cancer (cancer HR 2.98, 95% CI 1.33-6.68; CKD HR 2.92, 95% CI 1.10-7.76). Patients who were treated with NSAID monotherapy at the initial episode had a lower risk for pseudogout recurrence than patients who received no treatment. Age, sex, and treatments for the prior pseudogout episode were not associated with the risk of recurrent flare. Acute medical events in the 30

days prior to the recurrent episode were not associated with the risk of recurrent pseudogout flare in univariate analyses. We did not identify any significant predictors of pseudogout recurrence in multivariable-adjusted models.

Discussion

Among the 70 patients with at least one episode of definite or probable pseudogout, 24% had a recurrent flare. The flare rate was 11.4 per 100 person-years overall, and was twice as high in women (14.2 per 100 person-years) than men (7.1 per 100 person-years). The overall recurrence rate was similar to the population-based flare rate in gout, but the sex-specific flare rate in pseudogout was strikingly higher in women, in contrast to gout. We observed an increased risk for pseudogout recurrence in patients with cancer and CKD. Patients who were treated with NSAIDs only at the initial pseudogout episode had a lower risk for recurrence compared to those who received no treatment.

The proportion of patients with at least one flare and the median time to recurrence was similar to but slightly higher than the 19.1% and 17.5 weeks reported in a previous retrospective study of 50 patients with acute calcium pyrophosphate crystal arthritis.[2] Whereas Lee at el. found an associated between proton pump inhibitors, warfarin, and exposure to chemotherapy, we did not observe an association with recurrent flare in our cohort.[2] The differences in our findings may be due to our exclusion of 'possible' pseudogout flares, which was defined by Lee at el. as acute arthritis of the knee, wrist, shoulder, hip or ankle.

Our results suggest that a significant portion of patients diagnosed with pseudogout progress to experience multiple recurrences of disease; a small proportion (7%) experienced more than 5 total flares during follow-up. Approximately half of all recurrent pseudogout flares affected a joint that had been previously unaffected. Recurrent flares were usually diagnosed through the combination of synovitis and chondrocalcinosis on imaging. This likely reflects routine clinical care, during which

physicians may feel confident in the diagnosis after a diagnosis of crystal-proven pseudogout had previously been established.

We observed that treatment of the initial pseudogout episode differed between patients who did and did not have a recurrent episode. NSAID monotherapy was significantly associated with increased risk for flare recurrence in Cox models accounting for correlated data among patients with >=1 recurrent episode. Confounding by indication may explain these findings; it is possible that patients with a more severe initial episode were treated with steroids, and were also more likely to have a recurrent flare due to the pseudogout severity. It is also possible that patients treated with NSAID monotherapy had less severe symptoms at the initial episode, or that they had a contraindication to colchicine or steroids that also placed them at greater risk for pseudogout recurrence. We did not observe a relationship between treatment choice for the most recent pseudogout episode and the risk of subsequent recurrence.

Patient in our cohort were predominately White, overweight or obese, and had osteoarthritis. Two prior large-case control studies identified associations between pseudogout and hyperparathyroidism, osteoarthritis, loop diuretic use, and bisphosphonate use.[4,7] These studies, however, utilized large general practice databases and identified patients with pseudogout through general practitioner billing codes.[4,7] This approach allows for the relatively quick identification a large number of patients coded as having pseudogout, but did not use a validated algorithm, thus misclassification of patients with other types of arthritis or with chondrocalcinosis on x-ray but not synovitis is a concern.

Our study had several limitations including a small sample size and a small number of recurrent flares. However, we were able to collect granular detail on the clinical context surrounding each flare for each patient, and to identify and characterize recurrent flares in detail. Our patient population had similar age of initial onset as well as prevalence of hyperparathyroidism and loop diuretic and bisphosphonate

use as populations described in previous studies.[4,7] Data were collected retrospectively by reviewing the electronic medical record, so we were limited to the information documented as part of routine clinical care and we may not have captured every pseudogout flare, comorbidity, medication (particularly over-the-counter NSAIDs), or recent illness. However, osteoarthritis was more common, and not less common, among tertiary care center patients that fulfilled our stringent definition of pseudogout (59%) compared to population-based pseudogout cohorts (35.6% reported by Roddy et al. and 46.3% reported by Rho et al.). We applied a strict definition of pseudogout initial episode and recurrent flare, which may have resulted in omitting patients or flares for which synovitis was not clearly documented; therefore our flare rate may be an underestimate in this cohort. It is possible that patients experienced flares of pseudogout for which they did not seek treatment or they sought treatment at a facility outside of our medical record system; this is a limitation of EMR-based research. Our cohort was composed of patients who sought care at a tertiary care center, and thus the comorbidities and treatments may not generalize to community-based populations.

We observed that in a tertiary care cohort of patients with pseudogout, recurrence was common and occurred in nearly one quarter of patients. Pseudogout flare rate was similar to a published gout flare rate, and was twice as high among women than men. Cancer and CKD were associated with greater risk for pseudogout recurrence. Future work focused on interventions to decrease the risk of pseudogout recurrence is critically needed.

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Appendix

Table 1: Pseudogout definitions for chart review	
Pseudogout must be considered as likely or a more likely explanation for synovitis than other causes (e.g. gout, rheumatoid arthritis, septic arthritis)	
Label	**Description**
Definite pseudogout	Synovitis (joint pain, swelling, tenderness, +/- warmth) **AND** Synovial fluid crystal analysis positive for calcium pyrophosphate crystals
Probable pseudogout	Synovitis in a joint other than the 1st MTP **AND** 1) Rheumatologist or orthopedist evaluated the patient and thought pseudogout was the **most likely diagnosis**, but it was not crystal-proven (e.g. arthrocentesis performed and showed inflammatory cells AND crystal analysis was negative AND chondrocalcinosis present in that joint; or arthrocentesis not performed AND chondrocalcinosis present in that joint) **OR** 2) Clinical note (any clinician) documents **acute** onset in the wrist, knee or ankle, AND chondrocalcinosis present in that joint

Table 2. Baseline characteristics in patients without and with recurrent pseudogout flares

Baseline characteristic	All Patients (n=70)	No recurrent flare (n=53)	≥1 recurrent flare (n=17)
Age	72.3 (14.2)	72.1 (14.8)	72.8 (12.8)
Female	55.7	52.8	64.7
White	81.4	83.0	76.5
BMI			
Underweight or normal	28.6	26.4	35.3
Overweight	20.0	15.1	35.3
Obese	27.2	30.2	17.7
Missing	24.3	28.3	11.8
Basis for initial diagnosis			
Synovitis + synovial fluid crystals	45.7	49.1	35.3
Synovitis + chondrocalcinosis	54.3	50.9	64.7
Comorbidities			
Cancer	22.9	20.8	29.4
Coronary artery disease	20.0	20.8	17.7
Stroke	4.3	3.8	5.9
Hypothyroidism	20.0	22.6	11.8
Hyperparathyroidism	1.4	1.9	0
CKD	18.6	15.1	29.4
Hemochromatosis	1.4	1.9	0
Osteoarthritis	62.9	58.5	76.5
Gout	18.6	18.9	17.7
Rheumatoid arthritis	2.9	3.8	0
Osteoporosis	32.9	35.9	23.5
Medications 30 days prior to initial episode			
Bisphosphonate	5.7	7.6	0
Calcium	25.7	28.3	17.7
Thiazide	21.4	20.8	23.5
Loop diuretic	22.9	26.4	11.8
Proton pump inhibitor	35.7	32.1	47.1
Warfarin	18.6	17.0	23.5
Chemotherapy	2.9	1.9	5.9
Features of initial pseudogout episode			
>1 joint involved	11.4	9.4	17.7
Acute illness 30d prior	27.1	28.3	23.5
Hospitalized 30d prior	41.4	43.4	35.3
Joint trauma 30d prior	5.7	5.7	5.9
Post-op 30d prior	10.0	9.4	11.8
Treatment of initial pseudogout episode*			
No treatment	8.6	3.8	23.5
NSAID only	30.0	35.9	11.8
Colchicine +/- NSAID	10.0	11.3	5.9
Steroid (+/- NSAID, +/- colchicine)	51.4	49.1	58.8

Presented as percentage or mean (SD)

Table 3. Joints affected in index and recurrent flares of pseudogout.

	Index Pseudogout Flare	**Recurrent Flares (in order of occurrence)**
Patient A	Right Wrist	• Right Knee, Right Ankle
Patient B	Left Ankle	• Right Ankle • Right Knee • Right Ankle • Right Ankle
Patient C	Bilateral Hands, Bilateral Wrists, Right Knee	• Bilateral Hands, Bilateral Wrists, Right Knee • Bilateral Hands • Bilateral Hands • Left Hand, Left Wrist, Left Knee
Patient D	Left Wrist	• Left Shoulder • Bilateral Wrists, Left Knee
Patient E	Bilateral Knees	• Right Talonavicular Joint
Patient F	Left Knee	• Right Wrist
Patient G	Left Wrist	• Left Wrist • Left Wrist
Patient H	Right Elbow	• Right Elbow
Patient I	Right Knee	• Right Knee • Right Wrist
Patient J	Left Knee	• Left Wrist
Patient K	Left Wrist	• Right Wrist • Right Knee • Right Knee • Right Knee • Right Knee • Right Wrist • Right Wrist
Patient L	Left Ankle	• Bilateral Hands
Patient M	Right Knee	• Left Wrist • Right Shoulder
Patient N	Left Knee	• Right Knee • Left Knee, Left Ankle • Right Knee • Right Knee
Patient O	Right Knee	• Bilateral Wrists
Patient P	Left Wrist, Left Elbow	• Left Wrist, Left Hand • Left Wrist • Right Wrist • Bilateral Wrists • Bilateral Wrists
Patient Q	Right Wrist	• Right Wrist • Left Wrist

Table 4. Hazard ratios (95%CI) for pseudogout recurrence*

	Univariate model	Multivariate model
Comorbidities		
Cancer	2.98 (1.33, 6.68)	1.91 (0.79, 4.65)
CKD	2.92 (1.10, 7.76)	1.80 (0.66, 4.93)
Time-varying medications		
Proton pump inhibitor	1.81 (0.74, 4.42)	1.67 (0.67, 4.13)
Features of initial episode		
>1 joint involved	2.76 (0.91, 8.49)	2.08 (0.64, 6.75)
Treatment of initial episode		
No treatment	1.00 (ref)	1.00 (ref)
NSAID only	0.12 (0.02, 0.72)	0.23 (0.04, 1.43)
Colchicine +/- NSAID	0.39 (0.04, 4.10)	0.48 (0.04, 5.45)
Steroid (+/- NSAID, +/- colchicine)	0.63 (0.20, 1.97)	0.83 (0.24, 2,80)

* Presented for covariates with p<0.20 in univariate Cox models