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Influence of the natural history of disease on a previous diagnosis in patients with gout

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ABSTRACT

The clinical diagnosis of gout can be quite precise in clinically typical forms. However, in c hronic or atypical forms, such precision tends to be diminished in clinical practice.
A cohort of 248 patients with a diagnosis of urate crystal arthropathy was studied, sent with a definite clinical evaluation, and data such as severity of the disease, joint distribution, and the presence of tophi were gathered. Precision data was analyzed with respect to the referral diagnosis according to the severity parameters and the type of physician sending the patient.
The best diagnostic precision was seen in the monoarticular forms that were sent both by the emergency room as well as by family physicians, but not in those sent by other specialists. The presence of oligoarticular forms reduced significantly the diagnostic precision in all of the specialties referring patients. The presence of tophi did not improve diagnostic precision.
Chronic and severe forms of gout are frequently wrongly evaluated from the clinical standpoint.

Influencia de la historia natural de la enfermedad en el diagnóstico previo en pacientes con gota

Palabras clave:
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RESUMEN

El diagnóstico clínico de la gota puede ser preciso en formas clínicamente típicas. Sin embargo, en las formas clínicas crónicas o atípicas dicha fiabilidad parece no darse en la práctica.
Se ha estudiado una cohorte de 348 pacientes con diagnóstico de gota por cristales de urato, remitidos con una valoración diagnóstica definida, de los que se recogieron datos sobre la severidad de la enfermedad en cuanto a la distribución articular y la presencia de tofos. Se analizaron los datos de precisión respecto al diagnóstico de derivación según los parámetros de severidad clínica y los facultativos que remitían a los pacientes.
La mayor precisión diagnóstica se observó en las formas monoarticulares precedentes tanto en áreas de urgencias como en medicina familiar, pero no así en los remitidos por otras especialidades. La presencia de formas oligopoliarticulares redujo significativamente la precisión del diagnóstico de referencia en todos los grupos de facultativos. La presencia de tofos no favoreció la precisión diagnóstica.
Las formas crónicas y severas de la gota son frecuentemente mal evaluadas desde el punto de vista clínico.

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Introduction

The gold standard for the diagnosis of gout is the observation of crystals in samples of synovial fluid.[1] EULAR recommendations for the diagnosis of gout argue that the presence of acute asymmetrical arthritis with erythema, typically localized (podagra, tarsal arthritis) could be reasonably precise, even when not definite, for the diagnosis of gout.[1]

However, we do not have data on confusion factors in the diagnosis of gout in the common clinical practice and in addition, know that the administrative databases are not trustworthy.[2] Although the general perception could be that gout, including its diagnosis, is a generally well known disease, diagnostic errors are frequent both by defect as by excess,[3] making such an affirmation doubtful.[4]

Patients and methods

Data from a cohort of patients with a longitudinal follow-up in a gout clinic was performed using a systematic data gathering protocol.

Baseline visits occurred from 2000 to 2008 and general patient data, the confirmation of the diagnosis through the visualization of monosodium urate (MSU) crystals in synovial fluid or subcutaneous nodule samples, time since onset of disease, the presence of subcutaneous tophi by examination, the number of joints affected during disease progression up until the initial rheumatology visit and the presence of comorbidities (arterial hypertension, diabetes, hyperlipidemia, renal litiasis, alcoholism, clinically relevant history of vascular pathology), the motive for which the patients was referred and the specialist of the referring physician to the rheumatologist, were all documented.

The number of affected joints was characterized as monoarticular (a single joint with clinical manifestations), oligoarticular (2 to 4 joints affected over the course of the disease) and polyarticular (5 or more affected joints).

The origin of the patients was categorized according to the specialty of the referring physician (family medicine, emergency departments, traumatology, internal medicine, rheumatology, and other specialists). The motive for consultation was categorized according to the information available on the referral note into: *a)* joint pain or arthritis (joint pain, inflammation, or joint effusion without the mention of hyperuricemia, gout, or tophi), and *b)* gout (arthritis and hyperuricemia, hyperuricemia and pain, gout, or tophi).

An analysis using the SPSS 14.0 software package was performed. We excluded from the analysis: *a)* patients consulting on their own; *b)* patients without the confirmation of MSU crystals; and *c)* patients in which no minimal clinical data was available to categorize the prior diagnostic suspicion (such as a "rheumatologic evaluation," "study," "wishes to be evaluated by the specialist," etc).

Results

Of a total of 495 patients evaluated during their first visit in the abovementioned period, 76 were excluded from the analysis for lack of a diagnostic confirmation through the visualization of MSU crystals (25 did not consent to the arthrocenthesis, 25 had been under treatment for years with uric acid lowering drugs and an arthrocenthesis was not performed, in 26 no crystals were found), 28 patients had no clinical data from their visit, and 43 by their own request, with 348 patients undergoing analysis.

The population consisted mainly of males (93.5%), mean age 58 (12) years (median, 57; range, 28-86), with a progression mean since the onset of disease of 6.9 (5.8) years (median, 5; range, 0-32), mean serum uric acid 9.0 (1.4) mg/dL (median, 8.7; range, 5.9-15.3) and a number of acute joint inflammation episodes of 3.7 per patient per year (median, 3; range, 1 20).

The motive for consultation was the suspicion of gout in 163 patients (52.5%; 95% confidence interval [CI], 39.7-56.2). Progression of the clinical distribution of the disease in the first visit was monoarticular in 45 patients (13%), oligoarticular in 164 patients (47%), and polyarticular in 139 patients (40%). The prior diagnosis of gout was less frequent in patients with olioarticular or polyarticular forms. The diagnostic suspicion of gout was mentioned in 151 of 303 (50%) patients with oligo or polyarticular affection versus 32 of 45 (71%) of patients with monoarticular affection (excess rate, 0.40; 95% CI, 0.20-0.80; $P<.01$).

At least one tophi was seen upon examination in 124 patients (35.6%). One hundred and thirty-one of 224 (58.5%) of patients without tophi had a clinical suspicion of gout, while only 52 of 124 (41.9%) patients with tophi expressed such a suspicion in the referral note (excess rate, 0.51; 95% CI, 0.32-0.80; $P=.01$). Stratified analysis depending on the topography of clinical affection showed a higher frequency of diagnoses other than gout, in spite of the presence of tophi (excess reason, 0.79; 95% CI, 0.63-0.98; $P<.05$).

One hundred and fifty-nine (46%) patients from a total of 348 originated in the emergency department, 82 (23.5%) in family medicine, 21 (6%) in internal medicine/rheumatology, 22 (6.3%) from traumatology, and 64 (18.5%) from other specialists. To facilitate analysis, given the lack of distribution frequency in some reference groups, origins were grouped into three: family medicine, emergency department and other specialists, including the rest of the groups.

By origin, family medicine showed a reference diagnosis that suggested gout in at least two thirds of patients, both in the monoarticular as well as the oligo-polyarticular forms (Table 1). In the emergency department, monoarticular forms were the most frequently diagnosed (85%), but its yield was almost half when considering the oligo-polyarticular forms (45%). Other specialists that send patients include data that supports the diagnosis in less than half of patients, these being the patients with the most severe forms: in more than half the cases they were polyarticular and tophaceous (Table 2). It stood out that in the monoarticular forms, the diagnostic suspicion rate just reached 30% when patients came from other specialists. The analysis of the histories in these cases showed that 5 of the 7 patients without a diagnostic suggestion of gout had been sent due to the presence of severe synovial hypertrophy in magnetic resonance imaging studies (4 knees, 1 ankle) suggesting the diagnosis of pigmented villionodular synovitis. All of them had an oligo-polyarticular form of disease with episodes of recurring acute inflammation and the presence of subcutaneous nodules, even when the clinical data of the joint for which they were referred was chronic.

Table 1
Origin, diagnosis, and clinical form

Clinical form		Previous diagnosis		Total
		Joint pain/arthritis	Gout	No. (% gout/total)
Monoarticular [a]	Origin			
	FM	2	6	8 (75)
	OS	7	3	10 (30)
	ER	4	23	27 (85)
	Total	13	32	45 (71)
Oligo-polyarticular [a]	Origin			
	FM	23	51	74 (69)
	OS	57	40	97 (42)
	ER	72	60	132 (45)
	Total	152	151	303 (50)

ER indicates emergency department; FM, family medicine; OS, other specialists.
[a] χ^2 Pearson test ($P<.001$).

Table 2
Origin and severe affection

	Polyarticular [a] (%)	Tophi [a] (%)	Total
Origin			
Family medicine	35 (42.7)	26 (31.7)	82
Other specialists	60 (56.1)	58 (54.2)	107
Emergency department	44 (29.5)	40 (25.1)	159
Total	139 (40)	124 (35.6)	348

[a] χ^2 Pearson test (P<.001).

Table 3
Origin, prior diagnosis, and presence of tophi

Tophi		Prior diagnosis		Total
		Joint pain/arthritis	Gout	No. (% gout/total)
Absent [a]	Origin			
	FM	16	40	56 (71)
	OS	25	24	49 (49)
	ER	52	67	119 (56)
	Total	93	131	224 (58.5)
Present [a]	Origin			
	FM	9	17	26 (65)
	OS	39	19	58 (33)
	ER	24	16	40 (40)
	Total	72	52	124 (42)

ER indicates emergency department; FM, family medicine; OS, other specialists.
[a] χ^2 Pearson test (P<.001).

The presence of tophi, contrary to what would be expected, reduces the diagnostic suspicion rate in all of the reference groups, even when only in the case of other specialists or emergency departments does it fall under 50% (Table 3). Comorbidity, age, or gender did not influence the precision of the prior diagnosis or the clinical severity of gout, even when almost all of the comorbidity parameters (hypertension, history of vascular disease, diabetes mellitus, kidney failure, use of diuretics) were more frequent in patients sent by other specialists (which included mainly cardiologists, nephrologists, neurologists and endocrinologists) which was attributed to selection bias.

Lastly, 46 of 159 (29.8%) patients came from the emergency department and were seen on the suspicion of septic arthritis and 9 of 107 (8.4%) patients had been admitted due to other diagnosis into other units: one vasculitis (final diagnosis: allopurinol skin toxicity), 3 rheumatoid arthritis (final diagnosis: polyarticular gout and subcutaneous tophi), 2 reactive arthritis (final diagnosis: gout and diarrhea due to elevated doses of colchicine), 1 gait disability (final diagnosis: chronic tophaceous gout).

Discussion

In spite of the evident limitations due to the selection bias that occurs when studying a population sent to specialized care, the fact that more than half of the patients sent were done so not to be evaluated and treated for severe or complex forms of gout, refractory to allopurinol or due to severe morbidity, but rather due to the presence of unrecognized joint disease that turned out to be gout.

Errors in the diagnosis of gout have been previously studied,[3] presumably due to a high prevalence of hyperuricemia in the adult population[5] that is even higher in elderly patients due to the frequent use of diuretics[6] as well as other joint diseases, mainly osteoarthritis.

In a diagnostic precision evaluation of an administrative database, 2 to 4 visits with an ICD-9 gout code had a positive predictive value that did not surpass two thirds when taken as a reference of different classification criteria.[2] The authors observed that the greater prediction value was seen when a rheumatologist had evaluated the patient; obviously rheumatologists have a tendency to be guided by the Wallace 1977[7] criteria and therefore it seems obvious that agreement of the observer applying the criteria with the criteria themselves is high. However, a detailed analysis of the original article by Wallace et al shows that the gold standard used by the authors of the preliminary criteria for the classification of acute primary gout attacks was the clinical diagnosis and the proposed criteria are designed to evaluate acute and typical gout attacks (tarsal or first metatarsophalangeal joint), compared to monoarticular forms in other joints (septic arthritis or pseudogout, more frequent on the knee) or symmetrical polyarticular (rheumatoid arthritis). The authors themselves emphasize the fact that they have not been contrasted with spondyloarthropathies,[7] diseases which frequently affect the lower limbs, are asymmetrical and recurrent, therefore limiting the applicability of the preliminary classification criteria—criteria for diagnosis.

Our results complements the scarce knowledge that chronic gout can present a clinical evolution to polyarticular, symmetrical forms and even affect upper extremity distal joints,[8,9] because the natural history of untreated disease is the progression to a polyarticular form with tophi in half of the patients after more than 10 years since onset.[10]

Natural history of disease seems to complicate the diagnosis of gout in a different way than the different groups of professionals that send the patients. Therefore, in primary care, although the polyarticular or tophaceous forms are less well recognized, the prior diagnosis of gout appears in 65% to 75% of patients. Prior clinical follow up can give more data to the clinician in this assistance level at the beginning of disease, allowing its identification.

On the contrary, patients from traumatology presented infrequent clinical forms that avoided diagnosis by complex imaging techniques because they could be confused with chronic infections or tumors.[11] But which were diagnosed with a simple and highly practical technique fro the cost-efficacy standpoint: prior history of joint disease, diagnostic arthrocenthesis and the observation of synovial fluid under the microscope.[12] The latter is not usual in daily practice, even in specialized care, because only a fourth of patients are diagnosed on the basis of direct observation of crystals of MSU.[13] However, diagnostic arthrocenthesis is included in the EULAR recommendations for the diagnosis of gout. And not only that: in its proposal 4 “the routine search for crystals in synovial fluid of joints with no defined diagnosis is recommended”.[1]

The severity of acute episodes (25% of patients were hospitalized for fever and leukocytosis) seem to be a confusion factor in the emergency department, and recent academic formation—which emphasizes diseases with an attractive pathophysiology (rheumatoid arthritis as a paradigm of polyarticular disease, septic arthritis as a paradigm of acute monoarticular disease) versus diseases considered as commonplace, such as gout—faced with the knowledge of what is frequent in daily clinical practice, can add greater confusion to the differential diagnosis.

In conclusion, gout does not seem to be an easily recognizable disease, except its more characteristic clinical forms (asymmetric arthritis of the tarsus or the first metatarsophalangeal joint). The natural history of the disease seems to have a greater impact in some groups of professionals than in others (for example, the emergency department, traumatology), and the performance of systematic diagnostic arthrocenthesis including the search for crystals in synovial fluid, seems to be, in light of the data presented, at least highly advisable.

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