Severe tophaceous gout. Characterization of low socioeconomic level patients from México.

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Abstract Objective

To describe a group of patients with frequent tophaceous gout, the variables associated with severe tophaceous gout and to compare them with other patients with gout described elsewhere.

Methods

We looked for 65 demographic clinical and paraclinical variables from patients with gout who attended our gout clinic from 1995-2000 and were evaluated by the same group of physicians.

Results

Three hundred and sixteen patients were included, 98% males, 82% live in México city, the mean age at onset, educational level and disease duration were 37.5 ± 12.4 , 6.3 ± 3.9 and 12.6 ± 10.3 years respectively. Tophaceous gout was present in 62% of the patients with a mean tophi number of 4.7 ± 6.3 and mean HAQ score 0.13 ± 0.37 . Severe tophaceous gout (≥ 5 tophi) was found in 34% and these patients had significantly: earlier age at onset, longer duration of the disease, lesser frequency of obesity and higher frequency of: intradermal tophi, HAQ > 0.5, hospitalizations, radiographic score III/IV, uric acid under-excretion, renal function impairment and previous (oral and parenteral) auto-prescribed chronic glucocorticoid treatment compared with patients with non-severe tophaceous gout. In the multiple logistic regression the significant variables were renal function impairment (p = 0.000) and previous chronic parenteral glucocorticoid treatment (p = 0.011).

Conclusions

Our patients compared with those from other countries who have earlier age at onset, very low frequency of gout among females, frequent tophaceous gout and severe tophaceous gout. Severe tophaceous gout in this group is associated with renal function impairment and previous chronic parenteral glucocorticoid treatment.

> Key words Gout, tophaceous gout, glucocorticoids, uric acid, tophi.

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Introduction.

Gout is the most frequent cause of inflammatory arthritis in men. In México, the prevalence of this disease has been estimated in 0.7 percent (1). The use of urate lowering drugs and lifestyle modifications are highly effective in controlling the disease. Unfortunately, patients with gout are often inadequately treated or even not treated at all. In consequence, they may suffer from recurrent episodes of arthritis accompanied by the appearance of tophi as well as severe and life-threatening complications.

The consequences of prescribing the wrong medication, poor patient compliance, use of alternative therapies and drug self-prescription have all been identified in patients from several populations (2-5).

Medical errors and proposals to improve them had been published recently, as well as the data of gout patients poor compliance, use of alternative medicine and - in some countries - frequent auto-prescription (2-7).

The interplay between them, as well as genetic and environmental factors have a significant effect on the clinical picture in some patients of developing countries, that resembles what was seen 50 years ago - before the introduction of allopurinol - in developed nations (5, 7, 8).

At our centre, most patients were presented with long-term, badly-treated disease complicated by co-morbid conditions, which appear related with genetic, environmental and therapeutic factors. Therefore, in this study, we have investigated the clinical features and the role of several factors in the clinical expression of a large population of low socioeconomic level Mexican patients with gout and compared them with previous reports.

Methods

In this study, we reviewed the demographic and clinical data of consecutive patients with "Primary gout" seen at the Rheumatology Department between 1995 and 2000 by the same group of investigators. The Rheumatology Department takes care of five to seven new patients with gout per month, most of them from México city, who are mostly referred by other patients or physicians. Most of these patients are deprived from private or public health insurances and belong to the low social and economical level of the country.

Demographic and clinical studies included the investigation of 65 variables at baseline and follow-up. To evaluate the socio-economical level, we used one scale (9) which is particularly useful in our country for assessing poor people. It includes housing characteristics (number of people/number of rooms, type of floor, presence or absence of drainage and water) and the educational level of the head of the family The score ranged from 0-12; twelve means elementary housing conditions. The definitions for other variables are: age at onset and age at first acute arthritis attack. Alcoholism, was considered in those patients who drink more than 3 times/week and get drunk at least once/week. Obesity, BMI >30 (kg/m²). Hypertension and diabetes, were considered in patients with previous diagnosis and who received specific treatment for them or if they had blood pressure > 130/95 mm/Hg at least twice or fasting glucose > 126mg/dL at least twice [10]. Lithiasis, as history of previous urolithiasis. Renal function impairment, if creatinine clearance at first visit was ≤ 50 mL/min.

Severe tophaceous gout was defined as the presence of ≥ 5 tophi at first visit. Intradermic tophi, patients having intradermic, not subcutaneous plaques of monosodium urate (MSU) in sites distant to the joints (11).

Gout related radiographic changes were classified with a classification previously used in our Service for these patients (11) in four different grades: I) increased soft tissue volume around the involved joint; II) tophaceous deposits: eccentric or asymmetric soft tissue masses, with or without calcifications: III) cartilaginous and osseous destruction: intra-articular or extra-articular erosions of bone and/or joint space narrowing; IV) advanced gout: intraosseous calcifications, subperiosteal apposition of bone, or bony ankylosis. Health and functional status were evaluated by self-administering the validat-

ed version of the HAQ-Di (12).

Previous glucocorticoid treatment, was considered in the patients that received any form of glucocorticoid therapy in the last 6 months or more, specifically three times a week for oral therapy and at least once a month for parenteral administration.

Statistical analysis was carried out with Students t-test, chi square test and multiple logistic regression.

Results.

Demographic features.

There were 375 patients with gout seen at the clinic in the 5 year period of the study. The analysis, included data of 316 patients - mostly (82.3%) living in México city - whose file records had complete clinical information. Three hundred and twelve (98.7%) patients were males, their mean age at onset was 37.5 \pm 12.4 years (range 10-76 years) and the length of follow-up was 1.6 \pm 2.4 years.

The mean \pm SD of educational and socioeconomic levels were 6.3 \pm 3.9 years and 5.4 \pm 2.2 respectively. Jobs consisted of informal trade, selfemployment (shoe-makers, plumbers, carpenters), bus drivers, masons, farmers, employees, factory workers, dancers or singers.

Gout clinical characteristics

There was a family history of gout in 77 (24.4%) patients involving siblings in 56% and parents in 35.4%. Interestingly, 12% of the patients had two or more relatives affected by gout.

Fifteen percent of the patients had early-onset gout (first episode of acute arthritis < 25 years of age). The disease duration at their first visit to our clinic was 12.6 \pm 10.3 years. In this first visit, 195 patients (62%) had tophi, the mean tophi number was 4.7 \pm 6.3, median 2. Forty patients (12.7%) had intradermic tophi, and the mean HAQ score was 0.13 \pm 0.37. Nine per cent of the patients had HAQ > 0.5 (Table I).

The mean highest uric acid value recorded was $9.63 \pm 2.3 \text{ mg/dL}$ in the serum and $417 \pm 263 \text{ mg/24}$ h in the urine. Forty-six percent of the patients had serum uric acid values >10 mg/dL and 88% of the patients were consid-

Table I. Demographic and clinical data.

	Severe tophaceous gout n = 106	Non-severe tophaceous gout. n = 210	Whole group n = 316	р
Age at onset, years mean ± SD	35.4 ±13.3	38.5 ± 11.8	37.5 ± 12.4	0.036
Disease duration, years mean \pm SD	14.9 ± 9.8	9.5 ± 8.1	12.6 ± 10.3	0.000
Socioeconomic status, mean \pm SD	5.3 ± 1.9	5.6 ± 2.2	5.4 ± 2.1	NS
Educational level, years mean \pm SD	6.0 ± 4.1	6.5 ± 3.9	6.3 ± 3.9	NS
Alcoholism (%)	82	81	82	NS
Intradermal tophi (%) HAQ, mean ± SD	$34 \\ 0.38 \pm 0.64$	$2 \\ 0.04 \pm 0.15$	$13 \\ 0.13 \pm 0.37$	$0.000 \\ 0.000$

Table II. Associated diseas

	Severe tophaceous gout n = 106	Non-severe tophaceous gout. n = 210	Whole group n = 316	р
Obesity (%)	50	68	62	0.001
Dyslipidemia (%)	87	84	86	NS
Hypertension (%)	41	32	35	NS
Hyperglicemia (%)	15	16	16	NS
Diabetes (%)	5	9	8	NS
Creatinine clearance < 50mL/min (%)) 42	19	27	0.000
Hospitalizations (%)	26	15	18	0.02
Lithiasis (%)	6	9	8	NS
Death (%)	4	2	3	NS

ered uric acid under-excretors in the baseline evaluation. Radiographic stages were III or IV in 61% of the patients.

Concomitant diseases

Two hundred and fifty-eight patients (82%) were alcoholics and 189 (60%) were actual or previous cigarette smokers. Eighty-six percent had dyslipidemia (hypertrigliceridemia in all and hypercholesterolemia in 70%), 62% obesity, 35% hypertension, 16% hyperglicemia and 8% diabetes (Table II).

The mean Creatinine clearance was 71.7 ± 32.3 mL/min, yet 27 percent had renal function impairment. On the other hand, we could document a previous history of renal stones in eight percent of the patients.

Previous treatment

Previous treatments consisted of a huge variety of modalities including drugs and alternative therapies, which were prescribed by either the general physician, pharmacists, relatives, friends and the patients themselves. Most patients (79%) had received non-steroidal antinflammatory drugs (NSAID) and only a few (5.4%) colchicine. Two hundred and nine (66%) patients were receiving glucocorticoids - mostly by self prescription; 101 (32%) took them orally and 108 (34%) were on parenteral glucocorticoids for a mean of 4.01 ± 4.05 years. Only 44% of the patients received allopurinol, but dosage and administration was mostly on an irregular basis. Eight percent of the patients received low dose aspirin and 3% diuretic agents (Fig. 1).

Subsequent treatment

At the first visit, the patients were prescribed with life-style measures (diet and exercise) and drugs, including allopurinol, colchicine as prophylactic and NSAID if needed. Regarding patients receiving glucocorticoids, we prescribed them prednisone at equivalent doses and then slowly tapered the dose until complete withdrawn from these drugs, which occurred after a mean time of 7.5 ± 9.1 months. During follow-up, all the patients received allopurinol at mean doses of 306 ± 93.6 and 5 patients additionally received benzobromarone. Twenty percent of the patients have some structural damage to the joints, which required daily

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Fig. 1. Previous treatment. *Non-significant differences.

Previous auto-prescribed oral and parenteral glucocorticoids (p = 0.000).

Table III. Variables included in Multiple logistic regression.

	Severe tophaceous gout n = 106 (%)	Non-severe tophaceous gout n = 210 (%)	р	OR (95% confidence interval)
Age at onset < 25 years	24	10	0.001	2.8 (1.5 – 5.2)
Duration of the disease > 5 years	86	56	0.000	3.4 (1.8 - 6.5)
Obesity	50	68	0.001	0.45 (0.28 - 0.73)
Hospitalizations	26	15	0.02	1.9 (1.1 – 3.5)
Uric acid under-excretors	95	84	0.02	3.4 (1.1 – 10.3)
Creatinine clearance <50 ml/min	42	19	0.000	3.1 (1.8 – 5.5)
Oral glucocorticoid treatment*	49	23	0.000	3.2 (1.9 – 5.2)
Parenteral glucocorticoid treatment*	51	26	0.000	3.0(1.8-4.9)

* Previous auto-prescribed treatment.

NSAID. Nine patients developed adverse events, six to allopurinol (previously reported) (13) and the other three to NSAID and colchicine.

Disease complications and hospitalization

Fifty-eight patients (18.4%) required hospitalization, because of tophi infection (n = 14), surgical procedures (n = 12), upper gastrointestinal bleeding (n = 6), severe polyarticular acute gout (n = 5), chronic renal failure (n = 3), metabolic disturbances (n = 2) and miscellaneous causes (n = 16). Nine patients (3%) died during this short follow-up.

Severe tophaceous gout VS non-severe tophaceous gout

Compared with patients having < 5 tophi, those with severe tophaceous gout (\geq 5 tophi) had a significantly earlier age at onset, longer duration of the disease, lesser frequency of obesity and higher frequency of: intradermal tophi, HAQ > 0.5, hospitalizations, radiographic score III/IV, uric acid under-excretion, renal function impairment and previous (oral and parenteral) auto-prescribed chronic glucocorticoid treatment.

In the multiple logistic regression, renal function impairment (p = 0.000) and previous use of parenteral glucocorticoids (p = 0.011) were significantly associated with severe tophaceous gout (Table III). Three variables, HAQ > 0.5, intradermal tophi and high radiographic score were not included in this analysis, because they were all considered manifestations of severe tophaceous gout.

Discussion

Our patients have an earlier onset of gout, even earlier than the Chinese reports (14-19) and similar to the Indonesian (5). This age at onset is similar among other patients reported previously in México (20-24), in whom there is also a remarkably low frequency of gout among females. It is not clear if this is a consequence of lesser frequency of gout among Mexican women or if they are not diagnosed as having gout.

The prevalence of gout is increasing worldwide, probably because of longer life expectancy, higher prevalence of hypertension and more frequent use of diuretics and cyclosporine. Nevertheless, its prevalence (0.3-1.2%) seems similar in most ethnic groups, except for Taiwanese aborigins (14, 17). The variable demographic and clinical characteristics of gout are probably the result of the mean age of the population studied and environmental factors such as alcoholism, obesity, dyslipidemia, lead exposure and treatment.

Since gout is a familial disease in all the populations studied, several studies have looked for genetic markers specifically enzymatic deficiencies, HLA markers (25), apolipoprotein phenotypes (26), methylene tetrahydrofolate reductase gene (27) or polymorphisms in the interleukin-1 receptor antagonist (28). Although some genetic markers are associated with particular clinical characteristics, none have been found to be a clear risk factor for the disease. In this sense, gout is a polygenic disease. The National Heart, Lung and Blood Institute Family Heart Study (NHLBI), has estimated that the hereditary component for serum uric acid is around 40% (29).

Our patients represent in some way, the natural history of the disease as was described decades ago before allopurinol description (7, 8, 30). It is probable

Table IV. Gout clinical characteristics in some countries.

	England 1958-67 (8)	South Africa 1984-9* (26)	Togo 1989-99 (33)	China 1983-91 (16)	China 1992-99 (16)	China 1992-99 (19)	México 1995-2000
N	354	107	160	7836	19354	419	316
Males (%)	90	87	99	92	92	96	99
Age at onset, mean ± SD	40-50	51	61% (>40)	48	46	48	38
Familial history (%)	36	36	11	15	26		24
Alcoholism (%)	37	79	83	26	22		82
Tophi (%)	21	36	22	8	9	7	62
Obesity (%)	48	48	40	9	12		62
Hypertension (%)	52	3	26	36	23	6	35
Dyslipidemia (%)			6	28	32	57	86
Lithiasis (%)	11		0.6	10	12		8
Diabetes (%)		1	1.3	12	11		8
RFI** (%)	25		8	23	18	17	27
Population included	Caucasians 94%	Blacks	Blacks	Taiwanese	Taiwanese	Shantou (urban area)	Mexican mestizos

The years indicate the period in which the patients were studied.

* 49% with secondary gout.

** Renal function impairment.

that in many countries there is still a sub-group of patients who have been without adequate therapy for gout for many years (3-5).

There are many reports about the characteristics of gout patients in different countries (25-31-38) (Table IV), but none from a Latin American country in international journals. It seems that some of the clinical characteristics of gout could be different among countries, races, environmental and socioeconomic status. In Latin America there are around 520,000,000 people with a similar genetic and socioeconomic background, although in the same country there are clear differences, probably associated with socioeconomic factors.

In this study, severe tophaceous gout was associated and probably determines more complications such as worse functional class, more hospitalizations and higher radiographic score. But it is also associated with earlier age at onset, longer disease duration without adequate treatment, chronic autoprescribed glucocorticoids and renal function impairment. In the multiple logistic regression only the two latter were significantly associated.

Renal function impairment in this group of young patients - most of them without previous history of renal disease - is remarkable. For a long time it was considered in long follow-up studies, that hyperuricemia and gout *per se* were not associated with renal impairment (39), although in other recent studies this premise has been challenged (40-42). The differences between these results could be attributable to the populations included. It is possible that in some groups, other genetic and environmental factors contribute. One of them is environmental chronic lead exposure (40, 43, 44), which in turn seems to be higher in urban populations of low socio-economic level as our patients.

But also this clinical picture is dangerously modified by high dosage and chronic therapy with auto-prescribed glucocorticoids, particularly parenteral preparations which contain long-action corticosteroids. Glucocorticoids can be purchased without medical prescription in many countries and they have also been described as a component of "traditional medicine" (5, 45-47).

In our experience, since glucocorticoids are cheap and very effective during acute gout attacks, patients use them each time more frequently, at higher doses, without a regular uratelowering therapy or medical consultation until they get worse and seek medical attention.

The treatment of acute gout attacks with glucocorticoids has clear advantages in some patients and their benefit is well established in medical literature, but previously we also found their chronic usage associated with a higher number of tophi and intradermal tophi [11], and in the rat air-pouch model, glucocorticoid preparations promote the persistence of urate crystals and tophi formation (48).

In those countries where patients can obtain glucocorticoids easily - or traditional medicine with them - without medical prescription, the physician should alert them of the complications of its use and the importance of a regular and chronic treatment including life style changes, diet, urate lowering drugs and prevention or treatment of concomitant diseases. A recent report in gout patients from Indonesia concluded that self-medication in a developing country may become a health problem (5). In this study, self-medication seems to be common also among those with a high educational level. Gout patients frequently had one or more of the entities of Metabolic syndrome, all them can appear or worsen with chronic glucocorticoid usage (49). In our study, renal function impairment and glucocorticoid treatment were the main factors associated with severe tophaceous gout, but it is possible that in this population other factors also contribute: low socioeconomic and educational levels, delayed medical attention, frequent auto-prescription and environmental factors such as lead.

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