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Prevalence and factors associated to diffuse idiopathic skeletal hyperostosis in gout

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Abstract

Aim: To evaluate the prevalence, associated factors, and the impact of diffuse idiopathic skeletal hyperostosis (DISH) in patients with gout.

Methods: Patients with gout entering into an inception cohort were evaluated for either spinal or peripheral hyperostosis from January 2022 to April 2023. Age, gender, along with comorbid conditions associated to gout and DISH were analyzed, including the presence either axial or peripheral hyperostosis and associated calcium pyrophosphate arthritis (CPPA).

Results: The prevalence of DISH was 25.6% (31/121) patients, neat peripheral joint hyperostosis affecting 51.6% (16/31). CPPA was also present in 11.6% (14/121) patients. Only older age and male gender were independently associated to the presence of DISH. The presence of hyperostosis in peripheral joints was not associated to a worse initial evaluation of the severity of gout.

Conclusions: The presence of DISH in patients with gout seems to be related mostly to aging. Conditions apparently associated to DISH in gout patients seem therefore to be related to aging.

Keywords

Diffuse idiopathic skeletal hyperostosis, hyperostosis, gout, calcium pyrophosphate arthritis, calcification, ossification

Introduction

Skeletal hyperostosis is caused by ossifications on insertional elements of tendons and ligaments (enthesis). It was first described in 1950 as a disease involving the spine different to ankylosing spondylitis and

spondylosis, and then named "senile vertebral hyperostosis" [1]. It is also known as Forrestier and Rotes-Querol disease.

It was afterwards shown also to involve peripheral joints, and therefore named "diffuse idiopathic skeletal hyperostosis" or DISH [2]. Its radiologic and pathologic findings were rigorously described by Resnick and Niwayama [3] half a century ago.

Although mostly associated to aging, DISH has been also associated to metabolic disturbances such as overweight, hyperuricemia and diabetes [4], and also to the metabolic syndrome [5]. There is some evidence on the association of DISH with gout [5–7] and with the development of tophaceous gout [8, 9].

This study intended to evaluate the prevalence of DISH in patients with gout, the presence of spinal and peripheral joint involvement, and the association of DISH with comorbid conditions associated to gout, clinical characteristics of gout severity, and concomitant calcium pyrophosphate arthritis (CPPA). Also, it intended to study whether the presence of peripheral joint hyperostosis may influence the evaluation of severity in gout.

Materials and methods

Population

From 01 January 2022 to 30 April 2023, 121 patients who entered in a prospectively recruited inception cohort for evaluation and follow-up of patients with gout, the Cruces Gout Cohort (CGC) were studied for the presence of DISH. This gout-dedicated practice is settled in a third-level public university hospital with a reference population of 380,000 inhabitants, health assistance covering all nationals and foreign residents. Patients referred to this difficult to treat/severe gout-dedicated office is an aged population that have a very high frequency of comorbid conditions. All patients signed informed consent and the cohort was approved from the start by the local Ethics of Clinical Investigation Committee.

Variables

All data are available from the patients' electronic file that are the unique source for all public healthcare management and includes all data and all examinations results from. General data [age, gender, body mass index (BMI)], data derived from comorbid conditions (diabetes, hypertension, cardiovascular disease, medications), data regarding gout (time from onset, number of patient-reported flares the year previous to entrance into the cohort, number of reported joints involved, presence of subcutaneous tophi, presence of sonographic joint tophi, erosive disease in conventional X-ray, previous urate-lowering medications) were retrieved.

Presence of spinal hyperostosis was ascertained from available conventional X-ray of the spine, thorax, abdomen, and also from computed tomography (CT), or magnetic resonance imaging (MRI) available in the electronic file. Patients reporting spinal pain were asked for conventional radiographies if not yet available.

Presence of peripheral joint hyperostosis was ascertained from conventional radiographies of patient-reported gout-affected joints if available in the electronic file; additional radiographies were asked to patients depending on clinical history or physical examination retrieving joint pain or limitation although not initially attributable to gout.

Concomitant CPPA was based on the observation of calcium pyrophosphate (CPP) crystals in samples of synovial fluid prior or during follow-up in the gout cohort.

Analysis included serum urate (sUA), serum creatinine, estimated glomerular filtration rate (eGFR), and fasting glucose, total cholesterol, and cholesterol associated to low density lipoproteins (LDL, LDL-cholesterol), high density lipoproteins (HDL, HDL-cholesterol), and triglycerides.

Statistical analysis

Statistical analysis was made using an institutional license of the IBM SPSS statistical package version 29.0. Student t test was used to compare continuous variables between groups and Chi-square (χ^2) tests to compare discrete variables between groups. Variables found to be associated with $P < 0.20$ were included in multivariate analysis.

Results

One hundred and twenty-one patients were included. In 87/121 (71.9%), diagnosis of gout was based on demonstration of urate crystals in synovial fluid or material aspirated from tophi, 32 (26.4%) on sonographic findings of a tophus or the double contour sign, and in 2 (1.7%) based on clinical findings. There were 20 women (16.5%) and 101 men (83.5%), mean age was 71 years ± 13.6 years (median 73, interquartile range 63–80). Time from onset of gout was 5.8 years ± 6.0 years (median 4, interquartile range 1–9). Twenty-eight out of 121 (23.1%) showed subcutaneous tophi, and 38 (31.4%) reported ever having involvement of more than 4 joints (polyarticular involvement).

DISH was present in 31/121 (25.6%) patients, neat peripheral joint hyperostosis affecting 16 of them (51.6%). Fourteen out of 121 patients (11.6%) had also a confirmed previous or present diagnosis of CPPA. Diagnosis was based on conventional X-ray in 26 and in 5 on CT scans.

Aging, male gender, increased number of flares, higher baseline sUA levels, lower eGFR, lower HDL-cholesterol, polyarticular joint disease, hypertension, and CPPA were shown to be associated ($P < 0.20$) with DISH in bivariate analysis (Tables 1 and 2). Other variables (see Tables 1 and 2) showed no apparent association with DISH.

Table 1. Comparison of continuous variables between patients showing (DISH+) and not showing (DISH–) radiological features of DISH

Variables	DISH	*N*	Mean	SD	*P*
Age (years)	(–)	90	69.34	14.48	0.011
	(+)	31	75.74	9.03	
Time from onset (years)	(–)	90	6.60	7.18	0.767
	(+)	31	6.90	6.57	
Flares (per year)	(–)	90	2.84	2,34	0.019
	(+)	31	4.23	4.86	
sUA (mg/dL)	(–)	90	9.30	1.18	0.183
	(+)	31	9.56	1.83	
eGFR (mL/min)	(–)	90	59.07	25.33	0.094
	(+)	30	52.26	21.40	
Glucose (mg/dL)	(–)	83	112.12	34.57	0.410
	(+)	26	113.85	30.80	
Total cholesterol (mg/dL)	(–)	83	171.69	46.84	0.272
	(+)	25	178.80	63.52	
HDL-cholesterol (mg/dL)	(–)	38	51.16	13.72	0.049
	(+)	11	43.18	14.07	
LDL-cholesterol (mg/dL)	(–)	38	112.50	44.59	0.346
	(+)	11	119.36	67.10	
Triglycerides (mg/dL)	(–)	78	149.08	135.34	0.274
	(+)	24	168.46	144.51	

N: number; SD: standard deviation

Multivariate analysis showed that aging was the only variable that remained significantly associated to DISH, although male sex was also close to significance (Table 3).

Table 2. Comparison of discrete variables between patients showing (DISH+) and not showing (DISH–) radiographic features of DISH

Variables		DISH+/total	Percentage of DISH+ among the total (%)	*P*
Sex	Male	30/101	29.70	0.021
	Female	1/20	5.00	
Diuretics	Yes	17/62	27.42	0.642
	No	14/59	23.73	
Tophi	Yes	8/28	28.57	0.683
	No	23/93	24.73	
Previous ULT	Yes	12/49	24.49	0.814
	No	19/72	26.39	
Hypertension	Yes	29/100	29.00	0.063
	No	2/21	9.52	
Hyperlipidemia	Yes	18/74	24.32	0.682
	No	13/47	27.66	
Diabetes	Yes	11/41	24.39	0.827
	No	20/80	25.00	
Vascular event	Yes	11/46	23.91	0.736
(previous)	No	20/75	26.67	
Polyarticular	Yes	15/38	39.47	0.018
(joint involvement)	No	16/83	19.28	
Obesity (BMI > 30)	Yes	3/14	21.43	0.702
	No	28/107	26.17	
CPPA	Yes	6/14	42.86	0.116
	No	25/107	23.36	

ULT: urate lowering treatment

Table 3. Multivariate analysis of variables associated to DISH in gout patients

Variables	Quadratic mean	*F*	*P*
Age	0.317	10.088	0.002
Gender (male)	0.103	3.285	0.070
HDL-cholesterol	0.038	1.209	0.272
CPPA	0.005	0.161	0.688
eGFR	0.004	0.132	0.701
Flares (per year)	0.001	0.041	0.839
Polyarticular	0.000	0.007	0.932

To ascertain whether peripheric joint hyperostosis could influence patient-reported flares and joint distribution, further analysis was made showing that only aging was associated to peripheral radiographic hyperostosis: 77.13 years ± 6.81 years *vs.* 74.27 years ± 10.99 years for presence or absence of peripheral joint hyperostosis respectively. No difference in the rate of polyarticular gout distribution was observed between patients showing or not peripheral hyperostosis.

Discussion

DISH is a very prevalent, but commonly undiagnosed disease and its prevalence increases with age. Using CT scans, the prevalence of DISH was found to be 19.1% out of 1,815 trauma patients aged over 20 years, and up to 45.5% in those ages over 80 years. The mean age of patients was over 60 years and the prevalence was observed to be higher among males (20.2%) than for females (14.9%) [10].

In our study, in aged patients, the prevalence was 25.6%, lower that in the previous study. CT scans were not systematically available, and CT imaging was used for diagnosis when there was a CT scan available for evaluation and no clear findings were observed in X-ray. A recent transversal study in 1,519

patients in Japan only using conventional X-ray in emergency-room patients showed a prevalence of 17.4%, much lower than that observed using CT, aging being the only difference observed [11].

Metabolic factors have been considered to play a part in the pathogenesis of DISH, including those frequently associated to gout such as hyperuricemia, increased BMI, and diabetes. In a series of 131 patients with DISH matched for age with 131 patients with spondylosis, patients with DISH showed higher BMI and sUA levels, and more frequent diabetes [4], whereas in a series of 47 patients with DISH compared to 48 sex and age-matched controls, patients with DISH had a higher BMI and waist circumference, but no differences for total cholesterol, HDL, LDL, or triglyceride serum levels [5]. In a large retrospective series, diabetes, obesity, and ischemic heart disease were significantly more frequent in patients with DISH [10].

Nevertheless, in a series of 133 patients with diabetes and 133 nondiabetic controls matched for sex, age, and weight, the prevalence of DISH using conventional X-ray was higher in patients with diabetes (12.0%) than in the control group (6.8%); patients with DISH showed a mean age that was a decade older than that of controls. No statistically significant differences were found for fasting blood glucose levels, glycosylated hemoglobin, triglyceride, very LDL (VLDL), LDL, HDL, sUA, insulin, and insulin-like growth factor-1 (IGF1) levels among both groups [12]. Despite of these inconsistent findings, some investigators still suggest that metabolic disturbances to play a part in the pathogenesis of DISH, as elevated serum growth hormone levels have been found in DISH, although they were not coupled to changes in serum IGF1 [13].

In our series, only male sex and aging were associated with higher prevalence of DISH in patients with gout, as other variables apparently associated could be well explained by aging. A very large series showed that only aging seemed to be associated with DISH [11]. Despite the presence of inflammation in DISH has been advocated by some authors [14], neither factors related to gout severity were associated with DISH nor peripheral joint involvement of DISH associated with gout severity, even if considering that the presence of peripheral joint involvement in DISH has been shown to interfere with the clinical evaluation of inflammatory arthritis [15].

We could not find an association of DISH with CPPA in gout patients, what could be explained by the association of CPPA itself with aging [16]. CPPA and DISH have been shown to be associated in some populations [17], and even genetic variants identified for such a phenotype [18]. The presence of calcaneal achilleal and plantar spurs has been reported to be over 40% in patients with gout and may reflect the presence of peripheral DISH [19].

Our study has valuable strengths, as previously published series did not evaluate variables related to gout severity. Also, diagnosis of both gout and associated CPPA was mostly or completely based on optic microscopy, respectively. Limitations include the bias of selection of severe gout patients in a gout-clinic, mostly aged and men, and a relatively small number of patients included. In addition, a systematic X-ray screening of all segments of the spine and peripheral joints was not performed, but only of that previously performed or clinically indicated in symptomatic patients. Therefore, we may have underrated the prevalence of DISH and our results cannot be extrapolated to the general non-gouty population.

In summary, the presence of DISH in patients with gout seems to be related mostly to aging. Future investigation should be directed to prospective studies evaluating plausible associated factors and different imaging modalities.

Abbreviations

BMI: body mass index

CPPA: calcium pyrophosphate arthritis

CT: computed tomography

DISH: diffuse idiopathic skeletal hyperostosis

eGFR: estimated glomerular filtration rate

HDL: high density lipoproteins

LDL: low density lipoproteins

sUA: serum urate

Declarations

Author contributions

FPR: Conceptualization, Data curation. FPR, Nuria PH, CVP, MdCMC, Nerea PH, and AMHB: Data curation. FPR, Nuria PH, CVP, MdCMC, Nerea PH, and AMHB: Writing—review & editing. FPR, Nuria PH, CVP, MdCMC, Nerea PH, and AMHB read and approved the submitted version.

Conflicts of interest

FPR is consultant for Arthrosi, Horizon, LG pharma, Protalix, and SOBI; member of DMSB for Selecta; speaker for Menarini, EULAR, and Spanish Foundation for Rheumatology.

Ethical approval

The study was included within a prospective inception gout cohort study approved by Cruces University Hospital Ethics and Clinical Investigation Committee (CEIC Cruces).

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

Data could be obtained on request by contacting Prof. Dr. Fernando Pérez-Ruiz (fernando.perezruiz@osakidetza.eus).

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