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SYSTEMIC AND LOCAL FACTORS ARE INVOLVED IN THE EVOLUTION OF EROSIONS IN HAND OSTEOARTHRITIS

J. Bijsterbosch, J.M. van Bemmel, I. Watt,
I. Meulenbelt, F.R. Rosendaal,
T.W.J. Huizinga, M. Kloppenburg

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ABSTRACT

Objective. In order to gain insight in the pathogenesis of erosive hand osteoarthritis (OA), the evolution of erosions in hand OA and risk factors involved were investigated.

Methods. The 6-year evolution in radiographic Verbruggen-Veys anatomical phase was assessed in interphalangeal joints of 236 patients with hand OA (mean age 59 years, 83% women) from the Genetics ARthrosis and Progression (GARP) sibling pair study. Erosive evolution comprised phase transitions from non-erosive to erosive phases and from active erosions to remodelling. Clustering of erosive evolution within patients was assessed using the chi-squared test. Familial aggregation was evaluated in sibling pairs by estimating odds ratios (OR) for siblings and probands sharing erosive evolution. Local baseline determinants and the effect of high-sensitive CRP were assessed using generalised estimating equations.

Results. Erosive evolution took place in 181 of 4120 interphalangeal joints at risk (4.4%), corresponding to 60 patients (25.4% of study sample). Erosive evolution was found more often in multiple interphalangeal joints in one patient than would be expected by chance (chi-square 373.0, $p<0.001$). The adjusted OR (95%CI) for a sibling having erosive evolution if the proband had erosive evolution was 4.7 (1.4 to 15.8). Systemic inflammation was not associated with erosive activity. Independent local determinants were joint space narrowing (OR (95%CI) 8.9 (4.8 to 16.4)) and self-reported pain (OR (95%CI) 2.3 (1.1 to 4.7)).

Conclusion. Erosive evolution was clustered within patients and families. Local factors were also involved in the evolution. This increase in insight in the pathogenesis of erosive hand OA will contribute to the development of new treatments.

INTRODUCTION

Hand osteoarthritis (OA) is a common musculoskeletal disorder characterised by degradation of cartilage and changes in subchondral bone leading to pain and disability.[1] Because of its heterogeneous character, different subsets have been proposed, erosive OA (EOA) being one such subset that has attracted interest in OA research.[2,3]

EOA is a radiographic subset based on the presence of subchondral erosions mainly affecting the interphalangeal (IP) joints.[4] The prevalence of EOA was estimated to be 2.8% in the general population, rising to 15.5% in those with symptomatic hand OA.[5] Recently we have shown that the clinical burden of EOA is higher compared to non-EOA, mainly due to its nodal character.[6] The clinical course of EOA is characterised by episodes of inflammatory signs and symptoms that finally fade out leaving deformities and functional disability.[7] Radiographically, a dynamic erosive process takes place with loss of joint space, mostly accompanied by other OA features, preceding active erosions that ultimately become remodelled.[8,9]

Little is known on the risk factors associated with the development and progression of erosions in OA. Knowledge on these factors will increase understanding in the pathophysiological pathways involved in the erosive process of EOA, which is of importance when development of new therapies is considered. Therefore, we investigated the evolution of erosions in IP joints over time as well as systemic and local factors associated with the development and progression of erosions in a cohort of patients with hand OA followed for 6 years. Because the population comprises sibling pairs, it was possible to assess the role of familial factors.

PATIENTS AND METHODS

Study design and patient population

The Genetics ARthrosis and Progression (GARP) study is a cohort study aimed at identifying determinants of OA susceptibility and progression. The study population comprises 192 Caucasian sibling pairs with symptomatic OA at multiple sites in the hand or in at least two of the following sites: hand, knee, hip or spine. Details about the recruitment and selection have been published elsewhere.[10] In brief, probands were recruited from rheumatologists, orthopaedic surgeons and general practitioners. Subsequently, affected siblings were recruited via the probands. Both proband and sibling were required to have OA at multiple sites. The GARP study was approved by the medical ethics committee.

Patients were included for baseline assessment between August 2000 and March 2003. From April 2007 to June 2008 participants who consented for a follow-up evaluation were assessed. All consenters completed questionnaires and part of them visited the outpatient clinic for physical examination and radiographic evaluation.

Patients were eligible for the present study if they had hand OA as defined hereafter and if radiographic follow-up data were available. Hand OA was defined by the American College of Rheumatology (ACR) criteria for clinical hand OA[11] or the presence of either bony swelling in at least two of the ten selected joints from the ACR criteria or a Kellgren-Lawrence score ≥ 2 in any IP or first carpometacarpal (CMC-1) joint.

Radiographic assessment

Hand radiographs (dorsal-volar) were obtained at baseline and follow-up by a single radiographer, employing a standard protocol with a fixed film focus distance (1.15 m). Radiographs were scored paired in chronological order blinded for patient characteristics by consensus opinion of two experienced readers (JB, IW) using the anatomical phase score developed by Verbruggen and Veys.[8,9] In addition, osteophytes and joint space narrowing (JSN) were graded 0-3 using the Osteoarthritis Research Society International (OARSI) atlas.[12]

The Verbruggen-Veys anatomical phase score comprises five phases representing the evolution of hand OA as a dynamic process. The first phase represents joints without OA signs (N, normal). In the stationary (S) phase joints have a classic OA appearance with osteophytes and possible JSN. The third phase comprises total loss of joint space (J) in the whole or part of the joint. In the next phase the subchondral plate becomes eroded (E). This is followed by the remodelling (R) phase when new irregular subchondral plates are formed and a new joint space becomes visible. Each phase incorporates the structural abnormalities that occur in that phase. Intrareader reproducibility for the evolution of joint phases over 6 years based on 25 randomly selected pairs of radiographs was very good (kappa=0.81).

Determinants of outcome measured at baseline

Non-local factors included age, sex and body mass index (BMI). In addition, we assessed clustering of erosive evolution in multiple IP joints of the same patient as well as familial aggregation of the erosive process. Baseline serum high sensitive CRP (S-HsCRP) levels were used a measure for systemic inflammation. Serum samples were collected in the morning, processed within 4 hours upon collection and stored at -80°C until measurement. S-HsCRP was assayed using an ultrasensitive immunonephelometry method (N Latex CRP mono; Behringwerke AG, Marburg, Germany) on a BNA Behring nephelometer by a specialised laboratory (Synarc, Lyon, France).

Local factors on the joint level were the presence of self-reported pain and stiffness, pain upon lateral joint pressure, nodes, limited motion, osteophytes and JSN. Self-reported pain and stiffness were assessed using a standard diagram including all hand joints on which the patient marked painful and stiff joints. The presence of pain upon lateral joint pressure, nodes and limited motion were assessed by a single observer during physical examination. For analysis we distinguished between osteophytes and JSN grade 0-1 and grade 2-3 as measured with the OARSI atlas. On the patient level self-reported hand pain and functional limitations were assessed with the pain (5 items) and function (9 items) subscales of the Australian/Canadian Osteoarthritis Hand Index (AUSCAN), on a five-point Likert scale (0=none to 4=extreme).[13]

Statistical analysis

Data were analysed using SPSS, version 16.0 (SPSS, Chicago, Illinois, USA). Only IP joints were included in the analyses since EOA is said to predominantly affect the IP joints.[4] For each IP joint the evolution of the anatomical phase over 6 years was obtained.

The E- and R-phases were considered as EOA. Although the J-phase could be regarded as a destructive phase, we felt that it comprises a phase that precedes the

true erosive phase. To assess the effect of this classification, sensitivity analysis was carried out including J-phase joints as erosive. Joints in the R-phase at baseline were not included in the analysis since they are no longer at risk for ongoing evolution. Erosive evolution was regarded a dynamic process defined by phase transitions from the N-phase, S-phase or J-phase to erosive phases (E-phase or R-phase) and from the E-phase to the R-phase.

To test whether erosive evolution is likely to cluster in multiple IP joints of the same patient, we obtained the prevalence of erosive evolution for each IP joint. Using these observed frequencies the numbers of patients expected to have an erosive transition in 0, 1, 2, or at least 3 joints were calculated, assuming that the occurrence of erosive evolution in different IP joints of a patient is independent. Observed frequencies of involved joints were compared to the expected distribution using the chi-squared test.

To assess whether familial factors play a role in the erosive process we compared siblings of probands who had erosive evolution in least one IP joint with siblings of probands without erosive evolution. This analysis requires availability of follow-up data for both proband and sibling. Odds ratios (ORs) were estimated for erosive evolution in siblings given erosive activity in the probands using logistic regression analyses. Additionally, we estimated the dose-response relationship between erosive evolution in the siblings and the number of joints with erosive evolution in probands. Adjustments were made for age, sex and BMI.

Risk factors for erosive evolution were assessed using generalised estimating equations (GEE) to take into account intra-patient and intra-family correlation. Additional adjustment was made for the anatomical phase at baseline. Multivariable analysis was carried out to assess the independent effect of determinants found to be associated with the outcome in univariable analysis adjusted for anatomical phase at baseline, age, sex and BMI. For all analyses ORs are reported with 95% confidence intervals (95%CI).

RESULTS

Study population

Of the 357 patients fulfilling the hand OA criteria at baseline, 300 (84%) consented to participate in the follow-up study of which 242 visited the outpatient clinic and 58 completed questionnaires only. Consent was not given by 43 (12%) patients, 12 (3.3%) were deceased and 2 (0.6%) were lost to follow-up. Most frequent reasons for non-consent were loss of interest (n=13), health problems not related to OA (n=7), unavailability of transport (n=7) and emigration (n=2). Of the 242 eligible patients 236 had radiographic data available at baseline and follow-up and were included in the present study, comprising 4232 IP joints. There were 87 sibling pairs with follow-up data for both proband and sibling for the analysis on familial aggregation. The mean follow-up time was 6.1 years (range 5.0-7.8 years).

Baseline characteristics for the whole study sample as well as for the complete sibling pairs are shown in table 1. There were no differences between probands and siblings. Patients not included in the present study were somewhat older. Other

Table 1. Baseline characteristics of the whole sample of 236 patients with hand osteoarthritis (OA) and 87 complete sibling pairs from this group.

		Complete sibling pairs*	
	Whole study	**Probands**	**Siblings**
Age, mean (SD) years	58.9 (7.1)	58.9 (6.6)	58.6 (7.5)
Women, no (%)	196 (83)	75 (86)	69 (79)
Postmenopausal women, no (%)	176 (90)	69 (92)	62 (90)
Body mass index, mean (SD) kg/m^2	27.1 (5.0)	27.5 (5.4)	26.8 (4.9)
ACR criteria hand OA, no (%)	183 (78)	72 (83)	66 (76)
Right handed, no (%)	188 (80)	67 (77)	68 (78)
Additional OA sites, no (%)			
Knee	76 (32)	31 (36)	22 (25)
Hip	49 (21)	20 (23)	19 (22)
Spine	185 (78)	67 (77)	70 (81)

*Sibling pair with follow-up data available for both proband and sibling.
ACR: American College of Rheumatology.

clinical and radiographic baseline parameters did not differ between consenters and non-consenters (data not shown).

Erosive evolution

At baseline 203 IP joints (4.7%) in 48 patients were classified as EOA, little more than half being in the remodelling phase (table 2). After 6 years 315 IP joints (7.4%) in 65 patients were in erosive phases, of which two-third had reached the remodelling phase.

Of the 4120 IP joints at risk at baseline (4232 minus 112 in R-phase), 181 (4.4%) had development or progression of erosions, comprising 60 patients (25.4% of study sample). This erosive evolution took place in 14 of the 2542 normal IP joints (0.6%), 76 of the 1450 joints in S-phase (5.2%), 22 of the 37 joints in J-phase at baseline (59.5%), and 69 of the 91 joints with active erosions (76.0%). Phase transitions were most frequent in the distal interphalangeal (DIP) joints, except for the newly developed stationary OA, which occurred more often in the proximal interphalangeal (PIP) joints.

Systemic determinants of erosive evolution

There was clear evidence for clustering of erosive evolution within patients (table 3). There were 31 patients with at least three IP joints showing erosive evolution, compared to 3 patients expected in this category.

The adjusted OR (95%CI) for a sibling having erosive evolution if the proband had erosive evolution was 4.7 (1.4 to 15.8) (table 4). A dose-response relationship was found between the number of IP joints with erosive evolution among the probands and the presence of erosive evolution in siblings, although patient numbers were small (table 5).

Age, sex, BMI and S-HsCRP levels were not associated with development or progression of erosions. The ORs (95%CI) adjusted for anatomical phase at baseline and family effects were 0.97 (0.94 to 1.01) for age, 1.13 (0.40 to 3.19) for female sex, 0.98 (0.92 to 1.04) per point BMI and 1.00 (0.96 to 1.05) for S-HsCRP.

Table 2. Distribution of anatomical phases at baseline and follow-up and the evolution of anatomical phases over 6 years in 4232 interphalangeal (IP) joints from 236 patients with hand osteoarthritis.

	Baseline	Follow-up	Transition	IP joints	DIP joints	PIP joints*
N-phase	2542 (60.1)	2387 (56.4)	N-N	2387 (56.4)	868 (46.1)	1519 (64.6)
			N-S/J	141 (3.3)	44 (2.3)	97 (4.1)
			N-E/R	14 (0.3)	4 (0.2)	10 (0.4)
S-phase	1450 (34.3)	1501 (35.5)	S-S/J	1375 (32.5)	724 (38.5)	651 (27.7)
			S-E/R	76 (1.8)	55 (2.9)	21 (0.9)
J-phase	37 (0.9)	29 (0.7)	J-J	15 (0.4)	11 (0.6)	4 (0.2)
			J-E/R	22 (0.5)	15 (0.8)	7 (0.3)
E-phase	91 (2.1)	91 (2.1)	E-E	22 (0.5)	19 (1.0)	3 (0.1)
			E-R	69 (1.6)	55 (2.9)	14 (0.6)
R-phase	112 (2.6)	224 (5.3)	R-R	112 (2.6)	87 (4.6)	25 (1.1)
Total	4232	4232		4232	1882	2350

*The IP-1 joint was included in the PIP joint group.
N=normal, S=stationary OA, J=joint space lost in part or whole joint, E=erosive, R=remodelled.
Abbreviations: DIP: distal interphalangeal; PIP: proximal interphalangeal.

Table 3. Observed and expected number of patients with interphalangeal joints showing erosive phase evolutions over 6 years.

Number of joints with erosive evolution*	Observed	Expected
0	176	110
1	18	87
2	11	36
≥3	31	3
Chi-square	373.0	
P-value	<0.001	

*Erosive evolution comprises phase transitions from N-phase, S-phase or J-phase to the erosive phases and from the E-phase to the R-phase.

Table 4. Odds ratios (OR) for concordance between probands and siblings for the presence of erosive evolution* in at least one interphalangeal joint in 87 sibling pairs with hand osteoarthritis.

	Erosive evolution sibling		Crude OR	Adjusted OR
Erosive evolution proband	Absent	Present	(95%CI)	(95%CI)**
Absent	53	6	1	1
Present	19	9	4.2 (1.3 to 13.3)	4.7 (1.4 to 15.8)

*Erosive evolution comprises phase transitions from N-phase, S-phase or J-phase to the erosive phases and from the E-phase to the R-phase.
**Adjusted for age, sex and BMI

Table 5. Dose-response relationship between the number of interphalangeal joints with erosive evolution* in probands and erosive evolution in siblings.

Number of IP joints with erosive evolution in proband	Erosive evolution sibling		Crude OR (95%CI)	Adjusted OR (95%CI)**
	Absent	Present		
0	53	6	1	1
1	5	1	1.8 (0.2 to 17.7)	1.9 (0.2 to 19.9)
2	6	3	4.4 (0.9 to 22.4)	5.2 (0.9 to 29.0)
≥3	8	5	5.5 (1.4 to 22.4)	6.2 (1.4 to 27.5)

* Erosive evolution comprises phase transitions from N-phase, S-phase or J-phase to the erosive phases and from the E-phase to the R-phase.
**Adjusted for age, sex and BMI

Local determinants of erosive evolution

Self-reported symptoms at patient and joint level as well as pain on pressure during physical examination were associated with erosive evolution (table 6). The presence of a node or limited motion in a joint was also related to this process. The largest effect for erosive activity was found for JSN with an OR (95%CI) of 9.8 (5.7 to 16.6). Osteophytes and self-reported functional limitations were not associated with erosive evolution.

Multivariable analysis including all variables found to be associated in univariable analysis showed that self-reported pain at the joint level and JSN are independently associated with the development and progression of erosions (table 6). Sensitivity analysis regarding the J-phase as EOA did not substantially change the estimates from both univariable and multivariable analyses.

DISCUSSION

This longitudinal study over 6 years is the first to investigate the evolution of erosions in hand OA as well as determinants of this process. We found that erosive evolution took place in 4.4% of the IP joints at risk, which corresponds to 25.4% of the patients. Phase transitions involving this erosive activity were clustered within patients and within sibling pairs. JSN and self-reported pain at the joint level were independent local predictors for erosive evolution. These findings give insight in the course of EOA and contribute to the understanding of its pathogenesis and nature.

Very few studies report on the evolution of EOA. Verbruggen et al. found that over 3 and 5 years 5.6% and 9.1% of the IP joints showed erosive evolution, respectively.[9] The difference with our findings may be explained by the higher proportion of patients with EOA at baseline and the exclusion of the thumb IP joint in the study by Verbruggen et al. Although it is hypothesised that the so-called decompensation phase (J-phase or E-phase) will always be followed by remodelling, we found that 41% of the joints in J-phase and 24% of the joints in E-phase remained in the same phase over 6 years. This is in line with the findings by the study on the course of EOA mentioned earlier, showing that over 5 years almost a quarter of the J-phase joints and almost half of the E-phase joints did not evolve to subsequent phases.[9] Since OA

Table 6. Association between local factors and erosive evolution in 4120 interphalangeal joints from 236 patients with hand osteoarthritis.

	Univariable analysis OR (95%CI)*	Multivariable analysis OR (95%CI)**
Joint level		
Self-reported pain	2.8 (1.7 to 4.7)	2.3 (1.1 to 4.7)
Self-reported stiffness	2.3 (1.3 to 4.0)	1.4 (0.6 to 3.1)
Pain on pressure	2.2 (1.4 to 3.4)	1.1 (0.6 to 1.8)
Node	2.7 (1.7 to 4.5)	1.8 (0.9 to 3.5)
Limited motion	2.6 (1.2 to 5.4)	1.6 (0.8 to 3.1)
Osteophyte grade 2-3	0.7 (0.3 to 2.0)	-
JSN grade 2-3	9.8 (5.7 to 16.6)	8.9 (4.8 to 16.4)
Patient level		
AUSCAN pain (per point)	1.07 (1.02 to 1.12)	1.00 (0.94 to 1.06)
AUSCAN function (per point)	1.02 (0.98 to 1.06)	-

*Taking into account intra-familial effects and anatomical phase at baseline.
**Including all baseline determinants found to be associated in univariable analysis and additionally adjusted for family effects, anatomical phase at baseline, age, sex and BMI.
Abbreviations: AUSCAN: Australian/Canadian Osteoarthritis Hand Index, JSN: joint space narrowing.

is a slowly progressive disease a longer follow-up period may be needed to confirm the hypothesis that decompensation phases always remodel.

To our knowledge, risk factors for the development and progression of EOA have not been studied before. We found that phase transitions involving erosive activity were clustered within patients, meaning that EOA is more likely to occur in certain patients than in others. In other words, it is likely that only part of all hand OA patients will develop EOA. Differences in genetic background may explain this predisposition to erosive disease. This is strengthened by the finding that familial factors play a role in erosive evolution, although apart from genetic factors shared environmental influences may also explain this familial aggregation. We tried to minimise this effect by including only one sibling per proband. Stern et al. showed an association between EOA and the presence of a single nucleotide polymorphism (SNP) of the interleukin-1β gene.[14] In view of the role of IL-1 as mediator of erosions in rheumatoid arthritis[15], its association with EOA makes sense. Another study found an increased frequency of the MS α1-antitrypsin genotype in EOA patients compared to non-EOA patients.[16] Our data on clustering suggest that EOA is a distinct, more severe OA phenotype, but it cannot answer the question whether EOA is a separate disease entity.

Looking at local processes, we showed that pain predicts erosive evolution. A recent study in patients with hand OA showed a strong dose-response relationship between pain and signs of inflammation on ultrasound.[17] Therefore, it might be that local inflammation is involved in the erosive process. A second independent risk factor for the evolution of erosions was moderate to high grade JSN. Since JSN is thought to reflect articular cartilage loss, all processes involved in cartilage damage may potentially contribute to the development and progression of erosions in IP joint OA.

We did not find an association between systemic inflammation measured by S-HsCRP and erosive transition over 6 years. This may be due to the fact that S-HsCRP is an acute phase protein that was measured only at baseline whereas the erosive phase transition could have taken place at any moment in the 6 years of follow-up. Cross-sectional data on CRP in EOA are conflicting, showing higher as well as lower serum levels in EOA compared to non-EOA.[18,19] It could be that local inflammation has more important role in EOA than systemic inflammation.

For clinical practice these findings imply that IP joints of hand OA patients with moderate to severe JSN on radiographs are at a high risk of developing erosions. The same is true for pain although this effect is much smaller. Other factors to consider are presence of erosions in other IP joints and a family history of EOA. The identification of patients at high risk for development or progression of erosions has consequences for treatment since EOA is associated with high disease burden.[6]

There are a number of potential limitations to address. First, the GARP study was not designed to investigate the evolution of EOA. As a consequence the number of joints developing this uncommon feature was relatively small, but sufficient to derive valid results. The second concerns the possibility of bias due to differences between consenters and non-consenters. However, except age there were no differences between the two groups. We expect that the age difference has no effect on study outcome, since age was not associated with the outcome. Thirdly, our sample consists of patients with familial OA at multiple sites. Whether this specific hand OA phenotype affects our findings is unclear, and therefore similar studies in other OA phenotypes are warranted. On the other hand, this study sample gave the possibility to assess familial aggregation. The number of sibling pairs that was available for this analysis was relatively small, nevertheless effect sizes were considerable. Finally, the Verbruggen-Veys anatomical phase score was initially developed for the assessment of EOA. One might argue that this scoring system is not suitable for our sample since the majority of patients did not have EOA. However, our goal was to investigate the evolution of erosions over 6 years meaning that those without erosions were at risk to develop them. Therefore, the anatomical phase score is the appropriate method for our purpose. Recently, Verbruggen et al. extended their scoring system by quantification of the pathological changes that occur especially in the erosive phases.[20]

In conclusion, this study gives insight in the evolution of erosions in hand OA. We showed that patient, familial and local factors are involved in this process. These findings contribute to the unravelling of the pathogenesis of EOA, which is of importance when development of new treatment strategies is concerned. Whether genetic factors underlie the patient and familial factors is of interest. If so, it could provide evidence for EOA as separate disease entity.

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