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Genetic Anticipation in Rheumatoid Arthritis in Europe

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ABSTRACT. ***Objective.*** To investigate whether there is evidence for genetic anticipation in rheumatoid arthritis (RA) in Europe.

Methods. Cross sectional comparison of data from all affected parent-offspring pairs identified among (1) the RA population attending our department and (2) a large cohort of families from RA probands with both parents alive recruited by the European Consortium on RA families (ECRAF) for association studies. Longitudinal comparison between probands with and without parental RA. We used prospectively collected data on disease activity, therapies, and radiological outcomes from our Dutch inception cohort of patients with early RA during the first 6 years of followup.

Results. From a total of 683 Dutch and 170 European patients we identified 28 Dutch and 21 European parent-offspring pairs with RA. Probands with parental RA had an earlier disease onset compared with affected parents (Dutch $p < 0.002$, European $p < 0.0001$). In Dutch patients, the prevalence of HLA-DR4, DR4 double dose, and shared epitope (SE) double dose was slightly higher in probands with parental RA than in those without [odds ratios (95% CI) 2.0 (0.7–5.8), 2.79 (0.8–9.4), and 2.12 (0.6–8.7), respectively]. The same was true for European probands concerning SE double dose [OR (95% CI) 1.76 (0.6–8.7)]. No other relevant differences in demographic or clinical indices were found between probands with affected parents and those without. Disease course (Disease Activity Score) and therapies used during the first 6 years of followup were similar in Dutch patients with and without parental RA. Radiological damage at baseline was lower in the former group and this difference persisted after 3 and 6 years.

Conclusion. Our data suggest that genetic anticipation in RA does occur in terms of an earlier disease onset in the offspring. Despite a slightly higher prevalence of HLA alleles encoding for the SE, probands with confirmed parental RA had no worse outcome than those without. (J Rheumatol 2001;28:962–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — GENETIC ANTICIPATION
AFFECTED PARENT-OFFSPRING PAIRS — FAMILIAL AGGREGATION
EARLY RA INCEPTION COHORT — EUROPEAN CONSORTIUM on RA FAMILIES (ECRAF)

The concept of genetic anticipation describes the tendency of a certain disorder to develop at earlier age and to become more severe in subsequent generations. Firm evidence for genetic anticipation has been found in monogenic neurological illnesses such as Huntington's disease, myotonic dystrophy, and Friedreich's ataxia[1-3]. In these diseases genetic anticipation results from amplification of DNA triplet repeats, within or adjacent to the disease gene, occurring in successive generations[4,5]. In such cases the size of the expansion correlates directly with disease severity and inversely with the age of onset[6]. In certain disorders, there is an inverse correlation between paternal age of conception and the age of disease onset in the offspring that is believed to reflect ongoing mitosis of paternal germ cells[4,6,7].

The list of conditions exhibiting anticipation is growing rapidly. Recent studies suggest that genetic anticipation also might take place in genetically complex diseases such as bipolar affective disorders[8], schizophrenia[9,10], Crohn's disease[11,12], Behçet's syndrome[13], and nodal osteoarthritis[14].

Two recent studies in multicase families with rheumatoid arthritis (RA) performed in the UK and USA showed that in affected parent-offspring pairs, the former had a significantly higher mean age at disease onset[15,16]. In the UK study, disease severity tended to be higher in the offspring[15]. These

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2 studies were cross sectional, which hampers comparison of disease course and outcomes. Longitudinal studies in affected parent-offspring pairs in disorders with late onset are extremely difficult to perform.

We assessed whether genetic anticipation does occur in the Dutch and European RA population. Moreover, potential differences in demographic characteristics and in disease severity and outcome between probands with and without affected parents were studied. To this aim, prospectively collected assessments from Dutch probands with confirmed parental RA and a disease duration > 2 years from our early RA inception cohort were compared with those from single-case families. Though indirect, this method is less sensitive to procedure and recall bias than comparing patients from different generations.

MATERIALS AND METHODS

In the context of several studies on the genetic aspects of RA[17-20] in the last 2 years we ascertained the familial status of our RA population. Out of a total of 683 collaborative Dutch probands with RA[18] those with one (or both) parents affected were analyzed in the present study. Many of them participated in our early RA inception cohort[18]. This cohort includes patients who meet the American College of Rheumatology (ACR) criteria[21], have a disease duration less than one year, and have no previous treatment with disease modifying antirheumatic drugs (DMARD) at presentation[22-24].

Diagnosis of parental RA was ascertained using the familial history of RA reported at intake, updated and controlled by questionnaires and personal interviews from 1996 to 1998[18]. In relatives with self-reported past or present inflammatory articular complaints not attending our clinic, diagnosis was ascertained using external medical records and radiographs. If necessary for diagnostic purposes, physical, laboratory, and radiological examinations were repeated at our center. This information was checked for the 1987 American Rheumatism Association criteria modified for population studies[25]. If individuals reported to have RA were not alive at the time of this study, the diagnosis was accepted only in cases of confirmed history of gold therapy with a matching record of polyarticular disease and deformations.

We also analyzed 170 European families of RA patients with both parents alive, which were consecutively recruited by the ECRAF between 1996 and 1998 to perform association studies[26]. The diagnosis of RA according to ACR criteria[21] was ascertained by the rheumatologist or clinician in charge of the probands and relatives in these families.

To assess the influence of parental RA on disease course and outcome we compared prospectively collected disease activity measurements, therapies, and radiological scores from probands with and without parental RA in our Dutch inception cohort. For this analysis, only patients with a followup of at least 2 years were analyzed. Included in the analysis were demographic data (sex, age at onset, sibship size), clinical (Disease Activity Score, DAS, and its individual constituents), and laboratory assessments (erythrocyte sedimentation rate, rheumatoid factor, serological HLA-DR typing). The use of DMARD was analyzed for the lag time before starting therapy, number of DMARD per patient, and the followup time during which this therapy was prescribed. Therapeutic strategies were categorized as aggressive (methotrexate, sulfasalazine, cyclophosphamide, azathioprine, and combinations of these), intermediate (aurothioglucose and D-penicillamine), and mild (hydroxychloroquine, auranofin).

Outcome variables consisted of the radiographic damage scored at baseline and after 3 and 6 years by the same blinded observer using the modified Sharp method[23].

The study was approved by the ethics committee at the University Hospital Nijmegen.

Statistical analysis. Analysis was performed with the SAS statistical package (SAS 6.04). Between-group comparisons were tested using Student's t and the Wilcoxon test for continuous variables and chi-square tests for cross tabulations. Correlations were calculated using the Spearman correlation test. Process variables such as the DAS[22] and its individual components were compared using the area-under-the-curve (AUC) from baseline up to 3 and 6 year followup. P values in the text are reported without adjustments for multiple comparisons. Using the Bonferroni correction most p values would have to be < 0.017 for significance at the 0.05 level to be retained.

RESULTS

Patient characteristics. In the Dutch population, we identified a total of 28 affected parent-offspring pairs. Among those, mother, father, and both parents were affected in 15, 11, and 2 cases, respectively. Clinical and biological data of Dutch affected parents are not shown since 14 of them had already died at the time of the study (mean ± SD age 70.5 ± 10.4 yrs; disease duration 20.2 ± 11.8 yrs).

Six of the Dutch affected pairs comprised patients from the regular outpatient clinic and 22 included at least one patient from our early RA inception cohort. In 3 of these pairs, the parent was the index case. For the prospective analysis, data on 19 patients with early RA with parental RA were available and these were compared with 138 collaborative patients without parental RA and a followup > 2 years (Table 1).

Parental RA occurred in 21 of 170 European families of RA patients with both parents alive, recruited by the ECRAF for association studies (Table 2)[26].

In both Dutch and European families probands with parental RA were younger at disease onset than their affected parents (39 vs 55 yrs, $p < 0.002$; and 27 vs 44 yrs, $p < 0.001$, respectively) and younger than probands without parental RA. The latter only reached significance in the Dutch group (Table 2).

In both cohorts we found a highly significant correlation between parental age at onset of RA and disease anticipation, defined as the difference in age at onset between parent and offspring ($r = 0.73$ and 0.86 in Dutch and European pairs, respectively; $p < 0.0001$; Figure 1). As shown, only 9 of 49 pairs studied showed a later disease onset in the offspring than in the parents (Figure 1). The patients' characteristics of these probands were similar to those showing genetic anticipation in terms of age (data not shown).

Clinical characteristics from probands with and without affected parents did not differ much (Tables 1 and 2). As noted, in the European cohort, probands with parental RA were only slightly younger than those without, and they had a shorter disease duration than their affected parents. This is explained by the strategy used for patient recruitment, which required having both parents alive. The higher prevalence of subjective complaints of Sjögren signs among affected parents is probably due to the older age in the latter group.

Compared with probands lacking parental RA, possession of HLA-DR4 and the shared epitope (SE) was slightly more frequent in probands with parental RA in both cohorts.

Table 1. Baseline characteristics of Dutch probands. Data as mean ± SD unless otherwise stated.

	Patients with Parental RA	Parental RA Prospective*	Patients without Affected Parents*	p
Patients, n	28	19	138	
Female, %	77	74	63	NS
Age of onset, median, yrs	39	39	50	< 0.0001
(p25–p75)	(31–47)	(36–51)	(43–64)	
Followup, median, yrs	6.0	6.0	9.0	NS
(p25–p75)	(4–8)	(4–9)	(5–11)	
Sibship size, n	6.0 ± 2.7	5.8 ± 2.9	6.0 ± 3.0	NS
RF positive, %	90	89	81	NS
Sharp score, median		2.5	12	< 0.02
(p25–p75)		(1–9.5)	(4.3–20)	
DAS		4.1 ± 1.1	4.2 ± 1.3	NS
No. of swollen joints		16 ± 10.4	16 ± 8.1	NS
Ritchie index		11 ± 6.5	11 ± 8	NS
Global health (VAS, mm)		56 ± 24	43 ± 24	NS
ESR, mm/h		29 ± 19	39 ± 28	NS
HLA typing, %				
DR4 positive		72	57	2.0 (0.7–5.8)†
DR4 double dose		22	9	2.79 (0.8–9.4)
DR1 positive		17	25	0.54 (0.2–1.4)
DR10 positive		11	5	1.89 (0.4–7.8)
SE positive		83	75	1.6 (0.5–6.1)
SE double dose		22	11	2.12 (0.6–8.7)

*Patients with prospective followup from the inception cohort. †OR (95% CI). DAS: Disease Activity Score, VAS: visual analog scale, mm, SE: shared epitope.

Table 2. Characteristics of the European affected parent-offspring pairs and patients with unaffected parents.

	Affected Offspring	Affected Parents	p	Patients with Unaffected Parents	p
Patients, n	21	21		149	
Female, %	90	76	NS	88	NS
Age of onset, median, yrs	27	44	< 0.001	30	NS
(p25–p75)	(23–35)	(33–55)		(22–38)	
Followup, median, yrs	5	18	< 0.0001	7	NS
(p25–p75)	(3–9)	(8–25)		(3–12)	
RF positive, %	81	76	NS	99	NS
Erosive disease, %	76	81	NS	99	NS
Nodules, %	10	10	NS	12	NS
Subjective Sjögren signs	5	24	NS	7	NS
Extraarticular manifestations	0	5	NS	5	NS
HLA typing, %					
DR4 positive	67	57	1.5 (0.43–5.52)†	56	1.55 (0.59–4.06)‡
DR4 double dose	9.5	19	0.45 (0.07–2.76)†	10	0.94 (0.20–4.44)‡
DR1 positive	33	24	1.6 (0.41–6.19)†	23.5	1.63 (0.61–4.35)‡
DR10 positive	9.5	14.3	0.63 (0.09–4.23)†	6	1.64 (0.33–8.15)‡
SE positive	81	86	0.71 (0.14–3.64)†	74	1.51 (0.48–4.75)‡
SE double dose	33	19	2.13 (0.51–8.77)†	22	1.76 (0.66–4.71)‡

† Odds ratio (95% CI) affected offspring vs parents. ‡Odds ratio (95% CI) affected offspring vs patients without affected parents.

HLA-DR4 and SE double dose were also more frequent among the Dutch, and SE double dose among European probands with parental RA (Tables 1 and 2). Nonetheless, these differences were not statistically significant. The average sibship size of patients with and without parental RA was similar (5.8 vs 6.0).

Longitudinal comparison of disease activity, therapies, and outcome during 6 year followup. Among the 19 Dutch probands with prospective data, 14 were younger at disease onset than their affected parents, 5 were not. These 2 groups did not differ in clinical characteristics or outcome (Figures 2 and 3).

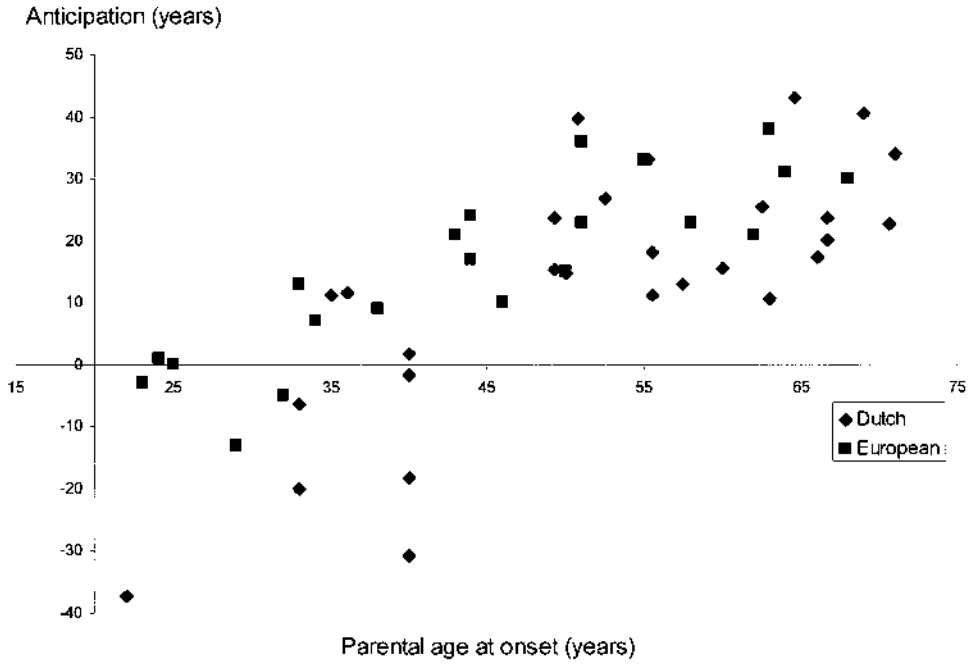

Figure 1. Correlation between age at onset in affected parents (*x* axis) and disease anticipation in the offspring (*y* axis) in the Dutch and European cohorts. Spearman correlation coefficients r = 0.73 and 0.86 for Dutch and European families, respectively; $p < 0.0001$.

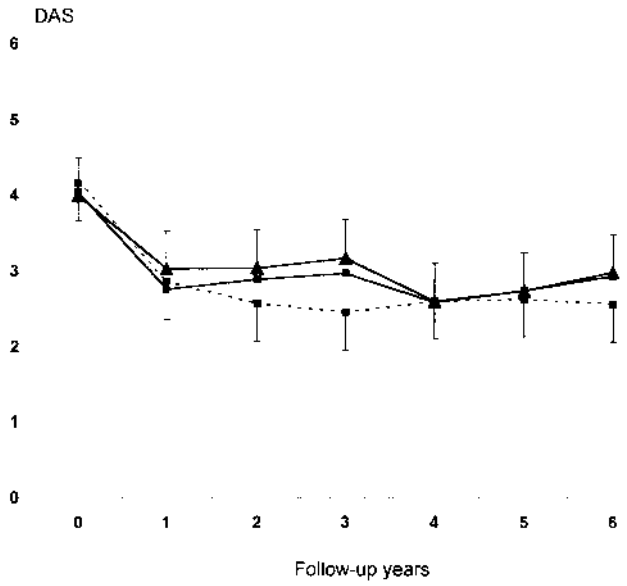

Figure 2. Disease Activity Score (DAS) at baseline and during 6 years of followup in Dutch probands. Probands without parental RA shown as a broken line (n = 138). Continuous lines represent probands with parental RA (▲: all patients, n = 19; ■: only those patients with disease anticipation, n = 14). DAS expressed as mean and SD.

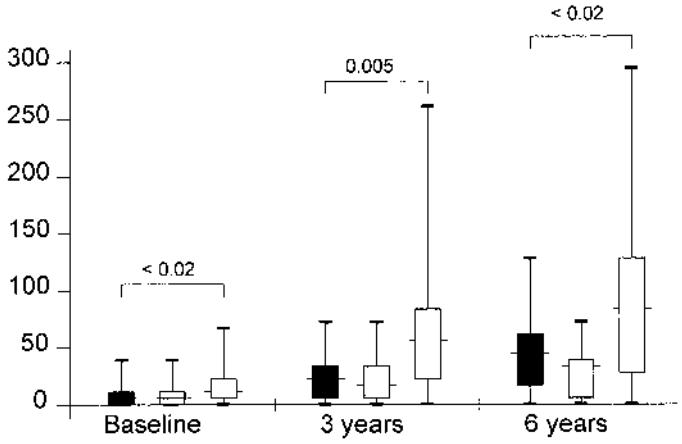

Figure 3. Total Sharp scores at baseline and after 3 and 6 years in prospectively followed Dutch patients. □: Probands without parental RA (n = 138). ■: Patients with parental RA (all, n = 19). Shaded boxes represent only those with anticipation (n = 14). Box plots show range (vertical line), median (horizontal line), and 75th and 25th percentile values (box).

In the early RA inception cohort, DAS scores and therapies (Tables 1 and 3) used in the first 6 year followup were similar in patients with and without parental RA. In both groups the DAS showed a marked decrease in the first year and levelled off thereafter (Figure 2). The DAS area under the curve (DAS_{AUC}) in the first 3 and 6 years of followup were similar for patients with or without parental RA (mean ± SD, DAS_{AUC} 0–3 yrs 2.9 ± 0.9 vs 2.9 ± 1.0, $p = 0.7$; and DAS_{AUC} 0–6 yrs 3.3 ± 0.7 vs 2.7 ± 0.9, $p = 0.04$, respectively). Individual constituents of the DAS showed a similar pattern (data not shown).

Baseline radiological scores were more favorable in probands with affected parents than in those without: median (range) 2.5 (0–38) vs 12 (0–26), respectively, p <

Table 3. Therapeutic interventions during the first 6 years' followup in the Dutch inception cohort. Data expressed as mean ± SD unless otherwise stated.

	Parental RA	Nonparental RA	p
Patients, n	19	138	
DMARD use			
No. per patient per yr	0.52 ± 0.3	0.49 ± 0.4	NS
Lag time, median days (range)	111 ± 250	101 ± 361	NS
DMARD/% disease duration	77	78	NS
Aggressive, %	63	69	NS
Intermediate, %	15	20	NS
Conservative, %	22	11	NS
No. patients using no DMARD	0	5	NS
Surgery			
TJA, n/pt/yr	0	0.02 ± 0.06	NS
NTJA, n/pt/yr	0.08 ± 0.15	0.07 ± 0.21	NS
Hospital admissions, n/pt/yr	0.08 ± 0.18	0.04 ± 0.10	NS

TJA: total joint arthroplasty, NTJA: non-total joint arthroplasty.

0.02. These differences persisted during the followup: 27 (0–71) vs 55 (0–258), p = 0.005, at 3 years; and 42 (0–129) vs 85 (0–297), p = 0.02, at 6 years, respectively (Figure 3).

DISCUSSION

Our study shows that, in both Dutch and European families comprising parent-offspring pairs with RA, there is an earlier disease onset in the offspring compared to affected parents. In the prospectively followed Dutch cohort, patients with parental RA were also younger than those without. This difference was not so pronounced in the European cohort, which is explained by the recruitment strategy that required having both parents alive. Moreover, we observed a positive correlation between parental age at onset and disease anticipation, defined as the difference in age at onset between parents and offspring. These findings support the hypothesis of genetic anticipation, in terms of onset of RA, in subsequent generations. Our results are in accord with 2 other studies[15,16].

Genetic anticipation in monogenetic disorders has been associated with increasing disease severity in subsequent generations[1-3]. However, RA is multifactorial and early disease onset does not necessarily imply a more severe disease[27-29]. Longitudinal studies comparing phenotype and outcome of patients with RA in different generations are hard to perform and difficult to interpret in view of the late onset of RA and the dramatic changes in therapeutic strategies during the last century. To compensate, we compared disease course and outcome of probands with and without confirmed parental RA. This comparison yielded no clinically relevant differences in phenotype, disease course, therapies, or outcome. We consider these findings are more robust and free from bias than a direct comparison of disease course between different generations. Interestingly, despite a slightly higher prevalence of HLA-DR4 and shared epitope among probands with affected parents, these did not have worse radiological outcome after 3 and 6 years' followup. This sustains our findings showing that HLA-DR4 is not prognostic for radiological damage[17].

These results, derived from families with RA in subsequent generations, reinforce the notion of similar phenotypes in familial and sporadic RA. Previous cross sectional and longitudinal studies in our population show that, except for a larger sibship size, probands with affected sibs do not differ from those derived from single-case sibships[17].

As shown in Figure 1, most of the affected parent-offspring pairs (82%) showed genetic anticipation in terms of age at onset. Although these groups become too small for accurate statistical analysis, no differences in any of the investigated variables were observed between probands with or without genetic anticipation (Figures 2 and 3).

We tried to avoid and/or control for common biases in assessment of genetic anticipation[30,31]. One of these is the potential increased awareness of the disease in families with affected individuals. There is no reason, however, to expect that this awareness is unequally distributed among Dutch patients with and without parental RA in our inception cohort.

We tried to minimize potential recall bias, occurring for instance in the elderly, by collecting data from more than one source (proband, relatives, and general practitioner or rheumatologist). A cohort effect in terms of geographical influence is not likely since anticipation was observed in Dutch and other European families. Another argument that there was no significant cohort effect is that there was no difference in age at onset between probands without parental RA and affected parents.

A potential nongenetic explanation for an apparent earlier onset of RA in offspring could be that early onset RA (or its treatment) decreases fertility. This would effectively limit the possible affected parents to those having late onset disease. This could not be the case in our study, since the

average sibship size of patients with or without parental RA was similar (5.8 vs 6.0). Another potential nongenetic reason for genetic anticipation, the possibility that having affected parents could be a marker for earlier or sustained exposure to environmental susceptibility factors, cannot be ruled out.

Our findings support the hypothesis of genetic anticipation in RA in terms of age, but not in terms of disease severity. Although our results do not allow conclusions on the prevalence of genetic anticipation in RA, the latter seems so low that genetic counselling does not seem warranted. In view of the consistent observations in this and other studies further investigation into a potential molecular basis of this phenomenon is warranted.

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