

## DIAGNOSIS AND COURSE OF EARLY-ONSET ARTHRITIS: RESULTS OF A SPECIAL EARLY ARTHRITIS CLINIC COMPARED TO ROUTINE PATIENT CARE

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### SUMMARY

**Objective.** Early arthritis patients referred to an Early Arthritis Clinic (EAC) ( $n = 233$ ) were compared to 241 patients from the routine out-patient clinic with respect to lag time between the onset of symptoms and the visit to the rheumatologist, clinical presentation and the consistency of the diagnosis after 1 yr.

**Results.** The reduction in median lag time for the EAC patients was at least 3 months. An insidious onset of symptoms was found more often in the rheumatoid arthritis (RA) patients in the routine clinic. In 70% of all cases, a diagnosis could be made after 2 weeks and, if the clinical diagnosis was definite RA, this hardly changed during the following year. Early erosions were seen in 25% of RA patients and were associated with a positive rheumatoid factor (OR 2.08, 95% CI 0.95–4.59).

**Conclusion.** An early diagnosis of RA at the EAC is possible and reliable; the high frequency of erosions illustrates the need for early treatment.

**KEY WORDS:** Early arthritis, Early rheumatoid arthritis, Diagnosis.

DURING the last decade, evidence has accumulated that emphasizes how crucial the early phase of rheumatoid arthritis (RA) is [1]. The number of swollen joints is maximal at this time of the disease and the rate of appearance of erosions is at its greatest in the early years of RA [2, 3]. Moreover, it has become clear that RA should be considered as a severe disease, which is illustrated by the association with an at least moderate disability in 80% of patients and with an increased risk of mortality [4]. Early treatment with disease-modifying anti-rheumatic drugs (DMARDs) appears to improve the outcome [4–6]. In order to start treatment of RA early in the disease course, a special Early Arthritis Clinic (EAC) was started in Leiden. One of the goals of this EAC was to establish an early diagnosis of RA at a time when the ACR criteria (which include a 6 weeks observation of the arthritis by a physician) are not fulfilled and to test reliability. The clinic was also meant to detect and promptly treat inflammatory disorders other than RA.

This paper reports on the occurrence, clinical presentation and lag time between the onset of symptoms and the visit to the rheumatologist of an early arthritis cohort as seen in a special EAC. These patients were compared to early arthritis patients who visited the routine out-patient clinic in the same period. In addition, the practicability of an early diagnosis and the consistency of the diagnosis after 1 yr were evaluated.

### METHODS

In order to obtain referrals of arthritis patients in an early phase of the disease, a general practitioner (GP) campaign was started by the rheumatology group of the Leiden University Hospital, which is the only referral centre for rheumatic patients in a semi-rural

area with 300 000 inhabitants. The GPs were motivated to refer patients if at least two of the following features were present: joint pain, joint swelling or reduction of joint mobility. Any of these features had to have a history of <2 yr.

All patients referred to the special EAC were seen within 1 week. The patients were included if (1) the arthritis was confirmed by a rheumatologist, (2) the history of symptoms indeed lasted <2 yr and (3) the patient had not been visiting a rheumatologist elsewhere for the same problem. Patients sent through early direct referral from the general practitioner (GP-EAC) were compared to patients seen in routine out-patient care (routine group) during the period 1993–1996, provided that these also met the inclusion criteria of the EAC.

The onset of the arthritis was designated as 'acute' in the case of onset of symptoms within 1 week, as 'insidious' when the complaints were gradually increasing during several weeks or months, and 'intermittent' when the patient had been suffering from periods with arthritis during several weeks or months.

In every patient, routine diagnostic screening was performed, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), haematological screening, liver enzymes, renal function, rheumatoid factor (RF) and antinuclear antibodies (ANA). In all patients, serology on *Chlamydia*, *Yersinia*, parvovirus and *Borrelia* was performed at the first visit, and in the case of *Yersinia* repeated after 2 weeks. In addition, stool cultures were obtained to exclude active *Salmonella*, *Shigella*, *Yersinia* and *Campylobacter* infections. On entering the study and yearly thereafter, a 53 joint count of painful (Ritchie score) and swollen joints, and radiographs of the chest, hands and feet were obtained. Information on the presence or absence of erosions was obtained by the examination of X-rays of the hands and feet by a trained radiologist.

Diagnoses were made according to international

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classification criteria after 2 weeks and revised after 3 months and 1 yr of follow up. The diagnosis 'probable' RA was made using both clinical judgement and the 1958 ACR criteria, but without the '6 weeks duration observed by a physician' [7]. After 3 months, 'definite RA' was defined according to the 1987 ACR criteria [8]. Treatment of most RA patients included non-steroidal anti-inflammatory drugs (NSAIDs) plus sulphasalazine or hydroxychloroquine. In the case of persistent disease activity, patients often switched to methotrexate, but prednisone was seldom used.

Systemic lupus erythematosus (SLE) was diagnosed according to the 1982 ARA criteria [9], infectious arthritis in the case of arthritis plus a positive culture of synovial fluid and/or a positive blood culture, reactive arthritis in the case of an arthritis with a proven infection elsewhere, gout according to the 1977 ARA criteria [10], spondylarthropathy according to the criteria of the European Spondylarthropathy Study Group [11] and the other diagnoses according to the rheumatology textbook [12]. The follow-up of patients with osteoarthritis, (pseudo-)gout and post-traumatic joint complaints ended after 3 months.

The comparison of disease occurrence, lag time between symptom onset and the first visit to the rheumatologist, and the clinical presentation between the GP-EAC group and the routine group during the period 1993–1996 was tested using a  $\chi^2$  test (presented as odds ratio with a 95% confidence interval) or Mann–Whitney test, where appropriate. The consistency of diagnosis is expressed as percentages of change in diagnoses after 3 months and 1 year.

## RESULTS

In the period 1993–1996, 335 patients were directly referred to the EAC, of whom 233 fulfilled the entry criteria (GP-EAC), whereas 102 patients could not be included because they did not have signs of arthritis. In the routine out-patient clinic, 241 patients satisfied the EAC inclusion criteria in the same period. The demographic and clinical data of the patients are presented in Table I. The duration of symptoms was significantly shorter and the number of patients with an acute onset of symptoms was significantly higher in the GP-EAC group than in the routine group. In both groups, 70% of the patients fulfilled any of the classification criteria 2 weeks after the inclusion visit. Patients were more likely to have RA (definite or probable) or psoriatic arthritis if referred to the routine out-patient clinic, and more likely to be diagnosed as sarcoidosis or crystal arthropathies if directly referred to the EAC (Table II).

After exclusion of the 88 patients with osteoarthritis, gout or post-traumatic arthritis, 340 patients were assessed after 1 yr of follow-up and 52 cases (13%) were lost. The cause of loss to follow-up in the 40 non-RA patients was: three died (one septic, one paramalignant and one unclassified arthritis), 11 did not have symptoms anymore (six sarcoidosis, two reactive and three unclassified arthritis), 25 refused further follow-up (four sarcoidosis, three reactive, three

TABLE I  
Demographic and clinical data of the patients presenting with arthritis who were referred directly to the Early Arthritis Clinic (GP-EAC) or to the routine out-patient clinic (routine)

	GP-EAC (n = 233)	Routine (n = 241)	OR (95% CI)
Women (%)	48	59	0.63 (0.43–0.93)
Median age (yr, range)	47 (14–88)	53 (16–84)	*
Median duration of symptoms (days, range)	31 (1–610)	122 (1–727)	†
Acute symptoms (%)	73	54	2.29 (1.53–3.45)
Diagnosis made after 2 weeks (%)	68	75	0.71 (0.47–1.05)

\* $P = 0.19$ , Mann–Whitney test.

† $P < 0.00001$ , Mann–Whitney test.

TABLE II  
Initial diagnoses of the patients presenting with arthritis who were referred directly to the Early Arthritis Clinic (GP-EAC) or to the routine out-patient clinic (routine)

	GP-EAC (n = 233) (%)	Routine (n = 241) (%)	OR*	(95% CI)
RA (definite/probable)	22	38	0.56	(0.32–0.97)
Psoriatic arthritis	3	7	0.44	(0.11–1.71)
Reactive arthritis	7	5	1.46	(0.46–4.67)
Sarcoidosis	9	2	4.80	(1.03–22.46)
Crystal arthropathy	16	6	2.89	(1.11–7.51)
Other diagnoses	11	17	0.65	(0.30–1.43)
Unclassified arthritis	32	25	1.38	(0.79–2.40)

\*OR: odds ratio (95% confidence interval) of a particular diagnosis versus all other diagnoses in both groups.

psoriatic, one paramalignant and 14 unclassified arthritis) and one moved away from the area (unclassified arthritis).

A diagnosis of 'definite' RA (according to the ACR 1987 criteria without the 6 weeks observation period) made at 2 weeks after the first visit rarely required revision in the following year (Fig. 1). In only four cases of 'definite' RA the diagnosis changed to SLE (one), unclassified arthritis (one), gout (one) and probable RA (one), whereas 89% remained 'definite' RA. In the case of the diagnosis 'probable' RA, 51% switched to the diagnosis 'definite' RA within 1 yr and 11 cases changed to other diagnoses (one Lyme arthritis, two gout, one psoriatic arthritis, two osteoarthritis, one paramalignant and four unclassified arthritis).

After 3 months of follow-up, a definitive disease classification was possible in 17 (15%) of the 115 patients with unclassified arthritis and in 47 (29%) after 1 yr. Twenty-three (50%) of these patients were classified as definite RA and the other patients as osteoarthritis, gout, psoriatic arthritis and other forms of arthritis.

The initial clinical presentation of early RA patients stratified for routes of referral is shown in Table III.

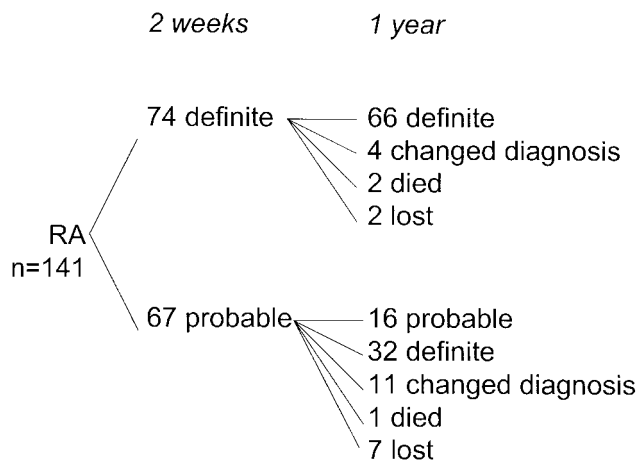


FIG. 1.—Change of diagnosis of definite and probable RA after 1 yr of follow-up.

An acute onset of symptoms and an atypical presentation of RA (with an asymmetrical arthritis, monoarthritis or oligoarthritis) were seen more often in the GP-EAC group than in the routine group. The localization of arthritis at the first visit showed more cases with involvement of the small joints in the routine group. Upper and lower extremities were equally involved in both groups from the start.

At least 25% of the RA patients in both groups already had erosions at their first visit, whereas 84% of the RA patients had <1 yr of symptoms. Among the eight RA patients with a duration of symptoms of <30 days, two cases were erosive at the first visit. Comparison between RA patients presenting with and without erosions revealed that the early development of erosions was increased in patients who were RF positive (Table IV). Patients with erosions more often presented with an arthritis of both upper and lower extremities than patients without erosive disease, who more often showed arthritis in only the lower or the

TABLE IV  
Differences between erosive and non-erosive early RA patients at the first visit

	Erosive (n = 37)	Non-erosive (n = 102)*	OR (95% CI)
Females (%)	23 (62)	68 (67)	0.82 (0.38–1.79)
Arthritis localization (%)			
Symmetrical	29 (78)	76 (75)	1.24 (0.50–3.05)
Polyarthritis	28 (76)	73 (72)	1.24 (0.52–2.94)
Upper + lower extremities	29 (78)	60 (59)	2.54 (1.06–6.10)
RF IgM +	25 (68)	51 (50)	2.08 (0.95–4.59)
Median age (yr, range)	60 (21–76)	56 (17–88)	<i>P</i> = 0.35†
Acute symptoms (%)	15 (43)	45 (45)	0.92 (0.42–1.99)
Median duration of symptoms (days, range)	170 (2–542)	125 (1–730)	<i>P</i> = 0.25†

\*Two patients could not be evaluated for erosions.

†Two-tailed, Mann–Whitney.

upper extremities. These results suggest that more widespread disease is associated with the presence of erosions early in the course of the disease.

At 1 yr, 340 patients were assessed, of whom 57% still showed signs of arthritis. Whereas in 87% of the RA patients signs of active arthritis were found, most cases of reactive and undifferentiated arthritis had subsided, showing active arthritis in only 11 and 25%, respectively.

## DISCUSSION

The clinical presentation of the arthritis patients at the special EAC differs from the presentation at the routine out-patient clinic. The EAC includes more acute forms of arthritis than the routine group. Diseases known to present acutely, like sarcoidosis and (pseudo-)gout, are indeed more frequent in the GP-EAC. Therefore, the finding that RA was two

TABLE III

Initial clinical presentation of early rheumatoid arthritis patients who were referred directly to the Early Arthritis Clinic (GP-EAC) or to the routine out-patient clinic (routine)

	GP-EAC (n = 50)	Routine (n = 91)	OR	(95% CI)
Acute onset (%)	54	39	1.88	(0.93–3.78)
Mono-/oligoarthritis (%)	30	25	1.27	(0.59–2.73)
Asymmetrical arthritis (%)	28	22	1.38	(0.63–3.05)
RF+ (%)	59	50	1.47	(0.73–2.95)
Erosive (%)	25	28	0.93	(0.42–2.03)
Females (%)	62	67	0.80	(0.39–1.65)
Median duration of symptoms in days (range)	104 (16–610)	164 (1–730)	<i>P</i> = 0.095*	
Median age in years (range)	62 (21–88)	56 (17–79)	<i>P</i> = 0.054*	
Arthritis localization (%)				
Small joints	36	43		
Large joints	34	22	<i>P</i> = 0.299†	
Small + large	30	35		
Upper extremities	32	26		
Lower extremities	8	7	<i>P</i> = 0.70†	
Upper + lower	60	67		

\*Mann–Whitney test.

† $\chi^2$ .

times more frequent in the routine group than in the GP-EAC group suggests that the onset of RA is insidious. Another explanation for the difference in presentation between the GP-EAC and the routine group may be caused by a selection of GPs who prefer to send patients to the GP-EAC in the case of an acutely developed arthritis. Other EAC, however, show a similar profile of diagnoses with an increase in arthritides with an acute onset [1, 13]. In contrast, most EACs have focused on polyarthritis patients only, whereas the present study includes the whole spectrum of arthritides.

Seventy per cent of the patients fulfilled any disease classification criteria 2 weeks after presentation. In the case of RA, however, only half of the patients could be classified according to the 1987 ARA criteria because of the 6 weeks observation prerequisite. A majority of the 'clinically definite' RA patients could later be classified as definite RA. These results suggest that an early diagnosis of RA is reliable and facilitates the strategy of early treatment of RA.

The clinical presentation of early RA showed an acute onset of symptoms in 54% of the GP-EAC patients and 39% of the routine patients, which does not differ much from the 35–51% mentioned in other studies [14–16]. A mono- or oligoarticular onset, which, according to Emery [1], is associated with a relatively good outcome of the disease, was found in 30% of the GP-EAC and 25% of the routine early RA patients. Others have found a similar presentation pattern in 21% [17], 35% [18] and 45% [19]. The localization of arthritis in only the upper extremity was found in 32 and 26% of the GP-EAC and routine patients, respectively, versus 62% in Jacobi's group [16]; this localization was not described separately in other EAC studies. As expected, arthritis in all extremities was the most frequently found pattern (60–67%) at the first visit. The combination of polyarthritis and signs of active arthritis after 1 yr in 89% of the RA patients is in contrast with one other study on inflammatory polyarthritis that shows 45% remission [20] and in accordance with another study [21] that shows remission in only 9% of the RA patients after 1 yr.

As in other studies [1, 19], the special EAC reduces the lag time between symptom onset and the first rheumatological consultation by at least 3 months. The comparison between the GP-EAC group and the routine group is based on the selection of patients with an arthritis of <2 yr duration in the routine group. If all patients visiting the out-patient clinic had been compared to the GP-EAC group, the difference in duration of symptoms would be considerably longer.

Although the median duration of symptoms in the RA patients was only 3 months, 25% of them already had erosions at their first presentation at the EAC. This could only partially be explained by the fact that erosive patients had a longer duration of symptoms than patients without erosions since the median difference was only 45 days. The fact that a considerable number of RA patients had erosions at the first visit suggests that erosive changes start very early in the

disease course, or that erosions develop during the phase of the illness before arthritis is clinically apparent. Since we currently aim towards treatment as early as possible, we have to find ways to get these patients earlier. Further studies are necessary, also in primary care, to develop strategies to identify RA patients at the very beginning of their disease.

## CONCLUSIONS

The diagnosis of 'definite' RA can be made within 2 weeks after the first visit by a rheumatologist in 70% of the cases, even when the presentation of the arthritis is atypical. An early diagnosis of RA appears to be reliable since the diagnosis of RA rarely changes in the following year. Furthermore, RA is often erosive at presentation, which justifies considerable effort to motivate both patients and GPs to regard early RA as a medical emergency and thereby to reduce the lag time even more.

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