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Ongoing Disease Activity and Changing Categories in a Long-Term Nordic Cohort Study of Juvenile Idiopathic Arthritis

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Objective. **To describe the disease characteristics, long-term course, and outcome of patients with juvenile idiopathic arthritis (JIA) in a population-based setting.**

Methods. **Consecutive cases of JIA from defined geographic areas of Denmark, Finland, Sweden, and Norway in whom disease onset occurred in 1997–2000 were included in a prospective, multicenter cohort study. The study was designed to be as close to a population-based study as possible, with centers participating only if they were able to include in their catchment area all children in whom JIA was diagnosed.**

Results. **Of 500 children included, 440 (88.0%) had repeated visits, with the last visit occurring at least 7 years after disease onset (median 98 months, range 84–147 months). Changes in the International League of Associations for Rheumatology category were observed in 10.8% of the children, and, in addition, extended oligoarthritis developed in 34.7% of the group with oligoarticular JIA. During the observation period, 58.0% of the children were treated with disease-modifying antirheumatic drugs, including biologic medications. Ongoing disease activity was mostly mild, but some JIA-related damage developed in 22.9% of the children. At the last followup visit, remission off medication was observed in 42.4% of the children, 8.9% were in remission on medication, and 48.7% were not in remission. The highest rates of remission were observed in patients with persistent oligoarticular JIA and in those with systemic JIA.**

Conclusion. **In this long-term prospective study of JIA in a population-based Nordic setting, ongoing disease was evident in a majority of the children. The present results underline the need to identify early predictors of outcome, to further improve therapy, and to continue long-term followup of patients with JIA.**

Juvenile idiopathic arthritis (JIA) is a diverse entity of chronic childhood arthritis. The disease spectrum spans from time-limited monarthritis to ongoing destructive polyarticular disease and may include severe systemic features or sight-threatening uveitis. In an era of modern medical treatment, updated knowledge on the clinical course and outcome of JIA is essential. Such knowledge provides a fundamental basis for making clinical decisions regarding treatment and followup, for presenting evidence-based information on prognosis to affected children and their parents, and for health planning for chronic childhood diseases on a societal level.

When studying the long-term outcome of JIA, one should be aware of 2 common pitfalls (1). First, the duration and chronicity of the disease may be underestimated, because studies of cross-sectional design will miss fluctuations of disease activity over time (1–3). Second, selection bias in studies from tertiary centers may overestimate the prevalence of the more severe cases and categories of JIA. Hospital-based cohorts and register studies have limitations in terms of validity and reliability, emphasizing the need for long-term followup

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in nonselected and well-defined study populations (4). The last revision of the International League of Associations for Rheumatology (ILAR) classification of JIA is stated to represent a work in progress more than a static framework (5). The presence of antinuclear antibodies (ANAs) and early-onset disease have recently been suggested as potential new category determinants in the less well-defined JIA categories, in order to make categories in the ILAR classification more homogeneous (5–10).

The uniform health system of the Nordic countries facilitates population-based studies and long-term followup (11–15). The main objective of this Nordic study was to describe the clinical manifestations, course, and outcome of JIA, according to the ILAR classification, in a multicenter cohort during the first decade after disease onset.

PATIENTS AND METHODS

Patients. In this prospective, multicenter cohort study, consecutive incident cases of newly diagnosed JIA from defined geographic areas of Denmark, Finland, Norway, and Sweden were included. The inclusion period was from January 1, 1997 to June 30, 2000 (for 3.5 years in Norway, 3.0 years in Sweden, Finland, and Copenhagen, Denmark, and for 1.5 years in Århus, Denmark). The incidence of JIA in the study area in 1997–1998 was 15 per 100,000 children/year, as previously reported (11).

During the study period, pediatric rheumatologists from 12 participating centers registered all children with JIA diagnosed according to the ILAR criteria. In the Nordic countries, all visits to primary care physicians and public hospitals are mostly free of charge for children under 16 years of age, and the healthcare systems include regular visits at a child health center for preschool children. With the aim of making the study as close to population-based as possible, letters were repeatedly sent to the primary health care and all orthopedic, pediatric, and rheumatology specialists in the catchment areas during the inclusion period, requesting referral of potentially eligible patients. Family histories, extensive clinical data including complete joint counts, medications used, patient/parent-completed health assessment measures, and results of blood tests were registered per protocol in a database at all study visits. A study visit was planned every 6 months during the first year after disease onset and then every 1–2 years during the observation period; in some centers, however, fewer visits were registered. The minimum requirement for continued inclusion in the followup study group was 2 registered visits, including the baseline visit and a followup visit more than 7 years after disease onset.

Scores for the Childhood Health Assessment Questionnaire (C-HAQ; 0 = best and 3 = worst) (16–20) and scores on a 10-cm visual analog scale (VAS) for pain (0 = no pain and 10 = worst pain) and overall well-being (global health; 0 = best and 10 = poorest) were provided by children who were older than age 9 years and by the parents of younger children. Global disease activity was assessed by the physicians, using a VAS (0 = no activity and 10 = maximum activity). HLA–B27 antigens were analyzed at the time of disease onset, and analyses of ANAs and rheumatoid factor (RF) were performed twice, at least 3 months apart. Each physician interpreted the results of the ANA and RF analyses as positive or negative according to the reference values used by the local laboratory. In Sweden, Denmark, Finland, and Trondheim, Norway, ANAs were measured using immunofluorescence on HEp-2 cells. In Tromsø, Norway, an ANA enzyme-linked immunosorbent assay (ELISA) was used; these results were later excluded from the analyses, due to the limited clinical value in JIA (21). RF status was determined by ELISA (Denmark), nephelometry (Norway and Sweden), latex agglutination testing (Sweden), and immunoturbidimetric testing (Finland). C-reactive protein was measured with immunoassays, with upper normal values ranging from <3 to <10 mg/liter; in the study protocol, the cut-off value for the whole population was set to <10 mg/liter.

At the final study visit, ~8 years after disease onset, extended information was collected, including an update on family history. The Juvenile Arthritis Damage Index (JADI) (22) was scored by the pediatric rheumatologist; articular damage was scored on a scale in which 0 = no damage and 72 = maximum damage, extraarticular damage was scored on a scale in which 0 = no damage and 17 = maximum damage, and global articular and extraarticular damage were scored on a 10-cm VAS in which 0 = no damage and 10 = maximum damage. Questionnaires on self-reported health-related quality of life were registered; the Child Health Questionnaire (CHQ) was used for patients younger than age 18 years (16–20), and the HAQ (23) (0 = best and 3 = worst) and Short Form 36 health survey (SF-36) (24) were used for patients older than age 18 years. The CHQ and the SF-36 are generic instruments comprising subscales on aspects of physical, emotional, and social health, yielding a physical score and a psychosocial summary score, with higher scores indicating better health (range 0–100, mean $\pm$ SD 50 $\pm$ 10) (25). For the final visit, participating patients received a letter of invitation followed by a reminding letter; patients who did not respond were contacted by telephone and asked to participate in a visit. In the minority of cases in which a final study visit was not possible, the patients were asked to participate in a telephone interview. The standardized telephone interview contained all information that otherwise, per protocol, was collected during visits, and these patients were asked to fill in and return relevant questionnaires.

JIA categories were determined according to the ILAR criteria (5), based on all available information that was registered at each visit during the study period, and for the majority of patients were determined separately by 2 of the authors (LB and EN). A few discrepancies were settled by joint evaluation. In case of missing or conflicting information, each center was asked for clarifications repeatedly during the study. Protocol details and definitions were clarified in the Nordic JIA cohort study steering-group meeting twice yearly during the study period. Disease onset was defined as the date when the child, according to anamnestic information, fulfilled the criteria for active arthritis or experienced the onset of systemic features, not necessarily confirmed by a physician. Uveitis was registered as present and active when an ophthalmologist prescribed treatment for inflammation of the uvea. Remission status was determined by the participating physicians accord-

Table 1. Clinical characteristics of patients in the Nordic JIA cohort at the first study visit, according to JIA categories*

Characteristic	No. of patients assessed	Total cohort (n = 440)	JIA category						
					Polyarticular				
			Systemic (n = 17)	Oligoarticular (n = 225)†	RF negative (n = 94)	RF positive (n = 4)	Psoriatic (n = 6)	Enthesitis-related (n = 34)	Undifferentiated (n = 60)
Female sex, no. (%)	440	291 (66.1)	11 (64.7)	156 (69.3)	70 (74.5)	3 (75.0)	0 (0.0)	6 (17.6)	45 (75.0)
ANA positive, no. (%)‡	391	107 (27.4)	0 (0)	66 (32.4)	29 (34.1)	1 (33.3)	0 (0)	2 (7.1)	9 (17.6)
HLA–B27 positive, no. (%)	385	83 (21.6)	0 (0)	30 (15.6)	16 (18.6)	0 (0)	0 (0)	25 (78.1)	12 (26.1)
Age at disease onset, years	440	5.5 (2.5–9.7)	4.7 (2.2–6.4)	4.9 (2.2–8.5)	4.8 (2.3–8.5)	11.7 (9.5–13.2)	5.9 (3.2–7.2)	10.5 (8.6–12.3)	8.1 (3.5–11.9)
Active joint count	399	3 (1–6)	3 (2–6)	2 (1–3)	7 (6–14)	11 (8–21)	1 (1–2)	2 (1–5)	4 (1–7)
CRP, mg/liter	332	14 (0–35)	146 (83–184)	11 (0–24)	24 (0–47)	27 (10–44)	12 (0–32)	23 (10–53)	0 (0–28)
ESR, mm/hour	333	35 (16–56)	101 (84–110)	30 (15–50)	42 (20–60)	28 (8–47)	16 (14–58)	41 (12–70)	24 (14–28)
Parent/patient's global assessment of well-being score (0–10-point VAS)§	271	1.0 (0.2–3.0)	1.6 (0.5–2.0)	2.2 (0.7–2.2)	2.0 (0.8–4.0)	1.5 (0.8–3.3)	1.4 (0.8–2.5)	2.4 (0.4–4.3)	1.1 (0.5–3.5)
Physician's global assessment of overall disease activity score (0–10-point VAS)	248	1.0 (0.5–3.0)	1.0 (1.0–4.5)	1.0 (0–2.0)	2.0 (1.0–5.0)	1.7 (0.5–2.4)	1.6 (0.8–2.3)	3.0 (2.0–5.0)	1.2 (0.6–3.0)
C-HAQ score (scale 0–3)	278	0.3 (0.0–1.0)	0 (0–0.1)	0.1 (0–0.8)	0.9 (0.3–1.4)	1.0 (0–1.3)	0.9 (0.4–1.9)	0.5 (0–1.1)	0.3 (0–0.6)
JADAS27 (scale 0–57)	197	5.0 (2.0–10.5)	3.0 (1.9–16.1)	3.0 (1.0–6.2)	10.3 (5.3–17.3)	5.2 (1.3–14.7)	5.5 (4.2–6.8)	9.3 (4.5–14.2)	6.9 (3.5–9.8)

* Except where indicated otherwise, values are the median (interquartile range). The first study visit occurred a median of 7 months after disease onset. Values for the active joint count are the cumulative numbers of joints with active arthritis during the first 6 months after disease onset. Values for the C-reactive protein (CRP) level and the erythrocyte sedimentation rate (ESR) are the maximum values reported during the first 6 months after disease onset. JIA = juvenile idiopathic arthritis; RF = rheumatoid factor; VAS = visual analog scale; C-HAQ = Childhood Health Assessment Questionnaire; JADAS27 = Juvenile Arthritis Disease Activity Score in 27 joints.

† Assessed 6 months after disease onset, according to the International League of Associations for Rheumatology classification criteria.

‡ Antinuclear antibody (ANA) positivity was defined as positive results of 2 tests performed >3 months apart.

§ Scores were provided by patients who were older than age 9 years and by the parents of younger patients.

ing to the preliminary criteria described by Wallace et al (26). Remission status was corrected by one of the authors (EN) if it was inconsistent with any of the recorded disease activity variables. The occurrence of periods with inactive disease and remission and the Juvenile Arthritis Disease Activity Score based on 27 joints (JADAS27; 0 = no disease activity and 57 = maximum disease activity) were assessed by one of the authors (EN), using all available registrations (27).

Approval from medical ethics committees was granted according to the regulations of each participating country. Written informed consent was obtained from the parents of children younger than age 16 years and from the children who were age 16 years or older.

Statistical analysis. Statistical analyses were performed using Stata version 11 software. Descriptive statistics were used to summarize the clinical characteristics of the population and measures of disease activity. Chi-square and Fisher's exact tests were used as appropriate for comparison of dichotomous variables, and the Mantel-Haentzel method was used for stratified analyses to control for confounding. The Mann-Whitney U test was used for comparing medians for skewed data. Student's *t*-test was used to compare means for continuous outcome variables between groups. *P* values less than 0.05 were considered significant.

RESULTS

Study group. Of 500 included children with JIA, 440 (88.0%) had a followup visit or telephone interview at least 7 years after the onset of disease (median 98 months, range 84–147 months). Of these final registrations, 376 (85.5%) were clinic visits, and 64 were telephone interviews. Telephone interviews were mainly performed when clinical followup had been transferred from the pediatric rheumatologist either to adult care because of age or to primary health care due to remission. During the disease course, patients had a median of 5 clinic visits with full data registration (range 2–10). To our knowledge, only 3 of all eligible patients with JIA did not agree to take part in the study. A comparison of the followup group and the 12.0% of children lost to followup revealed no significant differences in baseline characteristics with respect to the number of active joints during the first 6 months after disease onset, the C-HAQ and JADAS27 scores, or the proportion with oligoarticular arthritis.

Characteristics of the patients at the first study visit. The median time interval between disease onset and the diagnosis of arthritis by a physician was 47 days (interquartile range [IQR]) 14–98 days) (data not shown). The first registration was performed a median of 7 months (IQR 6–8 months) after disease onset. The age of the children at the time of disease onset ranged

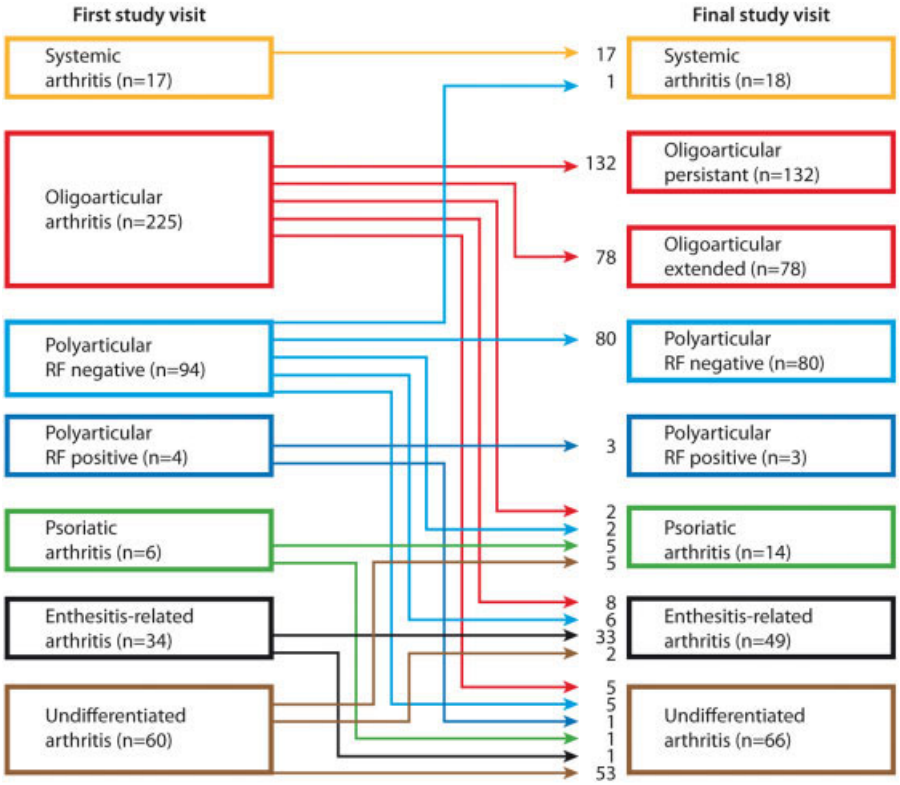

Figure 1. Distribution of International League of Associations for Rheumatology classification criteria categories in the Nordic juvenile idiopathic arthritis cohort, 6 months after disease onset and at the final study visit (median 98 months after disease onset). RF = rheumatoid factor.

from 0.1 to 15.9 years (median 5.5 years) (Table 1). The cumulative number of active joints during the first 6 months after disease onset ranged from 1 to 40 (median 3). The prevalence of oligoarticular category was 51.1%.

Disease course and outcome. *ILAR categories.* The distribution of ILAR categories continued to change from the time of the first evaluation 6 months after disease onset and throughout the observation period (Figure 1). Of the 225 children with oligoarticular disease at baseline, 78 (34.7%) had an extended course involving more than 4 joints. An additional 10.8% of the children changed the ILAR-defined JIA category during the disease course. There was a marked increase in the proportion of patients with enthesitis-related arthritis (7.7% at baseline versus 11.1% at the last followup) or psoriatic arthritis (1.4% versus 3.2%), and the number of patients with undifferentiated arthritis also increased. The reasons why a patient was moved from one ILAR category to another during followup were mainly either onset of enthesitis, sacroileitis, acute uveitis, or psoriasis, or new information on the onset of any of these conditions in a first-degree relative of the patient. Among the 66 children with undifferentiated arthritis at the final followup visit, 42 were excluded from other categories due to heredity, and 14 fulfilled criteria for >1 category. Ten patients did not fulfill the criteria for any category, including 6 patients with a polyarticular course who had no registered result for RF status and 1 patient with only 1 RF-positive test result.

Medication. During the study period, 74.1% of the patients received intraarticular corticosteroid injections (median 3, range 0–70) (Table 2). The proportion of children who received intraarticular corticosteroid injections was the same in the group with polyarticular disease and the group with oligoarticular disease, and 56.2% of the children received intraarticular corticosteroid injections within a median of the first 7 months. Disease-modifying antirheumatic drugs (DMARDs) were started within 7 months after disease onset in 9.3% of the group with oligoarticular disease, 47.6% of the group with polyarticular disease, and 24.8% of the registered cohort. During the disease course, 25.0% of the group with persistent oligoarticular disease, 76.9% of the group with extended oligoarticular disease, 83.7% of the group with polyarticular RF-negative disease, and 58.0% of the total cohort were treated with DMARDs (including biologic medications). Of the 185 children who were never treated with DMARDs, 59.4% received 1 or more intraarticular corticosteroid injections, and 93.5% received nonsteroidal antiinflammatory drugs.

At the final visit, 30.5% of patients were receiving DMARDs, including 22.5% who were receiving methotrexate and 12.5% who were receiving biologic agents. In the group with persistent oligoarticular disease, 9.8% were receiving DMARDs, and in both the group with extended oligoarticular disease and the group with RF-negative polyarticular disease, 46% were receiving DMARDs (Table 3). One patient with systemic JIA underwent autologous bone marrow transplantation and experienced a partial response. At the end of the study, 84.9% of the patients in the group with persistent oligoarticular disease and 64.5% of the total cohort were not receiving medications on a regular basis.

Table 2. Drug treatment received by patients in the Nordic juvenile idiopathic arthritis cohort*

Treatment	During the study period (n = 440)	At the final study visit (n = 440)
NSAIDs†	426 (96.8)	53 (12.0)
Corticosteroids		
Intraarticular	326 (74.1)	–
Systemic	142 (32.3)	5 (1.1)
Methotrexate, total	213 (48.4)	99 (22.5)
Methotrexate, oral	211 (48.0)	78 (17.7)
Methotrexate, parenteral	66 (15.0)	21 (4.8)
Biologic agents‡	77 (17.5)	55 (12.5)
Etanercept	54 (12.3)	27 (6.1)
Infliximab	31 (7.0)	20 (4.5)
Adalimumab	9 (2.0)	8 (1.8)
Other medications§	150 (34.1)	30 (6.8)
DMARDs¶	255 (58.0)	134 (30.5)
No medications	11 (2.5)	284 (64.5)

* Values are the number (%) of patients.
† Nonsteroidal antiinflammatory drugs (NSAIDs) administered periodically on demand were not included.
‡ One patient received anakinra, rituximab, and later adalimumab.
§ Hydroxychloroquine (80 during the study period and 13 at the final visit), sulfasalazine (63 during the study period and 10 at the final visit), cyclosporine (20 during the study period and 3 at the final visit), leflunomide (8 during the study period and 5 at the final visit), intravenous immunoglobulin (6 during the study period and 0 at the final visit), azathioprine (5 during the study period and 1 at the final visit), gold (2 during the study period and 0 at the final visit), and mycophenolate mofetil (2 during the study period and 2 at the final visit). Patients may have received more than 1 of these medications.
¶ Disease-modifying antirheumatic drugs (DMARDs) included methotrexate, biologic agents, or other medications.

Uveitis. Uveitis developed in 89 (20.2%) of the patients with JIA; in 83% of these patients, uveitis was diagnosed within the first 4 years after the onset of disease (data not shown).

Disease activity and damage at the last followup visit. The median cumulative number of active joints during the disease course was 6 (range 1–61). At the last visit, however, the median active joint count was 0 (range 0–42) (Table 3); the median number of joints with restricted movement was also 0 (range 0–21). The levels of inflammation markers and the median self-reported health assessment scores were within normal limits, and the median JADAS27 score was 0.9. The median VAS pain score was 0 (IQR 0–1.4), but one-

Table 3. Characteristics of patients in the Nordic JIA cohort at the final study visit, according to JIA categories*

Characteristic	No. of patients assessed	Total cohort (n = 440)	JIA category							
				Oligoarticular		Polyarticular				
			Systemic (n = 18)	Persistent (n = 132)	Extended (n = 78)	RF negative (n = 80)	RF positive (n = 3)	Psoriatic (n = 14)	Enthesis-related (n = 49)	Undifferentiated (n = 66)
Age at last visit, median (IQR) years	440	14.2 (10.8–18.0)	14.2 (11.1–15.1)	13.6 (10.8–16.9)	12.3 (10.1–16.4)	13.2 (10.7–17.4)	21.4 (19.1–21.5)	14.1 (13.2–15.1)	18.4 (15.0–20.7)	15.8 (11.2–19.9)
Active joint count, median (IQR)	438	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)
Cumulative no. of active joints, median (IQR)	438	6 (2–12)	6 (3–12)	2 (1–3)	9 (6–12)	13 (8–23)	13 (13–31)	7 (3–9)	5 (3–13)	10 (4–16)
ESR, median (IQR) mm/hour	272	8 (4–12)	5 (2–11)	7 (4–11)	9 (5–14)	8 (4–11)	4 (2–15)	7 (5.5–11)	8 (4–12)	9 (3–13)
JADAS27, median (IQR)	230	0.9 (0–3.5)	0 (0–3.2)	0 (0–1.6)	1.6 (0.3–4.4)	1.1 (0–3.5)	3.0 (0–8.7)	0 (0–3.0)	0.9 (0–3.0)	1.5 (0.1–5.3)
C-HAQ/HAQ score >0	352	113 (32.1)	3 (23.1)	13 (13.3)	29 (46.0)	28 (38.9)	2 (66.7)	4 (30.8)	13 (35.1)	21 (39.6)
VAS pain score >0	345	172 (49.9)	4 (30.8)	26 (27.1)	43 (70.5)	39 (54.9)	2 (66.7)	4 (30.8)	22 (61.1)	32 (61.5)
Parent/patient's global assessment of well-being score >0†	342	172 (50.3)	3 (23.1)	25 (26.0)	39 (67.2)	43 (60.6)	2 (66.7)	5 (38.5)	22 (61.1)	33 (63.5)
Physician's global assessment of overall disease activity score >0	312	145 (46.5)	3 (25.0)	21 (26.9)	34 (58.6)	37 (53.6)	2 (66.7)	5 (41.7)	19 (57.6)	24 (51.1)
CHQ physical summary score <40	207	40 (19.3)	1 (11.1)	4 (7.0)	10 (23.3)	8 (18.2)	–	1 (12.5)	7 (38.9)	9 (32.1)
CHQ psychosocial summary score <40	207	18 (8.7)	–	2 (3.5)	6 (14.0)	5 (11.4)	–	1 (12.5)	–	4 (14.3)
JADI global assessment of articular and extraarticular damage score >0	227	52 (22.9)	3 (25.0)	9 (15.8)	14 (34.2)	13 (30.2)	1 (100)	3 (50.0)	5 (16.7)	4 (10.8)
JADI articular score >0	227	30 (13.2)	2 (16.7)	3 (5.2)	7 (17.5)	9 (20.9)	1 (100)	2 (33.3)	4 (13.3)	2 (5.4)
JADI extraarticular score >0	227	27 (11.9)	3 (25.0)	7 (12.3)	8 (19.5)	3 (7.0)	–	1 (16.7)	2 (6.7)	3 (8.1)
DMARDs present‡	440	134 (30.5)	3 (16.7)	13 (9.8)	36 (46.2)	37 (46.3)	1 (33.3)	5 (35.7)	15 (30.6)	24 (36.4)
Continuously active disease§	390	116 (29.7)	3 (18.8)	13 (11.6)	28 (39.4)	28 (42.4)	1 (33.3)	3 (27.3)	15 (31.3)	25 (40.3)

* Except where indicated otherwise, values are the number (%) of patients. The last study visit occurred a median of 98 months after disease onset. Scores for parent/patient's global assessment of well-being, physician's global assessment of overall disease activity, and the Juvenile Arthritis Damage Index (JADI) were based on a 0–10-point visual analog scale (VAS). JIA = juvenile idiopathic arthritis; RF = rheumatoid factor; IQR = interquartile range; ESR = erythrocyte sedimentation rate; JADAS27 = Juvenile Arthritis Disease Activity Score based on 27 joints (range 0–57); C-HAQ = Childhood Health Assessment Questionnaire (scale 0–3); CHQ = Child Health Questionnaire (range 0–100).

† Scores were provided by patients who were older than age 9 years and by the parents of younger patients.

‡ Current treatment with disease-modifying antirheumatic drugs (DMARDs), including biologic agents.

§ No periods of disease remission off medication (inactive disease off medication >12 months) for a median of 98 months (range 84–147 months) after disease onset.

fourth of the children reported pain scores >1.4, and the maximum score was 8.5. Although the mean CHQ physical and psychosocial scores were within normal limits, 19.3% of the total group and 38.9% of the group with enthesitis-related arthritis had a CHQ physical score of <40. Damage was reported in 52 children (22.9%), and 19.2% of these had not received DMARDs or biologic agents. The highest JADI scores for articular and global damage were observed in children in the group with systemic disease and the group with polyarticular RF-negative disease.

Absence from school and physical education. At the last followup visit, 83.2% of the children reported no absence from school or work due to JIA during the previous 2 months, while 4.8% were absent from school or work for more than 5 days in the same period. At the last followup, 76.7% of the school-age children participated fully in physical education, while 17.2% participated partly, and 6.0% did not participate (data not shown).

Remission status. During the observation period, a continuously active disease course (with no remission off medication) was observed in 29.7% of the 390 patients with data sufficient for evaluation (Table 3). Approximately half of these children (48.7%) experienced a relapsing disease course, with periods of remission off medication lasting for ≥1 year, followed by new periods of disease activity. This relapsing disease course was observed in 45.1% of the group with persistent oligoarticular disease, 56.3% of the group with extended oligoarticular disease, and 51.5% of the group with polyarticular RF-negative disease.

At the last visit, 42.4% of the patients were in remission off medication, with inactive disease for the last 12 months; 8.9% had remission on medication, and 48.7% were not in remission (Table 4). Among the patients with disease in remission, 29.3% had used DMARDs including biologic agents (ranging from 13.3% in the group with persistent oligoarticular disease to 63.6% in the group with polyarticular RF-negative JIA). Four (2.2%) of the patients whose disease was in remission off medication had been treated with biologic agents; 3 of these 4 patients had systemic JIA. Among patients whose disease was not in remission, 77.9% had been treated with DMARDs, including 51.3% of those with persistent oligoarticular disease and 89.1% of those with RF-negative polyarticular disease. Among patients whose disease was in remission on medication, 94.7% had received DMARDs, including biologic agents. A significantly higher rate of disease remission off medication was observed among patients with persistent oligoarticular JIA and those with systemic JIA compared with patients in the rest of the cohort ($P < 0.0001$). The lowest rate of remission off medication was observed in the group with extended oligoarticular JIA.

Table 4. Remission status of patients in the Nordic JIA cohort at the final study visit*

JIA category	Remission off medication†	Remission on medication‡	Not in remission§
Systemic (n = 18)	15 (83.3)	0 (0)	3 (16.7)
Oligoarticular			
Persistent (n = 126)	83 (65.9)	4 (3.2)	39 (31.0)
Extended (n = 75)	16 (21.3)	12 (16.0)	47 (62.7)
Polyarticular			
RF negative (n = 79)	22 (27.9)	11 (13.9)	46 (58.2)
RF positive (n = 3)	1 (33.3)	0 (0)	2 (66.7)
Psoriatic (n = 13)	3 (23.1)	3 (23.1)	7 (53.9)
Enthesitis-related (n = 49)	15 (30.6)	4 (8.2)	30 (61.2)
Undifferentiated (n = 64)	26 (40.6)	4 (6.3)	34 (53.1)
Total (n = 427)	181 (42.4)	38 (8.9)	208 (48.7)

* Values are the number (%) of patients. The final study visit occurred a median of 98 months after disease onset. Inactive disease is defined as no joints with active arthritis, no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to juvenile idiopathic arthritis (JIA), no active uveitis, a normal erythrocyte sedimentation rate or C-reactive protein level, if tested, and a physician's global assessment of disease activity indicating no disease activity. RF = rheumatoid factor.
† Inactive disease for >12 months while the patient was not receiving medication.
‡ Inactive disease for >6 months while the patient was receiving medication.
§ No disease remission either on or off medication, as defined above.

The presence of ANAs was not associated with any particular outcome pattern with regard to disease remission in either the total JIA cohort or in select categories of JIA, excluding the systemic, polyarticular RF-positive, and enthesitis-related categories. However, remission off medication was achieved less frequently and remission on medication was achieved more frequently in children who were younger than age 5 years at the time of disease onset. The difference between age groups regarding remission rates was significant in select categories ($P = 0.035$) (in the total cohort $P = 0.05$), also when controlling for confounding by stratification for the different JIA categories (data not shown).

DISCUSSION

The results of this longitudinal study support the concept of JIA as a chronic disease (15,28,29) by showing that a majority of patients experienced continuously ongoing disease activity or a relapsing course during the first decade of JIA. Similar results for select categories of JIA were observed by Wallace et al (1), using the newly developed remission criteria in retrospective stud-

ies. Prospective longitudinal data have been sought to confirm these results, and the ongoing nature of the disease was demonstrated in this cohort study (1,3).

The paramount goal of current treatment in JIA is to achieve inactive disease and remission with or without medication (7,30,31). The use of biologic agents in pediatric patients represents the beginning of a new era in the medical treatment of JIA, and treatment with etanercept was first described at the same time as the start of our study (32). Indications and approvals have increased as efficacy and safety data on biologic agents in children have emerged (33–35). In our study, the use of biologic medications during the disease course in 17.5% of patients reflects the steadily increasing use of these agents during the last decade, and the percentage of treated patients might have been higher based on current recommendations.

In addition to the biologic agents, medical treatment was dominated by intraarticular corticosteroid injections and methotrexate, often in combination. Consistent with current treatment recommendations, intraarticular corticosteroid injections were commonly received, and very few patients were receiving systemic corticosteroids at the last study visit (36,37). The early timing and high number of intraarticular corticosteroid injections, together with the high number of patients receiving systemic treatment, may partly explain the favorable outcome with low disease activity and minimal damage in most patients. Similar results were observed in a recent study by Solari et al (38). However, in 2 Canadian JIA cohort studies, fewer patients were treated with intraarticular corticosteroid injections and DMARDs (28,39). The first Canadian study is older, and the followup time in the more recent study was short. Achieving inactive disease and remission may imply accepting the use of potent drugs with potentially serious long-term side effects.

A considerable and continuous change in JIA categories during the disease course was observed in this study. We observed that the onset of psoriasis or features of enthesitis-related arthritis in the child or a first-degree relative may occur at any age, and there is reason to believe that further changes will occur over time.

At the end of the study, the disease remission status of patients in the groups with persistent oligoarticular disease and systemic disease markedly differed from the status of patients in all of the other categories. Even though the number of patients in the group with systemic disease was small, the results indicate that in a population-based setting, the prognosis is also favorable for a considerable proportion of patients in this JIA category, which otherwise is known for having the most severe disease course (28). The high rate of remission observed in the group with persistent oligoarticular disease is consistent with that in previous studies (28,29). Prognostication based on ILAR categories at the time of disease onset is difficult, because one-third of children in the group with initial oligoarticular arthritis later experienced the development of extended disease, with outcomes and remission data similar to or even worse than those of children in the polyarticular, psoriatic, and enthesitis-related categories. These results underline the need to identify early predictors or biologic determinants of persistent oligoarticular disease (40,41).

Early-onset disease and the presence of ANAs are suggested as important descriptors to be incorporated in a revised ILAR classification system (7–10). Martini et al and Ravelli et al discussed the presence of ANAs as an important descriptor in select categories of JIA, such as oligoarticular JIA, polyarticular RF-negative JIA, and psoriatic JIA (7,10). Therefore, we chose to study the influence of ANA status and young age at disease onset on disease remission in our data both for the whole cohort and for select categories, excluding the systemic, polyarticular RF-positive, and enthesitis-related arthritis categories. We observed that remission status was not influenced by ANA status. However, fewer children with a young age at disease onset achieved disease remission off medication compared with children with late-onset disease, independent of ILAR categories. Recently, indications of biologic differences in JIA subgroups according to age at disease onset have emerged, showing that the B cell gene expression signature can distinguish between early-onset and late-onset JIA regardless of the number of affected joints (9). Recently, Hollenbach et al (42) reported that HLA class II associations with JIA were significantly different in patients with early-onset disease and those with late-onset disease.

The preliminary criteria for clinical remission described by Wallace et al (26) has certain limitations in longitudinal studies. Using these criteria, the remission status of an individual patient whose disease has been inactive for at least 6 months while he or she was receiving medication would change from remission on medication to inactive disease off medication. However, even if disease remains inactive, there is by definition no remission during the first 12 months after medication was stopped. Remission off medication is finally achieved when inactive disease off antirheumatic medication persists for more than 12 months (26). An additional definition of remission in a patient with persistent inactive disease that occurs during the first 12 months

after medication is stopped would make sense and be useful. The results of our study support the notion that remission is not a "steady state," which is consistent with recent findings by Knowlton et al showing that the gene expression profiles of patients with JIA in remission are not comparable with those of healthy individuals but are closer to those of patients with active JIA (43,44).

The prospective, longitudinal design and population-based context of this multicenter study are its strengths. The proportion of children lost to followup is small compared with the number of patients lost to followup in other longitudinal studies (15,28,29). The first registered visit took place at a time as close as possible to 6 months after the onset of disease; this implies that initial disease activity peaks are not necessarily shown in the baseline data. A weakness of the study is that for their last followup, 14.5% of patients were interviewed by telephone, making the clinical data for these patients, such as the presence of active joints or uveitis, less reliable. However, telephone interviews were mainly performed in patients older than age 16 years. Studies on rheumatoid arthritis in adults have shown that patient-reported swollen and tender joint counts correlate moderately to highly with joint counts performed by a rheumatologist (45). Study adherence is more difficult to achieve after transfer to adult rheumatology services for the oldest patients (28).

In conclusion, a considerable change in JIA categories occurred during the disease course. Extended disease developed in one-third of the patients with oligoarticular JIA, and the outcomes of these patients were similar to those of children with polyarticular JIA. In a majority of the children, disease was not in remission or regular medication was still being used at the time of their last followup, 8 years after disease onset. Although the levels of disease activity markers were generally low, a proportion of children reported pain and reduced quality of life, and JIA-related damage developed in one-fifth of the children.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Nordal, Dr. Straume, and Dr. Rygg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Nordal, Zak, Aalto, Berntson, Fasth, Straume, Rygg.

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