Clinical presentation, burden of disease and treatment in young-onset and late-onset rheumatoid arthritis: a matched-pairs analysis taking age and disease duration into account

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Abstract

Objectives

The aim of this study is to compare clinical features and treatment of young onset rheumatoid arthritis with late-onset rheumatoid arthritis.

Methods

Nine thousand five hundred forty-one patients with rheumatoid arthritis (RA) enrolled in the national database of the German Collaborative Arthritis Centres in 2007–2009 were stratified by age at disease onset: up to 65 years (YORA), >65 years (LORA). To enable unbiased comparisons between the two groups despite their systematic differences in age and disease duration, we performed two separate matched-pairs analyses: the impact of current age was assessed by matching YORA and LORA patients for disease duration and sex (n=1,550 pairs). To identify the influence of disease duration, a second sample matched for age and sex (n=1,158 pairs) was drawn.

Results

At identical age, YORA patients had higher disease activity (DAS28), worse functional capacity and were less frequently in remission when compared with LORA patients. YORA patients also suffered more frequently from RA-related co-morbidities such as cardiovascular disease, chronic renal disease and osteoporosis. Matched for disease duration, there were no differences between the two groups concerning disease severity and remission rates, global health or pain intensity. Independent of age or disease duration, YORA patients reported more sleep disorders and fatigue. LORA patients received significantly fewer synthetic or biologic DMARDs than YORA patients.

Conclusion

Duration of RA, rather than age, explains differences in disease burden between YORA and LORA patients. The lower prescription rates of synthetic and in particular biologic DMARDs, despite lower remission rates, indicate a potential treatment deficit in older patients.

Key words

RA, LORA, YORA, disease duration, age at onset, disease burden

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease with a prevalence of 0.5 to 0.8 per 100 adults and an increase in incidence and prevalence with age (1, 2). RA with disease onset at ages over 60 (3-6) or 65 years (7-9) is called Late-Onset RA (LORA), while RA starting at earlier ages is called Young-Onset RA (YORA). Increasing age at onset of RA (10) suggests a cut-off point at age 65 rather than at 60.

Several studies indicate that disease manifestation, severity, progression and prognosis of RA differ in relation to age at disease onset. A recent study has shown that the impact of sex on disability measured by the HAQ is evident at baseline, whereas the impact of age at symptom onset only becomes apparent at long-term follow-up (11). LORA has been described with a more equal sex distribution, more acute onset and more frequent involvement of large, proximal joints as well as less rheumatoid factor positivity than YORA (12, 13). Rheumatoid factor negative LORA, which shows some overlap with polymyalgia rheumatica, has been considered a more benign disease by some authors (14, 15). However, an older study, which prospectively observed a cohort with balanced proportions of seropositive and seronegative cases, reported a worse prognosis for LORA compared to YORA (5). Also, a comprehensive review summarising the evidence up to 1997 did not find any evidence for LORA being a more benign disease (16).

Comparing cohorts of YORA and LORA patients poses the obvious problem that with equal disease duration the two groups differ substantially in age and, thus, in outcomes that are correlated with age such as physical function or co-morbidity. On the other hand, within the same age group, patients with YORA have a much longer disease experience, associated with more damage and functional limitation. Most of the studies performed so far have not controlled for disease duration or used samples of patients with short disease duration. Their results reflect the impact of age on disease outcomes since, due to the disjunctive definition of YORA and LORA, it is not possible to control for age and disease duration at the same time.

To compare disease burden, clinical outcomes, co-morbidity and treatment in YORA and LORA, taking the mutual interference of age and disease duration into account, we took advantage of a large patient database and controlled for these two factors by separate matched-pairs analyses.

Methods

We analysed data from the national database of the German Collaborative Arthritis Centres. This database is an ongoing prospective study which has started in 1993 as a long-term monitoring system for German rheumatology (17-19). It contains annually updated clinical data and patient-reported outcomes for unselected outpatients with inflammatory rheumatic diseases. The database received study approval from the ethics committee of the Charité University Medicine Berlin (EA1/196/06). Nine thousand five hundred forty-one patients who were enrolled in the database between 2007 and 2009 and met the 1987 ACR criteria for rheumatoid arthritis (20) were included. Patients who were seen in more than one year were included with the first available visit. YORA was defined as disease onset at or before the age of 65 (n=7,990), and LORA as disease onset after 65 years of age (n=1,551).

To address clinical differences among patients of the same age with different ages at onset, we matched YORA and LORA by age (in 2-year increments) and sex. We formed 1.158 pairs, leaving 393 LORA patients unmatched. Forty percent of those with no or too few matches in the YORA group were men above the age of 73, and 60% were women older than 77 years of age. The matched groups had a female proportion of 73% and a mean age of 74 years.

We then matched YORA and LORA patients for disease duration and sex to compare the impact of the disease at different ages. For all LORA patients, at least one matching patient of the same gender and with similar disease duration (in 2-year increments) could

be found in the YORA group, thus adding up to 1.551 pairs. The matched groups had a female proportion of 69% with a mean disease duration of about 4.1 years.

Since rheumatoid factor negative LORA may overlap with polymyalgia rheumatica, whereas seropositive LORA is considered more similar to RA in general (14), we performed a further matched-pairs analysis for LORA and YORA patients with equal disease duration, stratified by seropositivity for anti citrullinated peptide antibodies (ACPA) or rheumatoid factor (RF).

Repetition of matchings ("bootstrap")

For each LORA patient, multiple matches could be found in the YORA group when matched for disease duration and sex. Controlling for age and sex, multiple matches could be found for younger LORA patients and for older YORA patients. Thus, each individual match is expected to deliver somewhat different results due to the random selection of patient pairs. To avoid relying on the results of one individual match, we simulated a bootstrap (21) process by repeating the matching for both combinations 1.000 times. For each match, numbers of interest such as mean and percentages of considered parameters were computed. Since some patients with very long-lasting disease would have caused a biased mean, for disease duration the 5%-trimmed mean was calculated. Tables 2 to 6 show the mean results of these 1.000 evaluations. Differences were considered statistically significant if the confidence interval, defined by the 2.5- and the 97.5-percentile of the 1.000 differences, did not include zero. IBM SPSS Statistics 19.0 was used for data analysis.

Outcomes

Physicians documented onset of symptoms, diagnosis, current treatment, global assessment of disease activity (numerical rating scale [NRS] from 0–10, with 10 as highest possible activity), disease activity score with 28 joints (DAS28) and Steinbrocker functional class (22). Remission was defined as DAS28 <2.6 (23). Patients recorded pain, fatigue and global health on NRS from 0–10, where 10 reflects the worst possible status. Disability was reported using the Hannover Functional Status Questionnaire (FFbH), which is an 18-item scale of activities of daily living similar to the Health Assessment Questionnaire (HAQ), but used more frequently in Germany. FFbH values, with scores in the range of 0 to 100, 100 reflecting full functional capacity, can be transformed into HAQ values (24).

Furthermore, the physicians were asked to document, among others, the presence of the following chronic co-morbid conditions: osteoporosis, hypertension, cardiovascular disease, chronic renal disease, gastritis or gastric ulcer and depression/psychic disorder.

Table I. Patient characteristics of cases classified as YORA or LORA.

		YORA (≤65 years)	LORA (>65 years)	Total
Number		7,990	1,551	9,541
Age, mean (years)		58.4	76.0	61.2
Female		76.4%	69.4%	75.2%
Disease duration, 5%-trimmed mean (years)		11.8	4.1	10.6
Disease severity	asymptomatic or mild	35.8%	46.6%	37.5%
	moderate	48.4%	46.2%	48.1%
	severe or very severe	15.8%	7.2%	14.4%
Steinbrocker	I/II	77.8%	85.4%	79.1%
	III/IV	22.1%	14.6%	20.9%
General health[#]	0–3	36.9%	35.7%	36.7%
	7–10	19.9%	16.6%	19.4%
Pain[#]	0–3	39.4%	43.1%	40.0%
	7–10	23.1%	19.0%	22.4%
RF-positive		67.6%	53.5%	65.3%
ACPA-positive		65.8%	47.0%	62.6%
CRP, mean (mg/dl)		1.2	1.4	1.2
Patients with remission (DAS28 <2.6)		34.7%	38.1%	35.3%
DAS28, grouped	<3.2	54.5%	60.0%	55.4%
	3.2–5.1	37.0%	31.5%	36.1%
	>5.1	8.5%	8.5%	8.5%
FFbH[§], mean		71.2	68.8	70.8
Patients with comorbidities		76.5%	86.2%	78.1%

[#]Numerical rating scale from 0–10 (0 indicating best status and 10 worst status).
[§]Score with range from 0–100 (100 indicating unlimited functional capacity).

Results

Stratifying disease onset at 65 years of age, 7,990 patients had YORA and 1,551 had LORA. Seventy-six point four percent of the YORA patients compared to 69.4% of the LORA patients were female. The mean age in the YORA group was 58.4 years, compared to 76.0 years in the LORA group, their mean disease duration was 11.8 and 4.1 years, respectively. Thirty-five point three percent of these unselected real-life patients were in remission and 55.4% were in a state of low disease activity (DAS28 <3.2). This applied to more LORA than YORA patients (60% compared to 55% DAS28 <3.2). YORA patients were more frequently rated by the rheumatologists as having "severe" or "very severe" disease, they had more pain and were more often RF or ACPA positive. Further patient characteristics are shown in Table I.

Among patients of the same age (mean 74 years, Table II), YORA patients had a mean disease duration of 20.1 years, compared to 3.4 years in LORA. More LORA patients were in DAS28 remission. Significantly more patients with YORA than with LORA were graded by the physicians as having severe or very severe disease, and they were significantly more often in Steinbrocker functional class III or IV. All patient-reported outcomes (function, pain, global health, sleep, fatigue) were significantly worse in YORA. Co-morbid conditions such as osteoporosis, cardiovascular disease, chronic renal insufficiency and gastritis/gastric ulcers were seen more frequently in YORA

Table II. Comparison of disease characteristics in YORA and LORA patients.

	Matched for age			Matched for disease duration		
	YORA	LORA	Sign.	YORA	LORA	Sign.
n=matched pairs	1,158			1,551		
Female (%)	72.5			69.4		
Mean age (years)	74.0–74.1			53.4	76.0	
Mean disease duration (years)	20.1	3.4		4.1		
Remission (DAS28 <2.6) (%)	30.4	37.8	*	39.2	38.1	
DAS28 3.2–5.1 (%)	39.4	31.6	*	34.3	31.5	*
DAS28 >5.1 (%)	8.4	8.7		8.5	8.5	
High disease severity (%)	23.5	7.2	*	7.0	7.2	
ACPA-positive (%)	68.6	47.4	*	60.1	47.0	*
RF-positive (%)	71.4	54.3	*	62.8	53.5	*
Steinbrocker III + IV (%)	37.5	12.5	*	10.1	14.6	*
FFbH[§] ≤50 (%)	36.0	21.6	*	14.1	25.0	*
Poor global health[#] (%)	23.7	15.9	*	17.0	16.6	
Severe sleep disorder[#] (%)	23.3	17.9	*	24.1	17.3	*
Severe fatigue[#] (%)	24.5	17.5	*	21.0	18.3	*
Severe pain[#] (%)	26.2	18.1	*	20.3	19.0	
Osteoporosis (%)	31.9	22.2	*	9.1	24.2	*
Hypertension (%)	47.6	46.4		24.3	46.0	*
Heart disease (%)	23.1	18.3	*	7.0	20.6	*
Chronic renal insufficiency (%)	13.5	11.6	*	3.4	12.6	*
Gastritis/gastric ulcer (%)	13.4	7.6	*	5.0	8.0	*
Depression/psychic disorder (%)	3.1	3.3		4.8	3.1	*

[#]Score 7–10 on a numerical rating scale from 0–10 (0 indicating best status and 10 worst status).
[§]Score with range from 0–100 (100 indicating unlimited functional capacity).
*The confidence interval, defined by the 2.5- and 97.5-percentile of the 1.000 differences, did not include 0.

Table III. Comparison of drug treatment in YORA and LORA patients.

	Matched for age			Matched for disease duration		
	YORA	LORA	Sign.	YORA	LORA	Sign.
n=matched pairs	1,158			1,551		
Mean age (years)	74.0–74.1			53.4	76.0	
Mean disease duration (years)	20.1	3.4		4.1		
Synthetic/biologic DMARDs (%)	88.1	80.4	*	84.7	78.9	*
Methotrexate (%)	60.6	57.3	*	58.7	56.9	
Leflunomide (%)	15.2	10.1	*	12.9	9.6	*
Biologic DMARDs (%)	18.1	5.9	*	16.0	5.7	*
Glucocorticoids (%)	59.7	59.4		55.6	60.5	*
NSAIDs (%)	41.2	24.9	*	36.8	25.5	*

*The confidence interval, defined by the 2.5- and 97.5-percentile of the 1.000 differences, did not include 0.

patients than in LORA patients of the same age.

Matched for disease duration (mean 4.1 years, Table II), LORA patients were 22 years older. They had a significantly worse functional capacity (Steinbrocker and FFbH questionnaire). Remission rates, percentages of patients with high disease severity, severe pain and poor global health were similar in both groups, while more patients with YORA reported severe fatigue and sleep disorders. When we compared younger YORA patients (aged 50 or less) to LORA patients of the same disease duration in a subanalysis (data not shown), we found even more pronounced differences in severe fatigue and frequency of depression or psychic disorders, despite significantly higher remission rates in YORA. ACPA or RF positivity were found significantly more often in YORA patients. Nearly all co-morbid conditions were significantly more frequent in LORA patients than in YORA patients of the same disease duration. Overall, irrespective of age or disease duration, YORA patients suffered more often from sleep disorders and fatigue than did LORA patients.

There were significant differences in treatment between YORA and LORA patients (Table III). Regardless of age or disease duration, LORA patients received significantly fewer synthetic or biologic DMARDs. YORA patients were prescribed biologic agents about three times more often than LORA patients. In contrast, glucocorticoids were given significantly more frequently to LORA patients compared to YORA patients with the same disease duration, whereas NSAIDs were given far more frequently to YORA patients.

When we compared ACPA or RF seropositive YORA with seropositive LORA with equal disease duration (Table IV), we found no significant differences in disease severity (physicians' judgements), patients' global assessments of health, pain, depression or fatigue. While in seronegative patients DAS28 remission was more frequently achieved in LORA than in YORA, in seropositive patients it was the other way round. Seronegative YORA patients suffered more frequently from pain, depression and fatigue and rated their health state worse than seronegative LORA patients with the same disease duration. The differences in treatment between LORA and YORA were even more pronounced when comparing seronegative cases only: Seronegative LORA patients received significantly more glucocorticoids and less synthetic or biologic DMARDs than patients with younger onset.

Discussion

Several studies have focused on differences in disease manifestation, severity, treatment and prognosis of RA in relation to age at onset. Certain features like acute onset, weight loss and polymyalgic presentation were reported to be more frequent in LORA as has been summarised by Yazici *et al.* (12). Studies comparing patients with equal disease duration found worse outcomes for LORA patients (5, 9), whereas older studies which did not control for disease duration reported a

Table IV. Comparison of ACPA or rheumatoid factor seronegative and seropositive YORA and LORA patients, matched for disease duration.

	Seronegative			Seropositive		
	YORA	LORA	Sign.	YORA	LORA	Sign.
n=matched pairs	678			873		
Mean age (years)	54.4	76.3		52.9	75.9	
Mean disease duration	3.7 years			4.4 years		
DAS28, mean	3.1	2.9	*	3.2	3.3	*
Remission (DAS28 <2.6) (%)	42.7	45.9	*	37.4	32.1	*
High disease severity (%)	4.0	4.6		8.6	9.2	
Steinbrocker III+IV (%)	6.4	7.9		12.5	20.3	*
FFbH[§] ≤ 50 (%)	14.9	24.3	*	13.8	25.5	*
Poor global health[#] (%)	18.8	16.1	*	16.3	16.8	
Severe pain[#] (%)	22.2	19.6	*	19.4	18.5	
Severe fatigue[#] (%)	23.0	17.1	*	20.3	19.2	
Synthetic/biologic DMARDs (%)	78.7	69.0	*	87.4	86.4	
Biologic DMARDs (%)	9.4	2.6	*	19.7	8.1	*
Glucocorticoids (%)	46.7	56.7	*	59.8	63.4	*
Comorbidity, any (%)	68.3	88.6	*	66.0	84.2	*
Depression (%)	5.8	2.7	*	4.2	3.4	

[#]Score 7–10 on a numerical rating scale from 0–10 (0 indicating best status and 10 worst status).
[§]Score with range from 0–100 (100 indicating unlimited functional capacity).
[*]The confidence interval, defined by the 2.5- and 97.5-percentile of the 1.000 differences, did not include the 0.

more favourable (25) or a similar (26) prognosis for LORA compared with YORA patients. One study comparing RA patients with age at onset <55 years to those with later onset in a cohort of early, rheumatoid factor positive RA (mean 14-month symptom duration) found very comparable disease activity and patient-related outcomes in both groups. After age adjustment, there was also no difference in acute phase reactants (27).

The aim of our study was to overcome the methodological limitations of previous studies by differentiating the impact of disease duration from that of age within one data set.

It is highly plausible that with the same disease duration an older patient will have more pronounced functional limitation (7), given the impact of age-related co-morbidities such as osteoarthritis or osteoporosis on functional status. In addition, age-related alterations in the immune system with a decline of protective immune responses and increased levels of proinflammatory cytokines (28, 29) make older patients more susceptible to cartilage damage from synovial inflammation (12, 30). While Camacho *et al*. found the impact of age at symptom onset on disability measured by the HAQ only becoming apparent at long-term follow-up of ≥5 years in women and >10 years in men (11), we have seen functional disparities measured by the FFbH at a mean disease duration of 4.1 years.

Co-morbid conditions are related to quality of life, RA prognosis and outcome. As expected from their higher age, LORA patients presented with osteoporosis more frequently than YORA patients when matched for disease duration. The impact of RA on co-morbidity was demonstrated in our study when comparing patients at the same age. In YORA patients, we found significantly more osteoporosis, cardiovascular, renal and gastric disease, which all are related to the RA or its treatment (31-35). With regard to the increased cardiovascular disease related mortality in inflammatory polyarthritis reported by Naz *et al*. particularly in patients with younger disease onset and positive rheumatoid factor (36), comorbid conditions should be a major concern when treating young- onset rheumatoid arthritis.

Comparing patients with the same disease duration, depression or psychic disorders was significantly more often reported for YORA patients. Additionally, YORA patients suffered from sleep disorder and fatigue more often than LORA patients, irrespective of age or disease duration. It can be assumed that the perception of a chronic disease depends on the phase in life in which its impact is most prominently experienced, substantiated by the even more pronounced discrepancies found in the subanalysis with younger YORA patients. Patients in gainful employment may feel limitations in their daily lives more intensely than those in retirement. Further, Ang *et al*. described comorbid depression as an independent risk factor for mortality in patients with RA (37). Therefore, this condition needs to be diagnosed and adequately treated.

Controlled for disease duration, we found ACPA or RF positivity significantly more often in YORA patients, confirming the findings of previous studies (7, 13, 38). In concordance with van Schaardenburg *et al*., in our study seropositive LORA was associated with a higher DAS28 and less frequent remission rates than seropositive YORA, which points to age and co-morbidity as risk factors for failure to achieve remission (39). Burmester *et al*. showed that co-morbidity is negatively correlated with remission (40). Focusing on the seronegative subgroup, YORA patients, despite their younger age, suffered more from pain and fatigue and reported a worse self-rated health status than their LORA counterparts. Yet, items assessed by the physician such as severity, DAS28 and remission, did not differ. This could indicate that older patients rate comparable health problems less severely than younger, taking comparisons with people of the same age without RA into account. Furthermore, overlap with polymyalgia rheumatica in the seronegative LORA group could also explain differences in the perceived burden of disease.

Our most striking result concerns the differences in anti-rheumatic medication. LORA patients were treated significantly less often with synthetic or biologic DMARDs than were YORA patients with the same disease duration, despite comparable disease activity. These results are in agreement with those of Tutuncu *et al*. (6), who found that patients with elderly-onset RA enrolled in the CORRONA registry were

less frequently treated with biologics or a combination of synthetic DMARDs than were YORA patients. A more hesitant prescription of DMARDs in elder patients was also seen in the Norfolk Arthritis Register, where younger age was an independent predictor of receiving biologic therapies (41). This might in part be due to the higher number of comorbid conditions in elder patients and, therefore, an increased number of contraindications (chronic renal or liver disease). Additionally, fear of interaction with other medications may limit prescription. The biggest differences were seen in seronegative cases, which may in part be explained by overlap with polymyalgia rheumatica in LORA.

However, since there is strong evidence that successful control of disease activity by methotrexate or anti-TNF agents decreases cardiovascular morbidity and mortality in patients with RA (42-44), the lower prescription rates of disease-modifying antirheumatic drugs in elderly patients also indicate a potential treatment deficit.

Our study has strengths and limitations. A strength is that, for the first time, both age and disease duration were taken into account when comparing the impact of YORA and LORA. Since, due to the age-related definition of YORA and LORA, it is impossible to control for age and disease duration simultaneously, the second best choice is to perform two parallel analyses in one data set. This was enabled by the availability of a large sample of real-life patients. A limitation is that our data are cross-sectional in nature, thus not allowing comparison of individual disease courses. Also, we have no data on co-medication for other chronic diseases, which might explain some of the differences in prescription of anti-rheumatic drugs.

Conclusion

In summary, according to our data, age at onset of rheumatoid arthritis appears not to be the most important factor for differences in disease burden, but rather disease duration. The significantly smaller number of LORA patients who received treatment with biologic agents, despite their comparable disease activity and lower remission rates, reflects more conservative drug prescription in the elderly and may indicate a treatment deficit.

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