Chapter 7
Juvenile Idiopathic Arthritis in Adolescence and Young Adulthood

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Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatic disease of adolescence and young adulthood affecting approximately 1 out of 1000 adolescents [1].

Classification

All chronic arthritides of unknown occurring before the age of 16 are referred to as JIA according to the International League of Associations for Rheumatology criteria [2]. Chronic inflammatory arthritis in AYA with age at onset after 16 is classified according to adult criteria.

JIA is a heterogeneous condition and currently classified into seven different categories based on clinical and laboratory features (Table 7.1). The JIA category distribution in AYA is

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Table 7.1 JIA categories and their specifics in adolescence and young adulthood

JIA category	Estimated relative frequency (in %)	Clinical features	To be considered in adult rheumatology
Oligoarthritis	35–45	Persistent oligoarthritis: <5 joints affected Extended oligoarthritis: >4 joints affected Most frequently affected joints: knee, ankle, elbow Anterior asymptomatic uveitis in 15–20% of cases	ANA can persist with inactive disease Flares may occur after years of remission, uveitis activity may not correlate with arthritis activity Insidious uveitis developing de novo in AYA is rare, but uveitis may flare after stopping MTX or adalimumab Acute phase reactants are often normal in active disease
Polyarthritis, RF-negative	15–25	>4 joints affected, often symmetric involvement of large and small joints Anterior asymptomatic uveitis in about 10% of cases	Can flare as oligoarthritis Arthritis may present with increasing joint restrictions and without relevant swelling Acute phase reactants can be normal in active disease, ANA can persist, anti-CCP antibodies are negative in >70%

Enthesitis-related arthritis	15–25	Asymmetric oligoarthritis in 60–80% (especially of large joints of lower limb) and/or enthesitis in 50–70% [4, 26] HLA-B27-positivity in 50%–70% Acute (symptomatic) anterior uveitis in about 10% Inflammatory back pain and/or sacroiliac joint tenderness in about one-third of the cases in early disease	Axial disease and sacroiliitis are rare at disease onset, but progressively appear months to years after the onset (in more than half of the patients after at least 5 years of disease) [4] Radiological alterations usually do not appear during adolescence, but incidence of defined ankylosing SpA increases over time (12–42% after 3–5 years, 19–90% after 9–11 years) [27]

(continued)

Table 7.1 (continued)

JIA category	Estimated relative frequency (in %)	Clinical features	To be considered in adult rheumatology
Psoriatic arthritis (PsA)	5–10	Arthritis (involvement of small joints, including distal interphalangeal joints) and psoriasis, dactylitis, nail abnormalities Two different phenotypic subpopulations, depending on age at onset: (i) early-onset PsA (<6 years) similar to early-onset oligoarticular and polyarticular JIA; often with dactylitis and small joint involvement. (ii) later-onset PsA, resembling SpA Anterior asymptomatic uveitis in 5–10% of cases with early PsA onset, symptomatic uveitis in late-onset PsA Family history of psoriasis in first-degree relative	Psoriasis in only 50% of cases, rash may appear years after arthritis Variable joint involvement, often polyarticular disease in adulthood

Systemic JIA	3–7	Arthritis, fever, rash Other manifestations: serositis, hepatosplenomegaly, lymphadenopathy Macrophage activation syndrome (MAS) in 6–10% No uveitis	Systemic signs may be absent in adolescence/adulthood, a severe polyarthritis may then be present MAS can occur at any stage of disease and can be triggered by infection or drugs
Polyarthritis, RF- positive	2–5	>4 joints affected, often symmetric involvement (especially hands and feet, shoulders and hips) Presence of rheumatoid factor IgM, anti-CCP antibodies Mostly adolescent females No uveitis	High risk of progressive disease course and of relapse after DMARD withdrawal Represents early onset of rheumatoid arthritis
Other (undifferentiated) arthritis	2–5	Overlap between categories Family history of psoriasis in first-degree relative RF may be present Uveitis (mostly asymptomatic) in 5–10%	

RF Rheumatoid factor, *ANA* antinuclear antibodies, *DMARD* disease modifying anti-rheumatic drugs, *MTX* methotrexate

different from that in children, AYA are more likely to have polyarticular JIA and enthesitis-related-arthritis (ERA). ERA and psoriatic arthritis (PsA) subsets can also be regarded as juvenile SpA, these patients usually meet the ASAS (Assessment of Spondylarthritis International Society) criteria for peripheral SpA [3]. In contrast to the traditional concept of SpA behind the ASAS classification, reactive arthritis and enteropathic arthritis are excluded from JIA in general and from ERA in particular.

Many young people will have ongoing care in adult clinics. They continue to have JIA and should not be reclassified in adulthood as having RA, because clinical phenotypes (with the exception of cases with spondyloarthritis and RF-positive polyarthritis), genetic background, laboratory findings (e.g., autoantibodies, inflammatory parameters), treatment responses and outcomes in JIA are different from adult-onset arthritis.

Presentation

About a third of all JIA cases start in adolescence. ERA, rheumatoid factor (RF)-positive polyarthritis and late onset of PsA have disease onset peaks in adolescence (Fig. 7.1). Clinical features of the different JIA categories are shown in Table 7.1. The juvenile form of SpA differs from that of adults by a more peripheral pattern of arthritis with less frequent axial disease, at least at disease onset (Table 7.1) [4].

Two-thirds of AYA with JIA are female and females predominate in all JIA categories, except in systemic JIA and ERA. AYA with JIA have been ill on average for more than 5 years. Having JIA burdens AYA in many ways [5]. Even though more than half have no functional limitations according to the Childhood Health Assessment Questionnaire (C-HAQ) [6], AYA report numerous functional limitations with far reaching consequences (Fig. 7.2).

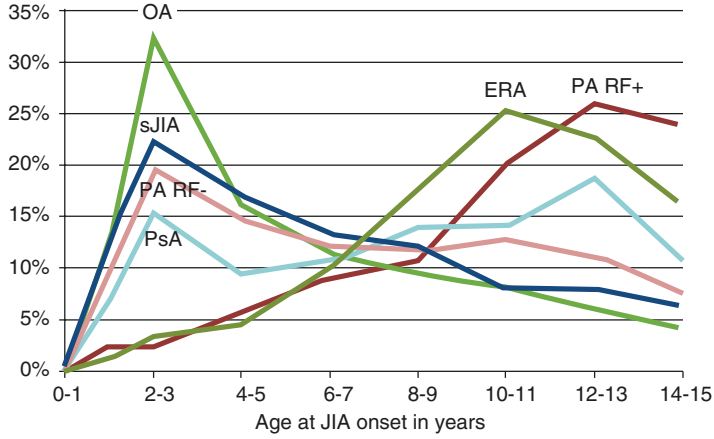

FIGURE 7.1 Age at onset of selected categories of juvenile idiopathic arthritis. Data were derived from 8935 patients with JIA recorded in the German paediatric rheumatologic database in 2016. ERA enthesitis-related arthritis, OA oligoarthritis, PA RF- rheumatoid factor-negative polyarthritis, PA RF+ rheumatoid factor-positive polyarthritis, sJIA systemic JIA, PsA psoriatic arthritis. (Figure modified according to Hochberg, Rheumatology, 7e – 2-volume set, Elsevier, Atlanta, USA, Copyright © 2018)

The inflammatory load of the disease often decreases over time. The vast majority of AYA in rheumatology care have low or no disease activity [6, 7].

Management

Specialised rheumatology multidisciplinary teams are integral to optimal management of JIA. Treatment includes drug therapy, physical therapy, occupational therapy and psychosocial support. Increasing evidence supports accelerated, early treatment pathways with a treatment goal of clinically inactive, or at least minimally active, disease.

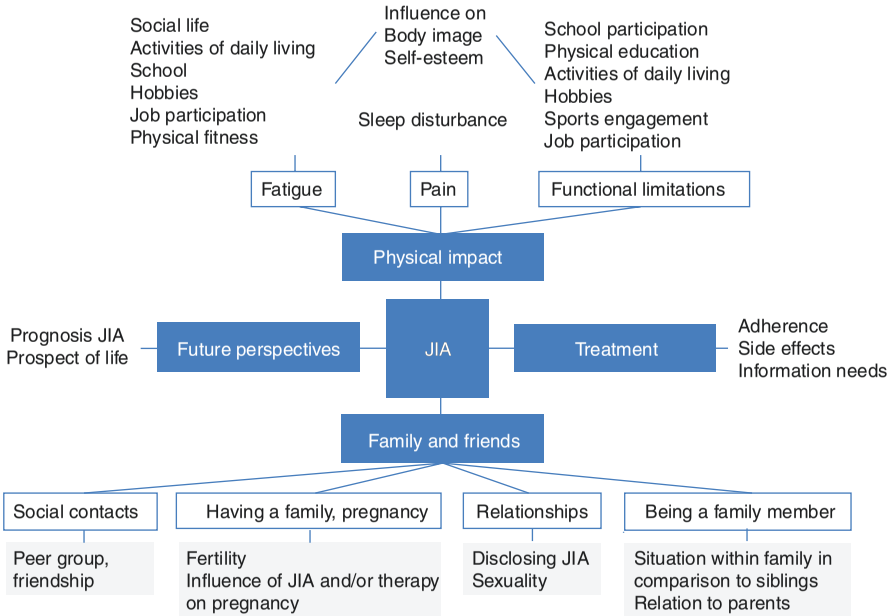

FIGURE 7.2 Areas of life on which JIA has a special impact from AYAs point of view (Eyckmans et al. [5], Fig. 1 adapted by permission from Springer Nature)

Such 'treat-to-target' approaches require standard evaluations of disease activity (see below).

Drug treatment is based on the use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional synthetic (cs) and biological (b) disease modifying anti-rheumatic drugs (DMARDs). NSAIDs and intra-articular corticosteroids (IAC) are the mainstay of treatment for oligoarthritis and used in all JIA categories in addition to other therapies as needed. IACs are usually administered under general anesthesia in children; adolescents must gradually get used to injections under local or inhaled nitrous oxide anesthesia, which is adult practice. Systemic corticosteroid use has become uncommon and is limited to severe polyarticular disease for which a short course of steroids may be advisable as bridging therapy before DMARDs reach their full effect. Given the side effects of steroids and their possible negative effect on AYA's body image, a prolonged course of steroids should be avoided particularly in the peripubertal phase when such side effects are often worse.

Methotrexate (MTX) is the most commonly used csDMARD in JIA. AYAs that fail to respond to or are intolerant to csDMARDs are candidates for bDMARDs. For the various JIA categories, different bDMARDs have been available (Table 7.2). There are no clinical trials in AYA to demonstrate efficacy or inform choice of drug or response to treatment.

Specific points in the management of AYA with JIA are summarised in Fig. 7.3 and discussed further in Chaps. 18 and 19.

Age-specific instruments should be used to measure treatment response and outcomes. Information about subjectively-perceived health has to be collected from AYA as parent-proxy ratings differ from self-assessments of functionality, pain, and global well-being [8].

Table 7.2 Drug therapy for the various JIA categories and JIA-associated uveitis

	Oligoarthritis	Polyarthritis (RF negative or positive)	Enthesitis-related arthritis	Psoriatic arthritis	Systemic arthritis	JIA-associated uveitis
First-line	NSAIDs ± intraarticular corticosteroids					Cortico-steroids locally (systemic)
		MTX	Polyarticular disease: cs DMARD (sulfasalazine, MTX)		IL-1- or IL-6-inhibitor or csDMARD	
Second-line	MTX	TNF-inhibitor IL-6-inhibitor	TNF-inhibitor	TNF-inhibitor	bDMARD change	MTX
Third-line	bDMARD: TNF-inhibitor IL-6 inhibitor	bDMARD change: TNF-inhibitor IL-6-inhibitor T cell co-stimulatory signal blocker	bDMARD change: TNF-inhibitor	bDMARD change: TNF-inhibitor IL-12/23-inhibitor	bDMARD change	Monoclonal anti-TNF antibody: adalimumab (infliximab, golimumab)

TNF-inhibitor (e.g., etanercept, adalimumab, golimumab, infliximab), IL-1 inhibitor (e.g., canakinumab, anakinra), IL-6 inhibitor (e.g., tocilizumab), IL-12/23- inhibitor (e.g., ustekinumab), T cell co-stimulatory signal blocker (e.g., abatacept) bDMARDs are often given in combination with MTX

• Provide developmentally appropriate care and empower young people with JIA by embedding health education and health promotion in consultations
• Be alert to flares (arthritis, uveitis) with breaks of treatment or after pregnancy, stop DMARDs only after about two years of clinically inactive disease
• Be aware of possible co-morbidities, regularly assess, treat, if necessary, and avoid future cardiovascular risk factors by giving advice on a healthy lifestyle (e.g., sports, healthy eating, avoiding nicotine and overweight)
• Provide anticipatory guidance, check vaccination status
• Provide counseling in regard to contraception and parenting
• Provide a planned, coordinated transitional care and transfer to a developmentally appropriate, proactive (e.g., explorative, appointment reminiscent) service provision in adult rheumatology

FIGURE 7.3 Key points in the management of AYA with JIA

Disease Status and Damage Measures

Core parameters to assess treatment response and disease activity include:

- Physician global assessment of disease activity (PGA, by visual analogue scale [VAS], numerical rating scale [NRS])
- Patient global assessment of well-being (by VAS, NRS)
- Functional ability up to the age of 17 by C-HAQ, from 18 years on by HAQ
- Active joint count (71-joint count)
- Restricted joint count
- Laboratory parameters (erythrocyte sedimentation rate [ESR], C-reactive protein)

Due to the specific joint involvement, disease activity in young people should be assessed by the juvenile arthritis disease activity score (JADAS) instead of the DAS-28. The use of DAS-28 instead of JADAS can lead to underestimation of disease activity and thus to under-treatment [9]. The JADAS is a simple sum score and includes four measures: PGA; patient global assessment of well-being; ESR, normalized to a 0–10 scale; and a count of active joints (10, 27 or 71, resulting in three JADAS-versions) [10]. A simplified three-variable version is available that does not include the acute-phase reactant (clinical JADAS [cJADAS]). For AYAs with ERA, in addition the Juvenile Spondyloarthritis Disease Activity Index (JSpADA) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) are evaluated tools for disease activity assessment.

Damage or permanent alterations in joint structures or extra-articular organ/systems as a result of JIA or its treatment can be evaluated by the juvenile arthritis damage index

Table 7.3 Instruments for assessing AYA-reported outcomes

Patient-reported outcomes	Examples of instruments
Health-related quality of life (HRQoL)	Ages 10–17 years: Pediatric Quality of Life Inventory (PedsQL) Generic Core Module and PedsQL Rheumatology Module Child Health Questionnaire (CHQ) Quality of My Life Questionnaire (QoMLQ) Paediatric Rheumatology Quality of Life Scale (PRQL) Juvenile Arthritis Quality of Life Questionnaire (JAQQ) Age > 17 years: Medical Outcomes Short-Form 36 (SF-36)
Overall well-being	VAS/NRS
Pain	VAS/NRS
Fatigue	PedsQL Multidimensional Fatigue Scale (ages 10–18 years)
Multidimensional outcome	Juvenile Arthritis Multidimensional Assessment Report (JAMAR) (ages 10–18 years)

(JADI). Instruments for assessing patient-reported outcomes are shown in Table 7.3.

AYA report more frequently about pain than children with JIA, but less often than patients with adult inflammatory joint disease. Approximately half of AYA with JIA report about pain, approximately 40% have functional limitations by HAQ [6, 11].

Morbidity and Extra Articular Manifestations of JIA

Anterior uveitis is the most frequent extra-articular manifestation of JIA. AYA with early onset of oligoarthritis, RF-negative polyarthritis and PsA and ANA (antinuclear antibody) positivity are at particular risk during the first 4 years of JIA. In these AYAs, asymptomatic uveitis flares may even occur in adolescence/young adulthood. AYAs with ERA and late-onset PsA may experience an acute (symptomatic) anterior uveitis.

Other extra-articular manifestations of ERA include inflammatory bowel disease, cardiac (e.g., aortic insufficiency or conduction disorders) and pulmonary manifestations (e.g., upper lobe fibrosis), of which the last two are very rare [12]. In RF-positive polyarthritis, less severe extra-articular manifestations (e.g., rheumatoid nodules) and severe (e.g., vasculitis, interstitial lung disease) may occur.

Altogether, AYA with JIA are more likely to develop depressive symptoms and anxieties than their peers without a chronic illness [13]. In addition, they are at increased risk of premature atherosclerosis and early-onset cardiovascular disease [14] and thus require anticipatory guidance to promote cardiovascular health (see Fig. 7.3).

Sexuality, Fertility and Pregnancy

Individuals with JIA show similar attitude to sexual activity, contraception, and wish for children [15, 16].

Fertility is not impaired in females with JIA, but fecundity was found to be reduced.

Women with JIA have higher rates of instrumental delivery and are at higher risks for adverse pregnancy and neonatal outcomes, such as preterm delivery, preeclampsia, and small for gestational age (SGA) infants [17]. Quiescent or minimal active JIA is not reactivated by pregnancy [18] and active disease at conception ameliorates in about 60% in pregnancy [19]. Within a few weeks after delivery, disease activity increases or DMARD treatment is required in approximately as many cases as were treated before pregnancy [20]. Developmentally appropriate counseling regarding contraception and pregnancy monitoring by an obstetrician and rheumatologist is important for AYA with JIA.

Prognosis

After 10 years of disease, less than 50% of patients have achieved a drug-free remission [20]. The probability of drug-free remission varies significantly with disease-onset type, being best for oligoarticular JIA and worst for polyarticular JIA (Table 7.4).

Apart from drug-free remission, all other clinical outcomes have dramatically improved in the biologic treatment era. Most AYA have a good functional capacity. Articular damage (most often in hip, wrist, and temporomandibular joints) is the most important component of global damage. However, an arthroplasty is rarely needed in young adulthood (<2%).

The most frequent extra-articular damage components are

- ocular damage
- growth failure (linear growth failure in up to 10% and localized growth abnormalities, such as limb length discrepancies and micrognathia)
- muscle atrophy and decreased bone mass.

Table 7.4 Long-term (≥7 years) outcomes of various JIA categories [6, 11, 28]

JIA category	No drug-free remission, %	Functional limitations[a], %	Damage[b], %	Other possible adverse outcomes
Oligoarthritis, persistent	20–50	15–30	15	Persisting active uveitis, ocular sequelae, leg-length inequality
Oligoarthritis, extended	50–80	40–50	35	Persisting active uveitis, ocular sequelae, leg-length inequality
Polyarthritis, RF- negative	50–85	40–60	15–30	Linear growth failure, mandibular dysfunction, decreased bone mass
Enthesitis-related arthritis	50–85	20–50	20–30	Ankylosing spondylitis, hip damage
Psoriatic arthritis (PsA)	45–80	30–50	10–50	Poorer physical health than oligo- or polyarthritis
Systemic JIA	20–30	25–60	25–40	Decreased bone mass, Linear growth failure, Hip damage, Cardiovascular risk factors
Polyarthritis, RF- positive	70–100	50–70	30–100	Severe joint destruction

[a]Health Assessment Questionnaire >0
[b]Juvenile Arthritis Damage Index >0

Ocular sequelae mainly develop as consequences of uveitis (in at least one-fifth of affected patients) [21]. Complications most frequently include band keratopathy, cataract, posterior synechiae, maculopathy, and ocular hypertension [22]. A significant visual loss results in 10–30% of patients. Blindness due to uveitis still occurs.

Reduced muscle mass and force contribute to bone loss. Abnormalities in body composition, i.e. a decreased lean body mass, an increased fat mass, and a reduced bone mineral density have been documented in AYA with JIA [23] (see Chap. 16).

AYA's academic achievement is comparable to that of the general population. Conflicting data on employment rates exist, from transitioning into employment at an earlier age than peers without arthritis [24] to lower employment rates due to unemployment, longer training periods or early retirement. Young people with JIA judge their quality of life still lower than age- and sex-matched controls, but in recent studies this is usually limited to physical health [25].

Summary

JIA in adolescence and young adulthood is characterised by specific clinical manifestations and requires a specific assessment and management. Rheumatologists need to be aware of the wide range of issues, including transitional care, sexual health and pregnancy, education and employment, potential adverse JIA outcomes and long-term comorbidities. A holistic life course approach to care for AYA is important to set the course for the future.

Key Management Points

1. Juvenile Idiopathic arthritis is the most common chronic inflammatory rheumatic disease in adolescents and young adults
2. JIA is commonly a lifelong disease: lack of long term remission into adulthood is reported to vary between 20% and 100% of young people depending on category of JIA
3. JIA specific rather than adult disease specific activity scores should be used when available
4. Morbidity of JIA includes the impact the disease has on psychological, social, educational and vocational adolescent and young adult development

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