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Adult outcomes of childhood-onset rheumatic diseases

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Abstract

A number of studies published over the past 10 years have examined the long-term health, functional and quality of life outcomes of adults with childhood-onset rheumatic diseases such as juvenile idiopathic arthritis, systemic lupus erythematosus, juvenile dermatomyositis and localized scleroderma. As increasing numbers of patients with these conditions survive into adulthood, understanding the adult outcomes of these pediatric conditions has become ever-more important. Identifying modifiable risk factors for poor outcomes is vital to improving care for these patients. In addition, as these conditions and their treatments can affect cardiovascular health, bone health and fertility, particular attention needs to be paid to these outcomes. Preparing patients and their families for a successful transition from pediatric to adult rheumatology care is an important first-step in the long-term management strategy for this expanding patient population.

Introduction

Characterization of the adult outcomes of childhood-onset rheumatic diseases and identification of the modifiable risk factors for poor outcomes are essential to improving care for this expanding patient population. Although some of these conditions were once associated with considerable rates of early mortality, the majority of patients with childhood-onset rheumatic disease now live well into adulthood. Over the past 10 years, several studies have examined the outcomes of adults with childhood-onset rheumatic disease, and the impact of these conditions on long-term health, function and quality of life. Findings from these studies are relevant to both pediatric and adult rheumatologists, who will be caring for these patients both in childhood and as they age into adulthood.

This Review summarizes the published literature on the adult outcomes of childhood-onset rheumatic disease, with a focus on the chronic rheumatic diseases that are most commonly seen by pediatric rheumatologists, including systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM) and localized scleroderma. The adult outcomes of oligoarticular,

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Author contributions

A. Hersh researched data for and wrote the article. All authors made substantial contributions to discussion of the content and to review/editing of the manuscript before submission.

Competing interests

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polyarticular and systemic-onset juvenile idiopathic arthritis (JIA) were discussed in a recent review by Minden,¹ so are not included here. As the outcomes of enthesitis-related arthritis (ERA) and psoriatic arthritis (PsA) were not specifically discussed in that review, these conditions are included here (Table 1). In addition, this Review highlights several understudied clinical outcomes (cardiovascular health, bone health and fertility) that are relevant to childhood-onset rheumatic diseases, and discusses the importance of a comprehensive transition-of-care process from pediatric to adult rheumatology as a way to ensure ongoing care and improved outcomes for this vulnerable population.

Systemic lupus erythematosus

Approximately 15–20% of patients with SLE are diagnosed during childhood.² Compared with adult-onset SLE, childhood-onset SLE typically has a more aggressive course, with higher rates of organ involvement, leading to a greater need for potentially toxic immunosuppressive medications over a longer disease duration.^{3–9} This combination of factors puts patients with childhood-onset SLE at increased risk of cumulative disease damage, which, according to some studies, is a strong predictor of early morbidity and mortality.¹⁰

Few studies have described the clinical outcomes of patients with childhood-onset SLE once they reach adulthood. In a retrospective study by Chalom and colleagues,¹¹ 29 adults with childhood-onset SLE were assessed after a mean disease duration of 13 years. At follow-up, 15 patients (51.7%) were found to have active disease, defined as an SLE disease activity index (SLEDAI) score >4. In addition, almost half of the patients had impairment of organ systems, and the 15-year survival rate was 79.5%.

With the use of data from the University of California Lupus Outcomes Study (LOS), we examined the outcomes of a cohort of adult patients with childhood-onset SLE (mean age 33 years [range 19–63 years], mean disease duration 19.5 years [range 4–51 years]).⁶ 56% of patients reported a history of renal disease related to their SLE, 48% had undergone renal biopsy, 19% required dialysis, and 12% had a history of renal transplant. Seizures occurred in 24% of patients, and 8% reported a history of myocardial infarction. With regard to disease activity, approximately 24% of patients reported a disease flare within 3 months of their annual follow-up interview and 68% were taking steroids at the time of follow-up.

Although the 10-year survival rate has improved dramatically for patients with childhood-onset SLE over the past several decades, this group remains at high risk for early mortality in their young adult years.^{7,12–14} In the LOS, 12% of the childhood-onset SLE cohort died during the first 5 years of the study's follow-up period. The median age at death was 33 years (range 19–49 years), and the mean disease duration at the time of death was 16 years (range 5–33 years). Childhood-onset SLE was a strong predictor of mortality in the entire LOS cohort (hazard ratio 3.4, 95% CI 1.3–8.6), which included patients with both childhood-onset and adult-onset SLE.¹⁵

Data on the psychosocial and quality of life outcomes for patients with childhood-onset SLE are limited. In the cohort described by Chalom *et al.*,¹¹ 24 (88.9%) of 27 patients completed high school, and 15 (55%) had either started or completed college. In the LOS, 95% of adults with childhood-onset SLE completed high school and 85% pursued a college education (A. Hersh, unpublished data). The majority of those in the Chalom cohort and the LOS were attending school or were employed (either full-time or part-time); however, approximately 20% of patients in both cohorts were not working (the majority of these in the LOS were described as being 'unable to work')—presumably owing to disease-related disability, as this population is not of retirement age. In the Chalom cohort,¹¹ the Short-

Form 36 Physical Component Scale (SF-36 PCS) scores were significantly lower for patients with childhood-onset SLE compared with the national mean.

Juvenile dermatomyositis

JDM has an annual incidence of 0.3–1.1 per 100,000 in the USA, and it is estimated that 15–20% of all cases of dermatomyositis have onset during childhood.²

A case–control study assessed the disease activity, organ damage, muscle strength and physical health of 59 Norwegian patients with JDM, of whom 39 (66%) were aged 18 years at the time of study follow-up at a median of 16.8 years (range 2.0–38.1 years) after disease onset.¹⁶ At follow-up, 42% of the cohort had elevated levels of muscle enzymes and 61% had a disease activity score (DAS) ≥ 3 (mean total DAS 4.75 [range 0–13]). The DAS consists of skin (range 0–9) and muscle (range 0–11) components, and a low score correlates with low disease activity. 42% of JDM patients had muscle weakness (compared with 3% of age-matched and sex-matched controls) as measured by the manual muscle test. Similar results were observed when the Childhood Myositis Assessment Scale—a performance-based instrument that evaluates muscle strength, physical function and endurance in children with JDM—was used. 90% of patients had a cumulative muscle damage index (MDI) score ≥ 1 , indicating damage in at least one organ system, most commonly the skin, muscular, skeletal, endocrine and pulmonary systems. The mean MDI score at follow-up was 4.2 (range 0–13). MRI of the thigh muscles revealed evidence of muscle edema and active inflammatory activity in 5 (9%) of 58 patients with JDM, whereas 30 (52%) had MRI-detected evidence of muscle damage. Over one-third of the cohort had calcinosis. Compared with patients followed for <10 years, patients followed for >10 years had higher rates of MRI-detected muscle damage. Early predictors of muscle weakness and muscle damage at follow-up included evidence of muscle damage and sustained muscle and skin disease activity at 1 year post-diagnosis.

In this study,¹⁶ Health Assessment Questionnaire (HAQ) scores were used as a measure of disability in the patients who were aged 18 years at the time of study follow-up ($n = 39$). 14 (36%) of these patients had HAQ scores >0 , which correlated moderately with the MDI score. Median SF-36 PCS scores were slightly lower in patients with JDM compared with healthy controls (53.9 versus 56.9, $P = 0.014$).

Localized scleroderma

According to the classification system developed by Peterson and colleagues,¹⁷ localized scleroderma can be subdivided into five types: plaque morphea, generalized morphea, bullous morphea, linear morphea/scleroderma and deep morphea. In the general population, the annual incidence of localized scleroderma is estimated to be 2.7 per 100,000. Although the incidence of pediatric localized scleroderma overall is not known, the majority of cases of linear scleroderma occur during childhood (mean age at onset 7.9 years).¹⁸ Patients with localized—and particularly linear—scleroderma are often co-managed by dermatologists and rheumatologists, and treatment might include immunosuppressive medications, such as systemic corticosteroids and methotrexate.¹⁹ While it is believed that most patients will enter spontaneous remission after 3–5 years of disease activity, those with the linear subtype have a considerable risk of developing physical disability.²⁰ In addition, cosmetic changes, particularly if the skin lesions involve the head and neck, can markedly affect quality of life.²¹

Little is known about the adult outcomes of childhood-onset localized scleroderma syndromes. Saxton-Daniels and Jacobse²² examined the adult outcomes of 27 patients diagnosed with morphea during childhood. The median age at study enrollment was 26

years, and the median age at morphea onset was 13 years. Morphea subtypes included linear scleroderma ($n = 20$), generalized morphea ($n = 5$) and plaque morphea ($n = 2$). 15 of the patients (all with linear scleroderma) had permanent skin or musculoskeletal sequelae, including limited range of motion, deep atrophy, limb length discrepancy and joint contracture. Across the entire cohort, 24 (89%) of 27 patients developed “new or expanding” lesions over time, with a time to recurrence from initial disease onset of 6–18 years. Given that the localized sclerodermas are thought to remit spontaneously, the high rate of disease progression is somewhat unexpected, and suggests the possibility of an enrollment bias in the study population. Nonetheless, as the authors conclude, there could be a subset of patients with localized scleroderma who go on to have active disease and need careful long-term follow-up. Better prospective studies are needed to identify this population and capture their outcomes.

Enthesitis-related arthritis

ERA accounts for approximately 11–16% of all cases of JIA.² Reported remission rates of ERA following treatment and prior to adulthood range from 17% to 37%, and the risk of developing sacroiliitis within the first 5 years after diagnosis ranges from 6% to approximately 50% across studies.^{23–25} A retrospective study by Flato *et al.*²⁶ examined the adult outcomes of 55 children with ERA (85% of whom were HLAB27 positive) at medians of 15.3 years and 23.0 years after diagnosis. After 15 years, the remission rate was 44%, and 35% of patients had evidence of radiographic sacroiliitis; after 23 years, 18 (45%) of 40 of patients were still receiving anti rheumatic drugs. Half of the cohort had an HAQ score >0 after a median disease duration of 15.3 years. Mean HAQ scores were significantly higher, and SF-36 scores significantly lower, in patients with ERA compared with age-matched and sex-matched control patients with oligoarticular or polyarticular JIA. A study of long-term JIA outcomes by Minden *et al.*²⁷ included 33 HLAB27-positive patients with ERA who were assessed at a median of 11 years (range 4–15 years) after diagnosis. At the time of assessment, the remission rate was 18%, and 76% reported current inflammatory back pain; 39% and 36% had definite and possible ankylosing spondylitis, respectively. 24% of patients developed uveitis during their disease course. The adjusted mean HAQ score among patients with ERA in this study was 0.16.

Psoriatic arthritis

PsA was included as a category of JIA in the 1997 ILAR (International League Against Rheumatism) classification.²⁸ Approximately 7% of JIA cases are classified as PsA.² A study by Flato *et al.*²⁹ described the adult outcomes of 31 children diagnosed with PsA between 1980 and 1985, and compared their outcomes to patients with oligoarticular or polyarticular JIA of a similar disease duration (median 14.9 years, mean age at follow-up 23.3 ± 3.9 years). At the time of follow-up, 17 (55%) of the patients with PsA had achieved remission without medication for at least 12 months; however, 10 patients (33%) were still receiving a DMARD and/or a tumor necrosis factor (TNF) antagonist for the treatment of active disease. Radiographic erosions were identified in 7 patients (23%). 14 (45%) of the PsA patients had an HAQ score >0.12 (indicating mild disability) compared with 30% of the cohort with oligoarticular or polyarticular JIA ($P = 0.098$), and 2 patients with PsA had HAQ scores between 1.25 and 2.00 (indicating moderate disability). SF-36 PCS scores declined with increased PsA duration, and, at a median disease duration of 22.8 years, SF-36 PCS scores were significantly lower in the PsA group than in patients with oligoarticular JIA ($P = 0.045$) and polyarticular JIA ($P = 0.050$). This study suggests that a substantial proportion of patients with juvenile PsA will continue to require DMARD or anti-TNF therapy into adulthood, and, if inadequately treated, PsA has the potential to cause significant levels of damage and disability over time.

Common morbidities

Given the substantial improvement in outcomes for patients with pediatric rheumatic diseases over the past several decades, there has been a shift in the literature from measuring short-term morbidity and mortality to examining long-term outcomes and preventing the adult consequences of childhood-onset disease. Particular attention has been paid to sequelae that can manifest as a result of the disease itself or as a consequence of treatment, such as cardiovascular health, bone health and prevention of osteoporosis, and preservation of fertility. Each of these areas is mentioned here briefly.

Cardiovascular health

It is well documented that adults with rheumatoid arthritis and SLE are at increased risk of premature atherosclerosis and early-onset cardiovascular disease, and cardiovascular events are well-known causes of early mortality in these populations.^{30–32} The etiology is probably multifactorial, attributable to manifestations of the disease itself (such as chronic inflammation, chronic hypertension, renal disease or abnormal lipid profiles), adverse effects of medication (such as steroids and NSAIDs) and lifestyle issues (such as decreased physical activity due to disease-related disability). Although patients with certain subtypes of JIA (for example, rheumatoid-factor- positive polyarticular JIA) or childhood-onset SLE are likely to be at an increased risk of early-onset cardiovascular disease, and could benefit from interventions to prevent these outcomes, the exact extent of this risk is unknown. Previously identified risk factors for early-onset cardiovascular disease in pediatric SLE include lymphopenia and nephrotic-range proteinuria.^{33,34}

Characterization of the risk of early-onset cardiovascular disease and the development of strategies to prevent early mortality from this condition have become priorities for the pediatric rheumatology community, and provided the rationale for the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial.^{35–37} The APPLE trial was a prospective, multicenter, randomized controlled study involving 221 children and adolescents with SLE, and was designed to determine the effectiveness of atorvastatin for preventing premature atherosclerosis. The primary outcome measure was change in carotid intima–media thickness (CIMT). The baseline data showed that increased CIMT was associated with longer disease duration, suggesting that patients with longstanding disease may be at greater risk of developing premature atherosclerosis.³⁶ Preliminary data from the APPLE trial demonstrated slower rates of CIMT increase among patients treated with atorvastatin, but the difference in CIMT between the atorvastatin and placebo groups after short-term follow-up (36 months) was not statistically significant.³⁷ Prospective studies are needed to identify those patients at risk of early-onset cardiovascular morbidity and to develop strategies to prevent these potentially life-threatening events.

Bone health and prevention of osteoporosis

The etiology of low bone mineral density (BMD) among patients with chronic inflammatory conditions is also multifactorial, and includes the direct effects of chronic inflammation on bone turnover (such as increased osteoclastogenesis and accelerated bone resorption), adverse effects of medications (such as steroids), vitamin D deficiency and decreased participation in weight-bearing activities due to disease-related disability. Most importantly, acquisition of a chronic inflammatory illness during childhood leads to an interruption of the normal accumulation of bone mass in a critical period of growth and development.³⁸ Studies examining the risk of low BMD in adults with JIA have demonstrated that those with inactive JIA have lower BMD than healthy adults—a difference that is most prominent when measuring BMD in the whole body and femoral neck (versus the lumbar spine only) and among women.^{39,40} This difference is even more marked among adult patients with

active JIA. The findings are similar for young adults with SLE, in whom there is an association between increased cumulative steroid dose and decreased BMD.⁴¹ Additional studies are needed to determine whether decreased BMD leads to an increased risk of sentinel events, such as pathologic fractures.

Fertility

Preservation of fertility is an area of particular concern to patients. Studies have suggested that patients with JIA, JDM or childhood-onset SLE may be at risk for decreased reproductive fitness as a consequence of their chronic inflammatory condition or the medications used to treat it (for example, alkylating agents such as cyclophosphamide), although the true risk of infertility in these populations is not known.^{42,43} Several other studies have indicated that pediatric SLE patients are at an increased risk of low follicular/ovarian reserve—a risk that increases substantially with exposure to cyclophosphamide.^{44–46} Studies to determine the best strategies for preserving fertility in at-risk patients are ongoing.

Transition of care

Given the chronicity of these diseases and the potential for cumulative morbidity and early mortality related to the conditions and their treatment, it is essential that pediatric patients diagnosed with a chronic disease during childhood are adequately prepared to independently manage their disease as they make the transition from adolescence to adulthood. A revealing qualitative study by Ostlie and colleagues,⁴⁷ which included focus groups of adolescents with JIA and health professionals, found that both the patients and the health-care providers desired that patients be ‘enabled’ to achieve autonomy in the management of their health. In addition, both groups perceived the existing transition and transfer process to adult care to be inadequate.

Other studies have identified difficulties in transferring pediatric rheumatology patients to adult care. In a Canadian study of patients with JIA, Hazel *et al.*⁴⁸ found that, despite a coordinated transfer process, only 48% of patients in their clinic population successfully transferred care from pediatric to adult rheumatology; a patient's transfer of care was classified as unsuccessful if they either never made contact with the adult rheumatologist (who was identified for the patient prior to transfer) or if they were lost to follow-up within 2 years of transfer. Hilderson *et al.*⁴⁹ described the outcomes of 44 Belgian adolescents with JIA who were transferred from pediatric to adult rheumatology care, and found that 13 patients (29.5%) were no longer in medical follow-up and 5 patients (11.4%) reported persistent pain. This led the authors to conclude that “the disease of patients leaving specialized rheumatology care is not necessarily controlled”.

We examined the change in disease status, treatment and health care utilization among young adults transferring from pediatric to adult rheumatology care at the University of California, San Francisco.⁵⁰ Of 31 patients with a chronic rheumatic disease, nearly 30% were hospitalized for disease treatment or management of flares in the year prior to transfer, and 58% had active disease at the time of transfer. During the first year after they transferred care, almost 30% of patients experienced an increase in disease activity, and one patient died. These data suggest that the transition period from pediatric to adult care is a vulnerable time for patients with chronic rheumatic disease. Although the full impact of unsuccessful care transfer on long-term outcomes is not yet known, it is likely that inadequate follow-up leads to worse outcomes.

Conclusions

Many children diagnosed with a rheumatic disease will continue to have active disease, or experience sequelae from their disease, into adulthood. For this reason, it is essential to assess the adult outcomes and long-term health and quality-of-life impacts of childhood-onset rheumatic diseases in order to understand the modifiable risk factors for poor outcomes. Establishing permanent mechanisms with which to follow pediatric patients into adulthood, such as long-term patient registries, is particularly important as the treatment options—and, subsequently, the approach to treatment—evolve over the next several years to decades. For example, we know that early treatment with biologic agents controls active disease in patients with polyarticular JIA, but does it prevent long-term damage and disability? Are there any long-term risks associated with exposure to these medications during childhood? These questions can be best answered through comprehensive, prospective, longitudinal studies that measure a wide array of clinical and functional outcomes.

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Learning objectives

Upon completion of this activity, participants should be able to:

1. Analyze adult outcomes of specific childhood-onset rheumatic diseases.
2. Evaluate broad health outcomes associated with childhood-onset rheumatic diseases.
3. Describe the transition of care between adolescence and adulthood among patients with rheumatic disease.

Key points

- Understanding the long-term morbidity and mortality of childhood-onset rheumatic diseases is critical to improving outcomes
- Existing studies have demonstrated that patients with childhood-onset rheumatic diseases are at increased risk of early morbidity and disability
- It is essential that pediatric patients with a chronic rheumatic disease have a seamless transition from pediatric to adult rheumatology care
- Prospective, longitudinal studies are needed to better characterize the outcomes of childhood-onset rheumatic diseases

Review criteria

The MEDLINE database was searched for abstracts published since 2000 using the search terms “long-term outcomes”, “adult-outcomes”, “morbidity” and “mortality” with each of the diagnoses presented in the manuscript. In addition, studies of specific outcomes related to the childhood-onset rheumatic diseases were identified using the search terms “cardiac” and “cardiovascular”, “bone mineral density”, “osteoporosis” and “osteopenia”, and “fertility” and “pregnancy”. Finally, a search was conducted to identify articles about “transition” or “transfer of care” in the pediatric rheumatic diseases. Non-English-language papers, single case reports, review articles and editorials were excluded. Full-text articles were then retrieved for further review.

Table 1

Studies of adult outcomes in childhood-onset rheumatic diseases

Study	Country	Adult patients assessed (n)	Median disease duration (years)	Patients with active disease (%)	Definition of disease activity
<i>Systemic lupus erythematosus</i>					
Chalom <i>et al.</i> (2004) ¹¹	USA	29	13	52	SLEDAI score >4
Hersh <i>et al.</i> (2009) ⁶	USA	90	16.5 (mean)	68	Receiving prednisone therapy
<i>Juvenile dermatomyositis</i>					
Sanner <i>et al.</i> (2009) ¹⁶	Norway	39 (66% of total cohort)	16.8	61	DAS 3
<i>Linear scleroderma</i>					
Saxton-Daniels & Jacobse (2010) ²²	USA	27	13	89	Presence of "new or expanding lesions over time"
<i>Enthesitis-related arthritis</i>					
Flato <i>et al.</i> (2006) ²⁶	Norway	55	15	56	Clinical assessment of active arthritis
Minden <i>et al.</i> (2002) ²⁷	Germany	33	11	82	Clinical assessment of active arthritis
<i>Psoriatic arthritis</i>					
Flato <i>et al.</i> (2009) ²⁹	Norway	31	14.9	45	Clinical assessment of active arthritis

Abbreviations: DAS, disease activity score; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.