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Pediatric Autoimmune Connective Tissue Diseases: An Update on Disease Characteristics, Associations, and Management

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Abstract There are several different autoimmune connective tissue diseases that may occur during childhood, each with variable clinical presentations. Gaining familiarity with these disorders and their systemic associations is important, because early therapy may help prevent potentially serious and permanent sequelae. In this review, we discuss the various juvenile autoimmune connective tissue diseases, highlight their clinical manifestations and potential complications, and provide an update on treatment options. In addition, we underline the differences between juvenile and adult-onset autoimmune connective tissue diseases.

Keywords Juvenile autoimmune connective tissue disease · Juvenile dermatomyositis · Juvenile morphea · Juvenile systemic sclerosis · Juvenile lupus erythematosus · Neonatal lupus erythematosus

Introduction

A wide array of autoimmune connective tissue diseases (CTD) affecting the skin can occur in childhood; amongst the more common are cutaneous lupus erythematosus, morphea, and dermatomyositis. Each of these diseases has unique cutaneous manifestations and potential associated complications, and characteristics of each may differ from their adult-onset counterparts [1•, 2, 3]. Although the overall incidence of autoimmune CTD is rare in the pediatric population, early recognition of such conditions is important given the potential for associated systemic complications and the fact that early initiation of therapy may help prevent joint contractures, functional disabilities, and cosmetic disfigurement [2, 4].

Cutaneous Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) is best categorized as acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), or chronic cutaneous lupus erythematosus (CCLE). Each of these forms has been reported in childhood, with CCLE being the most common, and SCLE and ACLE occurring only rarely in the pediatric population [1•]. Notably, disease characteristics of each subtype may differ in children compared with patients with adult-onset CLE.

In childhood, ACLE manifests similarly as in adults, generally presenting with erythematous and edematous plaques involving the malar cheeks. In both the pediatric and adult populations, ACLE is strongly associated with photosensitivity and systemic disease [1•, 5]. A recent review of 53 children with CLE found that of the 13 patients affected by the ACLE subtype, all met criteria for SLE, reinforcing that pediatric ACLE is strongly associated with systemic disease [1•]. Subacute cutaneous lupus also is commonly associated with systemic disease, with approximately 50 % of all SCLE patients meeting criteria for SLE [6]. First described by Sontheimer and colleagues in 1979, SCLE characteristically manifests with annular or psoriasiform erythematous plaques that heal without scarring and often is associated with musculoskeletal and constitutional symptoms [6]. In childhood, SCLE is

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exceedingly rare, with only 15 cases of childhood-onset SCLE reported to date [1•, 7]. A recent review by Dickey and colleagues noted that only 6 of 53 patients with CLE had the SCLE subtype [1•]. Compared with the adult SCLE population, children had a higher rate of progression to SLE (83 %) and were more likely to have lesions below the waist than adults with SCLE [1•].

Discoid lupus erythematosus, the most common subtype of CLE in childhood, manifests with erythematous scaly plaques and follicular plugging, often leading to dyspigmentation, atrophic scarring, alopecia, and potential disfigurement. Despite being the most common form of CLE to occur in childhood, DLE is much less common in children than in adults, with only approximately 85 cases of juvenile DLE reported to date [8, 9]. One review found that of patients with juvenile SLE, 19 % had DLE [10], which was higher than the 4-10 % incidence noted in previous studies [11, 12]. In terms of the number of patients with DLE presenting during childhood, a review of 224 patients with DLE noted that only 7 % of patients developed DLE during childhood, with less than 3 % presenting at younger than age 10 years [13]. However, it is worth noting that childhood DLE can develop at any age, and a more recent study suggests that more than 50 % of patients may present at younger than age 10 years [9]. In addition, rare cases of DLE have been reported in infants [14].

Acknowledging juvenile DLE as a subset distinct from adult DLE is important, as evidence suggests that aspects of juvenile DLE differ from adult-onset disease. For instance, although some studies have noted a female predominance in juvenile DLE similar to that seen in the adult population [15], several reports of juvenile DLE note an equal sex distribution [9, 13, 16]. Most recently, a review of 53 children with cutaneous lupus, 17 of whom had CCLE, reported a female predominance in postpubertal patients with CCLE, whereas in patients younger than age 12 years, no sex-predominant distribution was noted [1•]. In addition, photosensitivity rates are estimated to be approximately 40 % in patients with juvenile DLE [15, 16] compared with approximately 70 % in patients with adult DLE [17].

Perhaps the most important distinction between adult and juvenile DLE is that most [15, 16, 18, 19], but not all, studies [13] have reported a higher incidence of systemic disease in patients with juvenile compared with adult DLE. In 1993, George et al. reported that 5 of 8 patients with juvenile DLE went on to develop SLE, suggesting that rates of progression to SLE may be higher in pediatric populations [18]. Subsequent studies have estimated that approximately 25 % of pediatric patients with DLE will progress to SLE [16, 20], in contrast to the approximately 5-17 % rate of progression noted in adults [21, 22, 23•]. Although no established methods exist to predict reliably which DLE patients will progress to SLE, certain factors may occur more frequently in patients with associated SLE. One retrospective review of 34 children with DLE noted that only 19.2 % of patients without associated SLE had a positive antinuclear antibody (ANA) test, most often with low-titers (range: 1:40-1:160), whereas 87.5 % of patients with associated SLE had positive ANAs, usually of high-titers [15]. In addition, children with disseminated DLE were more likely to have associated SLE compared with patients with localized DLE [15]. This latter finding, however, has not been consistent across all studies, and it is known that patients with localized DLE, which most often occurs on the head and neck, also may develop SLE [15, 16, 20].

Management of DLE in children is similar to that in adults, with the goal of early intervention to prevent dyspigmentation, scarring, alopecia, and atrophy. Strict photoprotection, along with topical and/or intralesional corticosteroids are considered first-line [24], and in most cases, the addition of antimalarial therapy is warranted. If used at appropriate, ideal-body-weight-based doses (i.e., hydroxychloroquine (HCQ) 5 mg/kg/day or chloroquine 3.5 mg/kg/day), antimalarials are thought to be safe for use in children, with nausea and vomiting being the most common side effects [25]. Although the risk of ocular toxicity in children is low, regular ophthalmologic examinations are recommended for all patients treated with antimalarials [26]. In children with DLE refractory to antimalarials, systemic corticosteroids often are administered; however, consideration should be given to the use of steroid-sparing agents, such as methotrexate, in order to avoid steroid-related side effects [16, 27]. Rare reports of topical calcineurin inhibitors [28] and thalidomide [20] for juvenile DLE exist, and oral dapsone has been helpful in rare cases of linear cutaneous lupus [29]. In addition, because of a reported link between DLE and X-linked chronic granulomatous disease (CGD), screening for CGD has been recommended for female patients with DLE who experience or have a family history of recurrent suppurative infections [30].

Neonatal Lupus

Neonatal lupus erythematosus (NLE) is a condition in which maternal immunoglobulin G antibodies transfer to the fetus via the placenta. The condition is most commonly reported in association with anti-SSa/Ro autoantibodies, although anti-SSb/La, and rarely ribonucleoprotein (RNP) antibodies also may be associated with NLE [31–35]. Cutaneous lesions are the most common manifestation of NLE, and patients with NLE due to RNP antibodies generally have disease limited to the skin [32–34]. Photosensitive, erythematous patches and plaques, which often are annular or polycyclic in nature, are the most common cutaneous manifestations of NLE, although rarely lesions may be bullous, crusted, petechial, targetoid, or discoid, and cutis marmorata also may be present [31, 33, 36–38]. Because of their photosensitive nature, lesions of NLE may first be noted after phototherapy for neonatal

jaundice [33, 39]. Cutaneous NLE most commonly affects the face, periorbital skin, and scalp, but also may occur on the trunk and extremities, and lesions may be present at birth or develop several weeks thereafter [33, 38, 40]. The diagnosis of NLE is generally secured by testing for relevant autoantibodies in the serum of the mother and/or infant. Skin biopsy may be helpful when the diagnosis is unclear and will reveal findings similar to CLE in adults but is not pathognomonic [31, 40, 41]. Fortunately, cutaneous lesions tend to resolve spontaneously in 6–8 months without scarring, although dyspigmentation may occur [38, 40].

Neonatal lupus erythematosus also may affect internal organs, and a review of 17 cases of NLE noted that 70.6 % of patients had cutaneous lesions, whereas cardiac, hepatobiliary, and hematologic involvement were seen in 64.7 %, 52.9 %, and 35.3 %, respectively [33]. Splenomegaly or neurologic involvement (most often manifesting as hydrocephalus) also may be seen, and rare reports of chondrodysplasia punctata occurring in association with NLE exist within the literature [42, 43]. While hepatobiliary and hematologic disturbances generally self-resolve, complete heart block (CHB), the most common cardiac manifestation, is typically irreversible [31, 40, 44–46]. Although CHB most often is detected during the second or third trimester of pregnancy, it may go unnoticed until after birth [40, 46]. In a study from the National Neonatal Lupus Registry, 63 % of live-born infants with CHB required pacemakers, and there was an approximately 20 % mortality rate from CHB [46]. Thus, fetal cardiac monitoring is imperative for mothers with anti-SSa/Ro, anti-SSb/La, or anti-RNP autoantibodies, and the potential for NLE should be discussed with at-risk mothers, bearing in mind that most mothers of children with NLE are asymptomatic [46, 47]. Fortunately, only approximately 1-2 % of fetuses born to mothers with high-risk autoantibodies will develop CHB [48], although if the mother has already given birth to an infant with NLE, the risk of NLE in future pregnancies escalates to approximately 15-20 % [46, 49, 50•]. Aggregate multinational data suggest that maternal use of hydroxychloroquine may help to decrease the risk of cardiac NLE in subsequent pregnancies [50•].

Morphea

Morphea (also known as localized scleroderma) is an autoimmune inflammatory condition that leads to induration of the cutaneous and potentially subcutaneous structures, and most commonly manifests as an atrophic, indurated plaque with a rim of violaceous erythema. Untreated, morphea may lead to permanent contractures, functional limitation, and cosmetic disfigurement. A long-term follow-up study of patients with juvenile morphea found that 25 % of patients reported mild to moderate disability after 20 years [51]. The condition is distinguished clinically from systemic sclerosis (SSc) by the lack of associated Raynaud's phenomenon, sclerodactyly, and internal organ involvement [52]. The incidence of morphea is approximately 2.7 per 100,000 persons, and morphea is at least 10 times more common in children than juvenile-onset SSC [51, 53]. Females are more commonly affected than males, and a large retrospective review found Caucasians to account for 82 % of pediatric patients with morphea, a finding that had not been previously reported [53]. In terms of age of onset, juvenile morphea most commonly occurs between the ages of 6.8 to 7.9 years; however, morphea can be seen any age, and rare cases of congenital-onset morphea have been reported, with a review of 750 patients with juvenile-onset morphea reporting that 0.8 % had morphea lesions at birth [54].

Several different clinical subtypes of morphea exist, including plaque-type, deep morphea (including pan-sclerotic), generalized morphea, linear morphea, and mixed subtypes [55]. In children, linear morphea (which usually occurs on the face or extremities) is the most common form, with approximately 67 % of cases of linear morphea diagnosed during childhood [51, 56]. Plaque morphea (usually occurring on the trunk) is the second-most common form in childhood and may occur concomitantly in patients with linear morphea [53, 56]. A single-center review of 136 pediatric patients with morphea reported that 51.4 % of patients presented with the linear variant, whereas plaque-type morphea accounted for 37 % of patients [53]. The generalized and pansclerotic subtypes of morphea, which can be especially debilitating, are rare in childhood [53].

In the pediatric population, the linear morphea subtype is particularly concerning given that it often involves deeper structures, such as muscle and bone, and given the risk of permanent contractures, functional disability [53, 57•] and associated ocular, dental, and neurologic complications [58–61]. In children with linear morphea, considering potential complications is best aided by subdividing patients into those with involvement of the extremities and those with involvement of the head and neck (en coup de sabre [ECDS]). This distinction is important given that ocular, dental, and neurologic abnormalities more commonly occur in patients with ECDS, whereas joint contractures are the major concern in patients with linear morphea of an extremity [58, 61].

In one pediatric review, linear morphea of the extremities occurred unilaterally in 94.2 % of patients [53]. Undergrowth of the extremity occurred in 32.6 % of patients and contractures in 25.6 % [53]. In addition, a review of 27 adults with pediatric-onset morphea revealed that 56 % of patients developed permanent sequelae, including joint contractures, limb-length discrepancy, deep atrophy, and limited range-of-motion, with all of these permanent sequelae occurring amongst patients with linear morphea [62]. Although extracutaneous manifestations of morphea are typically rare, arthralgias and other

musculoskeletal complaints are common in patients with linear morphea of an extremity, with approximately 18-47 % of patients experiencing this manifestation [53, 63]. A study of 750 patients with juvenile-onset morphea across 70 international centers supported the notion that arthritis is the most common extracutaneous manifestation of morphea and found this manifestation to occur in association with rheumatoid factor (RF) positivity in 16 % of patients [56].

When linear morphea involves the face or scalp, it often occurs along the frontoparietal scalp and/or paramedian forehead, and is termed ECDS [64]. Progressive hemifacial atrophy (PHA, also known as Parry-Romberg syndrome), manifests with unilateral atrophy of the skin and subcutaneous structures and is a closely related entity, overlapping with ECDS in approximately one-third to one-half of patients [61, 64]. Both entities generally occur unilaterally, but bilateral involvement has been reported in approximately 7 % of patients, and extrafacial cutaneous involvement may occur in roughly 13 % [64]. One review of 26 pediatric patients with morphea noted that neurologic manifestations occurred in 30.8 % of patients, including in 7.7 % of patients without cutaneous involvement of the head/neck, and ocular involvement occurred in two patients, both of whom had linear morphea localized to the trunk-limbs [55]. In the cohort of 750 pediatric patients with morphea studied by Zulian and colleagues, a similar frequency of neurologic and ocular involvement was found amongst patients with ECDS and PHA, with neurologic involvement occurring in 18.6 % of patients with ECDS and 18.2 % of patients with PHA, and ocular involvement occurring 7.8 % of patients with ECDS and 18.2 % of patients with PHA [56]. Ocular complications generally consist of anterior uveitis, episcleritis, glaucoma, and keratitis [56], whereas neurologic involvement generally manifests with seizures, vascular malformations, headaches, behavioral changes, abnormal neuroimaging, and electroencephalography alterations [56]. These findings are consistent with existing literature, which suggests that seizures are the most common manifestation of neurologic involvement in ECDS/PHA [61, 65, 66], whereas headaches, and less commonly focal neurologic symptoms, movement disorders, and neuropsychiatric symptoms also may occur [66, 67].

It is worth noting that not all patients with neurologic involvement will be symptomatic. A review of 32 pediatric patients with ECDS/PHA at a single institution, along with 51 previously reported cases, found that 19 % of patients who underwent neuroimaging had intracranial abnormalities, whereas half of these patients were asymptomatic [59]. In the single-institution component of this review, 21 of 32 children with ECDS/PHA underwent computed tomography (n=2), MRI (n=16), or both (n=3). Nine of these patients were symptomatic, two of whom had neuroimaging findings. An additional two asymptomatic patients had abnormal MRIs, and T2 hyperintensities were seen on all abnormal MRIs [59]. Severity of cutaneous disease did not correlate with neuroimaging findings or symptoms [59]. In the review of 51 previously reported cases, 9 patients had MRI abnormalities in the absence of symptoms, and 6 patients were symptomatic but lacked abnormal neuroimaging findings [59]. Due to this lack of correlation between neurologic symptoms and radiographic findings, symptoms should not be relied upon for diagnosis of neurologic involvement, and MRI of the head with contrast is prudent in all patients with ECDS/PHA.

Routine ophthalmologic examinations also should be performed in patients with ECDS/PHA. Data from the multinational cohort of 750 children with morphea found that 3.2 % of patients had ocular involvement [58]. Of these patients, 66.7 % had craniofacial morphea, 20.8 % had linear morphea, and the remainder had either generalized- or plaque-morphea [58]. Adnexal abnormalities of the lacrimal gland, eyelids, and eyelashes accounted for the majority of ocular findings (41.7 %), and anterior segment inflammation, including anterior uveitis, also was relatively common (29.2 %). When uveitis was present, it was generally asymptomatic and unilateral [58]. Ocular involvement was associated with additional extracutaneous manifestations in 41.7 %, neurologic complications in 25 %, and arthritis in 8.3 % of patients [58]. The authors concluded that ocular examination should be considered in all patients with morphea and is obligatory in patients with ECDS or concomitant central nervous system involvement [58].

In addition to ocular examinations, dental examinations also are prudent in patients with ECDS/PHA, as several reports exist of patients with associated dental abnormalities [68–73]. One cross-sectional, multicenter study of 16 patients with ECDS/PHA, all of whom had dental complications, found malocclusion and overgrowth tendency of the lower third of the face to be the most common complications, whereas gnathologic alterations, dental anomalies, skeletal asymmetry, and bone and temporomandibular joint involvement also were seen [73]. Untreated, such odontogenic complications may result in masticatory, cosmetic, or speech defects.

Despite the association between morphea and arthritis, neurologic, ocular, and dental complications, morphea is best thought of as a disease that lacks internal organ involvement. An epidemiological study of 82 patients with morphea followed over 754 person-years found no cases of severe internal organ involvement, and no cases of progression to systemic sclerosis [51]. There have, however been rare cases of internal organ involvement, particularly restrictive pulmonary disease, reported in patients with morphea [53, 56]. Aside from these rare reports of internal organ involvement, the association between morphea and concomitant autoimmune disease is worth consideration. Associated autoimmune disease, such as psoriasis, alopecia areata, and vitiligo, has been reported to occur in approximately 18 % of patients with morphea [74]. These associations are much more common in patients with

the generalized subtypes, and children with morphea appear to be less at risk for an associated autoimmune disease compared with adults [56, 74].

Patients with morphea often experience a delay in diagnosis, and treatment regimens can vary widely across specialties [75] One study found the mean time from symptom-onset to diagnosis to be 1.2 years [53], and amongst 750 patients with juvenile-onset morphea, the mean delay in diagnosis was 1.6 years [56]. Another review of 50 pediatric patients with morphea found that even after referral to specialists, morphea was initially misdiagnosed as port-wine stains in 8 % of patients [76], an occurrence that has been reported in several cases, likely due to early inflammatory erythema [77, 78]. Diagnosis of ECDS/PHA in particular may be delayed even further, and a review of 54 pediatric patients with ECDS/PHA found the mean time to diagnosis to be 8.9 years [64]. In addition, in the review of adult patients with juvenile-onset morphea that revealed a 56 % rate of permanent sequelae, methotrexate (MTX) was prescribed in only 8 of 20 patients with linear morphea, and systemic corticosteroids in only 6 patients [62]. These data highlight the need for early intervention and aggressive systemic therapy in patients with linear morphea.

In selecting the appropriate treatment regimen for patients with morphea, it is important to first determine whether disease is in an active inflammatory phase or a later fibrosed stage, as ongoing inflammation may respond to therapy whereas fibrosis may be irreversible [79]. Given the relative rarity of pediatric morphea and the associated difficulty in performing trials, most data on treatment are limited to case series and rare comparative and placebo-controlled studies, although some level I evidence does exist [57•, 80•, 81, 82••, 83]. Despite a paucity of evidence establishing a standard treatment algorithm for pediatric morphea, in 2009, a web-based survey of 158 pediatric rheumatologists from 70 centers in the United States and Canada determined that most pediatric rheumatologists treat morphea with MTX and corticosteroids, with the most aggressive therapy being employed for recent-onset morphea and linear and ECDS/PHA subtypes [84•]. Topical therapy was generally reserved for limited plaque morphea [84•]. Cyclosporine, oral tacrolimus, hydroxychloroquine, and mycophenolate mofetil (MMF) were other medications occasionally used, and rarely, calcitriol, etanercept, intravenous immunoglobulin, D-penicillamine, azathioprine, imatinib, and pimecrolimus were mentioned as therapeutic options [84•]. Although there was general agreement regarding the use of MTX and systemic corticosteroids as first-line agents, respondents reported a wide range in preferred dosing regimens and duration. In addition, many respondents expressed a lack of confidence in determining remission, and 8 % stated they were uncertain when complete remission was achieved [84•].

There is one randomized, double-blind, placebo-controlled study assessing efficacy of MTX and corticosteroids in treating pediatric patients with morphea [82••]. In this study, 70 patients were randomized to receive oral MTX 15 mg/m^2 (maximum of 20 mg) once weekly or placebo for 12 months (or until treatment failure), and both groups received oral prednisone 1 mg/kg/day (maximum of 50 mg/day) for the first 3 months and folic acid 2.5 mg 48 hours after MTX or placebo [82••]. Infrared thermography, a computerized scoring system, and clinical examination were used to assess response. More than two-thirds of patients in the MTX group improved, whereas fewer than one-third of patients in the placebo group experience improvement, and the rate of relapse in the MTX group was 32.6 % as opposed to 70.8 % in the placebo group; both of these findings were statistically significant. MTX was well-tolerated, and interestingly, the frequency of corticosteroid-related adverse effects was lower in the MTX group [82••]. In an open-label extension study of the same cohort, the long-term benefit of MTX was assessed in 65 patients (7 of whom were lost to follow-up) over a mean of 40.3 months [85•]. Seventy-four percent of patients experienced prolonged clinical benefit, with 50 % of patients maintaining clinical remission for up to 5 years. A relapse rate of 12.5 % was noted in patients treated with MTX for less than 24 months, and no patient treated for longer than 24 months developed a relapse [85•]. For this reason, the authors recommend treatment with MTX for 24 months to decrease the chance of relapse [85•]. Amongst the roughly one-third of patients who are refractory to MTX, MMF is a commonly utilized second-line option, and a retrospective review of 10 patients with juvenile morphea refractory to MTX and corticosteroids, or with severe extracutaneous manifestations, found that all patients clinically improved with MMF [86].

Although this data helps establish guidelines for treatment of pediatric morphea, a lack of standardization exists amongst practitioners, and particularly between specialties. Whereas most rheumatologists treat juvenile morphea with corticosteroids and MTX, topical agents and phototherapy are commonly used by dermatologists [57•, 80•, 87]. For this reason, and given the lack of standardization of dosing regimens even amongst those who use systemic therapy, a core group of dermatologists, pediatric rheumatologists, and a lay advisor, was convened in 2012 by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) to develop consensus treatment plans (CTPs) for patients with juvenile morphea [57•]. Although physicians often treat patients with morphea for longer than 1 year, CTPs were developed for a 12-month period only, due to limited evidence guiding treatment beyond this timeframe [57•]. Consensus plans were developed for MTX alone, MTX plus intravenous (IV) corticosteroids, and MTX plus oral corticosteroids, although no plan was developed for MTX plus oral and IV corticosteroids, a regimen that may be preferred by approximately 25 % of CARRA members [57•]. The dose of MTX in all CTPs was 1 mg/kg/week administered

subcutaneously for 12 months with a maximum of 25 mg/week. If IV corticosteroids were preferred, the CTP specified methylprednisolone 30 mg/kg/dose IV with a maximum of 1 g, administered once per week for 12 weeks, or for 3 consecutive daily doses/month for 3 months [57•]. When oral corticosteroids were favored, the CTP specified prednisone 2 mg/kg/day orally, with a maximum of 60 mg, divided twice daily for 2-4 weeks, with a taper of 50 % by week 8, 25 % by week 16, 12.5 % by week 24, and discontinuation by week 48 [57•]. Mycophenolate mofetil was suggested as an alternative or additive agent to MTX based on physician preference, although evidence on MMF is limited to one level C study [57•, 86]. Folic acid (0.4-1 mg/day) or folinic acid (5 mg/week) supplementation were recommended with MTX [57•].

In addition, the core workgroup on juvenile morphea developed disease activity and damage measures guided by previously established indices, along with a scoring atlas and provisional treatment response criteria to help aid in standardization of assessment parameters and to guide future comparative effectiveness studies [86]. Although the CTPs are not meant as treatment guidelines given the limited evidence on which they are based, they emphasize that aggressive systemic therapy often is necessary for patients with juvenile morphea, particularly of the linear, ECDS/PHA, generalized, and pansclerotic subtypes, and these CTPs are hoped to help guide future prospective studies.

Systemic Sclerosis

Although data regarding the incidence of SSc in childhood is sparse, experts agree that juvenile-onset SSc is extremely rare. A nationwide study from Finland found the incidence of juvenile SSc to be 0.05 per 100,000 persons [88], and data from 5,000 patients with SSc within the European League Against Rheumatism Scleroderma Trials and Research cohort found that 1.2 % of patients had juvenile-onset disease [89].

Juvenile SSc appears to be less severe than adult-onset SSc. A study of 153 patients with juvenile SSc from 55 pediatric rheumatology centers across Europe, Asia, and North and South America found that internal organ involvement was much less common than in adults, with renal cerebral, and cardiovascular manifestations being exceedingly rare in childhood SSc [90]. Gastrointestinal and pulmonary involvement were found to be the most commonly involved internal organs (although still occurring less commonly than in adult-onset SSc), with 30 % of patients revealing evidence of gastroesophageal reflux on 24-hour pH monitoring and/or gastroscopy, and 23-29 % of patients revealing evidence of lung fibrosis depending upon the imaging modality [90]. This lower incidence of pulmonary disease was in contrast to a study describing abnormal pulmonary function tests in 12 of 13 patients with juvenile SSc [91] but was concordant with two Japanese studies of more than 300 patients with SSc, which revealed that approximately 9 % of patients with juvenile-onset SSc developed interstitial-lung disease (ILD) compared with approximately 45 % of patients with adult-onset SSc [92, 93].

In contrast to the lower occurrence of internal organ involvement, arthritis appears to be more common in childhood-onset SSc than in adult SSc [94]. Raynaud's phenomenon (RP) also is common in juvenile SSc, and in one study, RP was the most common symptom of juvenile SSc [90]. The authors conclude that given that RP may precede the development of SSc, children with positive antinuclear antibodies and RP should be followed carefully for the subsequent development of connective-tissue disease [90]. Additional data suggest that this is particularly important if concomitant abnormal nailfold capillaries are present [95].

In regards to long-term follow-up of patients with juvenile-onset SSc, a review of the literature found that the 5-year survival of patients with juvenile-onset SSc is 90-94 %, which is significantly better than 5-year survival rates in adults [94]. In addition, this survival advantage of childhood-onset disease persists at up to 20 years of follow-up, with the lower frequency of renal involvement enduring into adulthood [94]. It is important to note, however, that these data are observational in nature, and therefore the potential for survival bias exists. Additional standardized, prospective data are needed to clarify further the prognosis of patients with juvenile-onset SSc.

In part due to these observed differences in disease manifestations between adult and pediatric patients with SSc, an expert consensus conference developed classification criteria for juvenile-onset SSc that differ from criteria used to diagnose adult-onset SSc [96]. The authors proposed that the major criterion of proximal skin sclerosis, must be accompanied by at least two minor criterion (sclerodactyly, concordant serology, or peripheral vascular, gastrointestinal, cardiac, renal, respiratory, neurologic, or musculoskeletal involvement) in order to diagnose juvenile-onset SSc [96]. With these classification criteria, it is hoped that future studies will include a standardized population for appropriate comparison amongst populations with juvenile-onset SSc.

Juvenile Dermatomyositis

Juvenile dermatomyositis (JDM) is a chronic, inflammatory disease with an incidence of approximately 2.5-4.1 per million persons, and a predilection for occurrence in females [97]. Although JDM primarily affects skin and muscle, it is best viewed as a systemic process, and internal organs, such as the lungs, gastrointestinal tract, and heart, may be affected. In addition, amyopathic variants (no clinical or laboratory evidence of muscle involvement), and hypomyopathic variants (no clinical evidence of muscle involvement, but evidence of subclinical muscle disease on laboratory investigations) exist

[98, 99]. Characteristic cutaneous manifestations of JDM include Gottron's papules, heliotrope eruption, midfacial erythema, erythematous to violaceous scaling patches on the scalp, nonscarring alopecia, photodistributed poikiloderma, nailfold capillary changes, and rarely, flagellate erythema [100]. Cutaneous JDM manifests similarly to adult-onset dermatomyositis; however, patients with JDM are less likely to develop pulmonary disease and malignancy and are more likely to develop calcinosis and metabolic abnormalities [3, 4, 101–103].

Pulmonary Involvement in Juvenile Dermatomyositis

Pulmonary involvement is a known complication of dermatomyositis and can result from interstitial lung disease (ILD), aspiration pneumonitis, or hypoventilation secondary to respiratory muscle involvement. In adults, ILD is the most common cause of pulmonary involvement, occurring in up to 23-78 % of patients [104, 105, 106•]. Data on pulmonary involvement in JDM, on the other hand, are limited, and although the range of reported incidence of pulmonary involvement in JDM is broad, the most robust data suggests that pulmonary involvement in JDM is rare, occurring with an incidence that is many-fold lower than that seen in the adult population [3, 107•, 108–110]. One study of 436 patients with juvenile idiopathic inflammatory myopathies (JIIM), 354 of whom had JDM, found the incidence of ILD in JDM to be only 4.8 % [3]. In addition, a multinational study of 490 patients with JDM found that pulmonary involvement occurred in approximately 4.9 % [107]. Several additional reports assessing clinical characteristics of patients with JDM have found incidences of ILD ranging between 5-19 %, with the higher end of this range being detected in a Japanese cohort, in which all affected patients had elevated levels of serum KL-6, a glycoprotein associated with ILD in both adult and juvenile dermatomyositis [108–112].

Data has also suggested that pulmonary involvement in JDM may be more commonly due to respiratory muscle weakness and calcinosis of the chest wall, and high levels of disease activity also may play a role [113, 114, 115]. For instance in 2012, a prospective multicenter study of 21 patients with JDM found the incidence of respiratory involvement to be 76 %; however, only 3 of these patients had ILD, and 2 of these 3 patients had associated respiratory muscle weakness [113]. The remaining patients had lung disease due to respiratory muscle involvement (n=7), aspiration pneumonia (n=3), or nonspecific asymptomatic findings, thus highlighting the fact that unlike in adults, pulmonary involvement in JDM may more likely be the result of respiratory muscle weakness [113]. In addition to this latter finding, a review of 68 patients with juvenile-onset clinically amyopathic dermatomyositis revealed no cases of ILD, supporting the notion that respiratory muscle weakness may contribute to lung disease in JDM, and pulmonary involvement due to ILD in JDM is rare [116]. In another study, there was a trend towards evidence of a higher prevalence of restrictive lung disease amongst patients diagnosed prior to 1990, who tended to be treated less aggressively, indicating the potential for early treatment to decrease the risk of pulmonary involvement [114].

There are no formal guidelines for proper pulmonary screening in patients with JDM, and at the author's institution, pulmonary function studies are performed only when directed by abnormal findings on physical examination or thorough history and review of systems. Emphasis is placed on treating JDM early and aggressively, with the hopes of abating the risk for internal organ involvement, especially given that data suggest that prolonged disease activity early in a patient's course may predict future organ and muscle damage [114, 117, 118].

Calcinosis in Juvenile Dermatomyositis

Calcinosis cutis is a potentially debilitating condition resulting from deposition of insoluble calcium salts in the cutaneous and subcutaneous tissue. The four main subtypes of calcinosis are dystrophic, metastatic, iatrogenic, and idiopathic; dystrophic calcinosis is the form that most commonly occurs in connective tissue disease [119, 120]. The precise pathogenesis of dystrophic calcinosis is unknown; however, chronic tissue inflammation and damage and/or defective collagen synthesis, occurring in the setting of normal systemic calcium metabolism, is thought to play a role [119]. When calcinosis does occur, the extent can vary widely, and whereas some patients manifest only small localized subcutaneous nodules, others may develop severe, exoskeleton-like calcinosis [121]. Secondary complications of calcinosis include pain, infection, ulceration, nerve damage, and when calcium deposits occur around the joints or in the intermuscular fascial plane, severe functional limitation and long-term disability may result, potentially having an even greater impact on the patient than the underlying myopathy [4, 120, 122, 123].

While adults with dermatomyositis are rarely affected by calcinosis, in JDM calcinosis is common, with reported incidences ranging from approximately 23-70 % [102, 119, 122, 124–126]. Although calcinosis can occur at any time, it is most commonly noted 2-3 years after the diagnosis of JDM, whereas in the adult population, calcinosis tends to be a late complication [119, 127•]. Identifying calcinosis at its onset is imperative, because it can result in poor functional outcome, and once calcium deposits have occurred, treatment can be challenging [119, 122, 125]. This is especially important given that a review of 79 patients with JDM noted calcinosis to be associated with delay in diagnosis and treatment [128]. In addition, a review of 35 patients with JDM, aiming

specifically to address whether early, aggressive therapy could help to prevent the development of calcinosis, found that delay in diagnosis, delay to normalization of muscle enzymes, and longer disease duration were associated with the development of calcinosis [4]. These data support the notion that early, aggressive treatment of JDM may help prevent subsequent calcinosis. Systemic corticosteroids and MTX were the treatments most often employed in this study, and the authors contend that combination therapy, rather than systemic corticosteroids alone, provides superior control of JDM, an assertion that has been supported in other studies [4, 129].

In regards to specific treatments for calcinosis, high-dose diltiazem (2-4 mg/kg/day) often is employed and has been shown to be beneficial [130, 131]. Bisphosphonates also may be beneficial and function both through anti-inflammatory effects and the reduction of calcium turnover [127•, 130, 132]. Other treatment options for calcinosis cutis include intravenous immunoglobulin, probenecid, colchicine, warfarin, ceftriaxone, minocycline, sodium thiosulfate, aluminum hydroxide, and systemic and intralesional corticosteroids, carbon dioxide and erbium-doped yttrium aluminum garnet laser, and extracorporeal shock wave lithotripsy, however all yield mixed results, and no treatment option has been uniformly effective [119, 130, 133–135]. In a retrospective review of 68 patients with calcinosis cutis associated with autoimmune CTD (30 with dermatomyositis, of whom 14 had JDM) seen at the Mayo Clinic, diltiazem provided the most favorable results when medical therapy was employed; however, surgical excision provided superior results to medical therapy, and the best results overall were achieved in those patients treated with combined medical and surgical therapy [127•].

Malignancy in Juvenile Dermatomyositis

The association between adult-onset dermatomyositis and malignancy has been well-described, and several large studies, including a number of population-based studies, have confirmed this risk [101, 136–142]. Fortunately, in JDM, malignancy does not appear to occur with increased incidence. A large review of patients with idiopathic inflammatory myopathies within Northern New England of the United States found 0 cases of malignancy in 18 patients with JDM [140], and within a Scottish population-based cohort, no cases of malignancy were detected in 35 patients aged <15 years [101]. In 2010, a review of the literature from 1963 to 2008 detected only 12 cases of malignancy associated with JDM [143]. In nine of these patients, physical examination findings, such as extensive lymphadenopathy and splenomegaly, were detected at the time of diagnosis. Hematologic malignancies were the most common to occur (n=7), with lymphosarcoma, dysgerminoma, neuroblastoma, sarcoma, and nasopharyngeal carcinoma occurring in one patient each [143]. The authors concluded that abnormal physical examination findings in patients with JDM should raise the consideration for malignancy and in-depth screening [143]. Based on this data, there are no recommendations to perform blind malignancy searches in patients in JDM. Rather, a thorough history, review of systems, and physical examination should be performed regularly, and malignancy screening should be directed towards any abnormal findings. It should be noted that in Taiwan, a population-based study found a 16-fold increased risk of hematopoietic or lymphoid malignancies in patients with JDM [144], suggesting that demographic differences may play a role in determining malignancy risk in JDM. Future prospective studies would be helpful in guiding whether demographic-specific malignancy screening is necessary.

Metabolic Abnormalities in Juvenile Dermatomyositis

Metabolic abnormalities in JDM often are under-recognized but may be clinically relevant. Evidence has demonstrated that patients with JDM are more likely to be dyslipidemic [145, 146], and several cases of JDM occurring in association with diabetes mellitus have been reported [125, 147, 148]. In addition, lipodystrophy has been estimated to be clinically apparent in 10-40 % of patients with JDM [103, 146, 147, 149] and was noted in 23 of 353 (7.9 %) of patients with JDM within a large national myositis registry [103]. In this latter study, generalized and partial lipodystrophy were associated with insulin resistance and diabetes, and all forms of lipodystrophy were associated with dyslipidemia; these findings were independent of steroid use [103]. Severe, prolonged disease course and the presence of joint contractures, muscle atrophy, calcinosis, and panniculitis also were associated with lipodystrophy [103]. Increased disease activity has been related to metabolic abnormalities in JDM in several other studies [145, 150], highlighting the importance of considering JDM as a systemic disease. Moreover, a case-control study of 59 patients with JDM found evidence of subclinical cardiac disease in 22 % of patients and hypertension in 20 % of patients, whereas neither of these factors was present in controls [150]. In terms of long-term follow-up of patients with JDM, a pilot-study of eight adults with a history of JDM compared metabolic factors to eight cardiovascular disease controls and found that increased cardiovascular risk factors persist into adulthood in patients with JDM [151].

Treatment of Juvenile Dermatomyositis

A number of medications may be used to treat JDM, although there is a paucity of prospective data guiding their use. For cutaneous DM specifically, strict photoprotection and

topical corticosteroids should be employed but often are insufficient [152]. With regards to systemic agents, antimalarials [153], MTX [154, 155], MMF [156, 157], and intravenous immunoglobulin (IVIG) [158] often are used and can be effective for both muscular and cutaneous disease. Corticosteroids are a mainstay for myositis [159–161], and azathioprine [162], systemic calcineurin inhibitors [163–165], and cyclophosphamide [166] are occasionally used for refractory disease. Rituximab also has been shown to be beneficial in small series [167, 168], although a recently published randomized, placebo-controlled trial failed to demonstrate significant improvement in adult and juvenile DM [169••].

In 2010, CARRA members were surveyed to determine the most common treatment approaches utilized for JDM [170•]. The authors found that corticosteroids and MTX (usually used in combination) were the most commonly employed therapies, and IVIG and hydroxychloroquine often were used as well [170•]. In 2012, 30 pediatric rheumatologists and 4 lay participants convened to develop CTPs for moderate new-onset JDM [171•]. All initial CTPs involved the use of MTX and systemic corticosteroids for the first 4 weeks; one of these CTPs consisted of MTX along with oral and intravenous corticosteroids, another of MTX, oral and intravenous corticosteroids, and IVIG, and the last of MTX and oral corticosteroids only. In addition, dosing and tapering regimens were formulated along with these plans, and treatment algorithms were developed that extended beyond the first 8 weeks, based on whether the patient was improved, unchanged, or worsened as determined by physician judgment of muscular and cutaneous involvement [171•]. Ideally, future prospective comparative trials will aid the development of evidence-based treatment recommendations for JDM [171•].

Conclusions

There are several autoimmune CTDs that can occur during childhood, each with various presentations. Gaining familiarity with these conditions, along with their systemic associations, is imperative, especially given that early recognition and proper therapy may help to prevent potentially serious and permanent sequelae.

Compliance with Ethics Guidelines

Conflict of Interest A. Femia declares no conflicts of interest. R.A. Vleugels declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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