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REVIEW ARTICLE

A Practical Approach to Juvenile Dermatomyositis and Juvenile Scleroderma

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Abstract Juvenile dermatomyositis and juvenile scleroderma are rare multisystem autoimmune disorders. Although they share some pathognomonic hallmarks with adult onset myositis or scleroderma, there are significant differences in presentation, characteristics and associated features when the diseases present in childhood. In view of this, and the rarity of the conditions, it is important for care to be led by teams with expertise in pediatric rheumatology conditions. Prognosis has improved significantly in the West; likely due to early diagnosis and aggressive treatment with immunosuppressive medications. However, this trend is not replicated in the developing world. Early recognition of these diseases is crucial to achieve rapid and sustained remission and prevent disease or medication associated complications. This article aims to provide a practical overview for recognition, diagnosis and treatment of these conditions.

Keywords Juvenile dermatomyositis · Juvenile localised scleroderma · Juvenile systemic scleroderma · Mixed connective tissue disease · Overlap connective tissue disease

Abbreviations

ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
AST	Aspartate aminotransferase
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CMAS	Childhood Myositis Assessment Scale
CPK	Creatinine phosphokinase
CRP	C-reactive protein
DLCO	Diffusion capacity for carbon monoxide
DMARDS	Disease modifying anti-rheumatic drugs
dsDNA	Double-stranded DNA
ECG	Electrocardiogram
EMG	Electromyography
ENA	Extractable nuclear antigens
ESR	Erythrocyte sedimentation rate
HRCT	High resolution computerised tomography
IIM	Idiopathic inflammatory myopathy
ILD	Interstitial lung disease
IMACS	International Myositis Assessment & Clinical Studies Group
IVIG	Intravenous immunoglobulin
JDM	Juvenile dermatomyositis
JLS	Juvenile localised scleroderma
JSSc	Juvenile systemic scleroderma
LDH	Lactate dehydrogenase
LoSCAT	Localised scleroderma cutaneous assessment tool
MCTD	Mixed connective tissue disease
MMF	Mycophenolate mofetil
MMT	Manual muscle testing
MRI	Magnetic resonance imaging
MSA	Myositis specific antibodies
MTX	Methotrexate
PFTS	Pulmonary function tests
RCT	Randomised controlled trial
RF	Rheumatoid factor
SLE	Systemic lupus erythematosus

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STIR	Short T1 inversion recovery
UK	United Kingdom

Juvenile Dermatomyositis

Introduction

Juvenile dermatomyositis (JDM) is associated with significant mortality and morbidity in developing countries, with complications including calcinosis, lipodystrophy, contractures and muscle damage [1, 2]. Outlook can be improved by early recognition and aggressive treatment.

Epidemiology

JDM is the most frequent and best characterized juvenile Idiopathic Inflammatory Myopathy (IIM) with an incidence of 1.9–4 per million children per year and prevalence of 2.5/100, 000 [3]. Peak onset is 7 y of age, with female predominance. Seasonal variations suggest environmental triggers (*e.g.,* viruses / photosensitivity) which may instigate the disease in genetically predisposed individuals [4].

Clinical Features

JDM is characterised by proximal muscle weakness and distinctive cutaneous findings (Fig. 1), but presenting features are variable and onset often insidious, hence classical features may not be seen at presentation [5–8]. Weakness is progressive and can become profound; starting with difficulty in climbing stairs or combing hair, progressing to an inability to roll over in bed. Children will often use compensatory manoeuvres. Neck flexor and abdominal muscle weakness should be looked for. Palatal / cricopharyngeal weakness results in nasal voice, swallowing difficulties or coughing during eating/ drinking, reflux into the nasopharynx or tracheal aspiration. Silent aspiration is recognised.

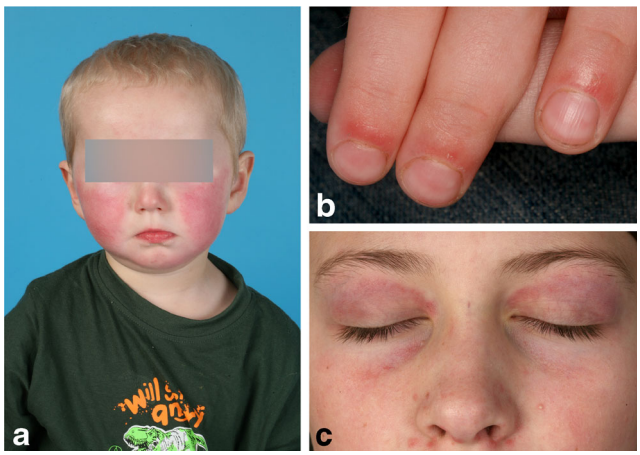

Fig. 1 Typical cutaneous features associated with JDM: **a** Malar rash; **b** Erythema and dilatation of nailfold capillaries; **c** Heliotrope discoloration of the eyelids

Gowers' sign is a useful screening test. Turning prone to rise from a supine position is a typical feature and is rarely seen in healthy children over 3 y of age [9]. Muscle strength should be assessed at diagnosis and serially during follow-up using the Childhood Myositis Assessment Scale (CMAS) and/ or Kendal Manual Muscle Testing (MMT8). Teaching videos are available on the International Myositis Assessment & Clinical Studies Group (IMACS) website [10].

Characteristic cutaneous features, reported in 72.9–97 % of cases at presentation, may be transient and precede muscle weakness [5, 7, 8]. The most frequent are heliotrope discoloration, often associated with periorbital edema, Gottron's papules/ sign, and nailfold capillary changes (Table 1). An otoscope/ dermatoscope can help magnify nailbeds in clinic. Changes may be difficult to see in darker skin. Formal nailfold capillaroscopy can measure capillary density; a valuable marker of skin and muscle activity [11]. Other skin signs are common (Table 1) and should be looked for. Generalised subcutaneous edema or skin ulceration (reported in 5–30 % of patients) predicts a severe disease course with persistent weakness [5, 6, 8, 12].

Calcinosis, reported in 27.7 % in a recent Indian cohort [1], can be present at onset or later in the disease course (typically 1–3 y). It isassociated with delayed diagnosis, chronic disease or inadequate treatment. Calcium deposits may form plaques, nodules, sheets or a widespread exoskeleton, or liquefy to form pools of 'milk of calcium'. These can extrude from the skin or become infected. They can cause pain, limit joint movement or cause tendons to shorten. Lipodystrophy (reported in 10–14 % patients), often difficult to reverse, can be associated with insulin-resistance or other metabolic abnormalities [1, 8, 12]. Skin disease is an important outcome measure in JDM, negatively impacting quality of life.

Fever, weight loss and fatigue are common constitutional features of JDM. Myalgia occurs frequently. Mouth ulcers, lymphadenopathy, Raynaud's phenomenon, abdominal and chest pain are familiar symptoms, although non-specific.

Arthritis (typically polyarticular) or arthralgia occurs frequently [5, 7, 8, 12]. Children may not complain of pain but rather joint stiffness in the morning/ after rest. Contractures and muscle damage remain common in developing countries [1]; preventable by early aggressive treatment.

Gastrointestinal involvement includes dysphagia, abdominal pain, or ulceration. Gut vasculitis, although rare, can lead to perforation, and is an important cause of death [2]. Respiratory symptoms include dysphonia and dyspnea. A multicentre prospective study (n=21) identified interstitial lung disease (ILD), aspiration pneumonia or respiratory

Table 1 Cutaneous features of JDM

Cutaneous feature	Description
Heliotrope discoloration of the eyelids	Purple, lilac-colored or erythematous patches over the eyelids, or in a periorbital distribution, often associated with periorbital edema.
Gottron's papules	Erythematous to violaceous papules, sometimes scaly, typically over extensor surfaces of joints.
Gottron's sign	Non-palpable erythematous to violaceous patches or macules, in the same distribution as Gottron's papules.
Nailfold capillary changes	Periungual erythema with dilatation of periungual capillaries / vessel dropout.
Malar or facial erythema	Erythema over the face; isolated to malar erythema or can extend to include the perioral, temporal, ear and frontal areas.
Shawl sign	Erythema over the upper back, posterior neck or shoulders.
V sign	Erythema over the anterior neck and upper chest.
Holster sign	Erythema over the outer surface of the hips or thighs.
Linear or extensor erythema	Erythema over the extensor tendon sheaths of the hands, forearms, feet or forelegs.
Erythroderma	Extensive areas of confluent erythema, including both sun exposed and non sun-exposed areas.
Livedo reticularis	Net-like / lace-like mottling of the skin on the trunk or extremities due to a fixed peripheral vascular condition.
Cutaneous ulceration	Extensive injury to dermis, subcutaneous tissue or deeper tissues. Skin ulceration can occur over flexor surfaces, trunk, or medial canthus of the upper eyelid.
Mechanic's hands	Lesions on the palmar or lateral aspects of the digits including fissuring, cracking, hyperkeratosis or scaling. Characteristic in adult IIM but rare in children.
Cuticular overgrowth	Enlargement or overgrowth of the cuticle on the nailbed.
Panniculitis	Inflammation of the subcutaneous fat causing painful erythematous or violaceous subcutaneous nodules.
Poikiloderma	Hyperpigmented or hypopigmented macules interspersed with fine telangiectasia and cutaneous atrophy.
Calcinosis	Dystrophic calcium deposits observed clinically or by imaging involving the skin, subcutaneous tissues, fascia, interfascial planes, muscle or occurring across the joints.
Lipodystrophy	Loss of subcutaneous fat: may be localised, partial or generalised.
Depressed scar	End stage lesions due to vascular occlusion or vascular insufficiency.
Alopecia	Hair loss: may be diffuse (non-scarring) or focal with scaling and erythema.

muscle involvement in 76 % of patients [13]. Although less frequent in other cohorts [6, 7, 12], interstitial pneumonitis and aspiration pneumonia are important causes of death [2]. Cardiac involvement (pericarditis, myocarditis or arrhythmia) is rare in JDM but can be fatal [2]. Subclinical cardiovascular changes are recognised [14]. Cardiac symptoms may include chest pain, syncope or palpitations [12]. Neurological or ophthalmological involvement is rare. Major organ involvement, severe weakness or ulcerative skin disease puts a patient at high risk and warrants urgent transfer to a specialist centre (Table 2).

Investigations and Diagnosis

Diagnosis of definite JDM (using Bohan and Peter criteria) requires a characteristic rash (heliotrope, Gottron's papules) plus three of the four muscle features: symmetrical muscle weakness, muscle biopsy evidence of myositis, elevation of serum levels of muscle-associated enzymes and electromyographic (EMG) triad of myopathy [15]. There has been a move away from using EMG or muscle biopsy in favour of MRI [4–7]. T2 weighted / STIR sequences detect edema in the myofascia and subcutaneous tissue. An MRI scoring system

Table 2 Clinical features that suggest that a patient is at high risk from severe disease and thus needs immediate / urgent referral to a specialist centre

1 Severe disability (inability to get out of bed).
2 Severe weakness (CMAS score <15, MMT8 <30).
3 Presence of aspiration or dysphagia, to the point of being unable to swallow.
3 Skin ulceration.
4 Major organ involvement including ILD, gastrointestinal vasculitis (determined by imaging / presence of bloody stools), myocarditis, or central nervous system disease (decreased level of consciousness or seizures).
5 Requirement for intensive care management.
6 Age <1 y

CMAS Childhood myositis assessment scale; *MMT* Manual muscle testing; *ILD* Interstitial lung disease

objectively defines acute inflammatory change [16]. Musculoskeletal ultrasound is a safe, inexpensive means of supporting diagnosis when MRI is unavailable or unsuitable, but requires operator expertise.

No one test is abnormal in all JDM cases. Investigations should be done to exclude systemic or neurological causes of myopathy, confirm diagnosis of IIM and define organ involvement. A muscle biopsy remains the gold standard and should be done where presentation is atypical; particularly when skin signs are absent, and to exclude muscular dystrophies/ mitochondrial cytopathies. Use of a standardized muscle biopsy tool helps to quantify severity of histological changes [17].

EMG or nerve conduction studies are no longer routinely carried out but remain important when diagnosis is uncertain to exclude neuropathy [5–7]. EMG does not reliably detect metabolic myopathies [18].

Measurement of muscle-derived enzymes should include creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT) and adolase (if available). Abnormalities are seen in 80–92 % of patients,but enzymes may be normal later in the disease course despite on-going disease activity or flare [6, 12]. More than 20 % of patients have normal CPK at presentation. CPK is moderately raised in IIM; if extremely high, consider other causes of myopathy.

Anti-nuclear antibody (ANA) is positive in approximately 70 % of patients but is non-specific and not diagnostic [12]. Other antibody tests may be useful in myositis overlap including anti-ENA, anti-dsDNA, Rheumatoid Factor (RF), and anti-thyroid antibodies. Myositis Specific Antibodies (MSA) such as anti-TIF 1-γ, anti-NXP2, anti-MDA5, anti-SRP, have the potential to aid diagnosis and prognosis by differentiating disease phenotypes but are not yet routinely available [4, 19].

Inflammatory markers (ESR, CRP) should be taken, but may be normal despite active disease. Likewise, raised serum von Willebrand factor may indicate disease exacerbations, but is not consistently elevated in active disease.

If clinically indicated, X-rays should be taken to determine extent of calcinosis and investigations done for ILD [chest radiograph, pulmonary function tests (PFTs), high resolution CT thorax (HRCT)], cardiac involvement (ECG, echocardiogram), or abdominal pathology (ultrasound). A speech and language assessment, videofluoroscopyand/or barium meal is indicated for dysphagia, dysphonia or symptoms of aspiration. Nailfold capillaroscopy is helpful when available.

Treatment

High dose corticosteroids (oral or intravenous) combined with methotrexate (MTX) has become the standard induction regimen for JDM [5–7]. This has been shown to result in shorter time to inactive disease compared to prednisolone alone in a randomised trial, with good safety profile [20]. If a newly diagnosed patient has inadequate response within the first 12 wk, intensification of treatment should be considered in consultation with an expert centre. Options may include addition of intravenous immunoglobulin (IVIG), or cyclosporin or switching MTX to mycophenolate mofetil (MMF) (Table 3) [4, 19, 21]. Consensus statements developed by Childhood arthritis and rheumatology research alliance (CARRA) propose combination therapies from time of diagnosis with steroid (oral plus / minus intravenous) with MTX, plus or minus IVIG [4].

Severe disease (such as skin ulceration, interstitial lung disease, gastrointestinal perforation) warrants treatment with intravenous cyclophosphamide [5–7, 19]. For refractory disease, B cell depletion therapy can be considered as adjunctive therapy if available but can take 26 wk to work [4]. Anti-TNF therapies are an alternative but infliximab and adalimumab may be more beneficial than etanercept [4, 19, 22].

Intensification of immunosuppressive therapy is recommended for developing or established calcinosis and may lead to regression of calcinosis over time. Anecdotal reports of treatments for calcinosis include diltiazem, infliximab, and bisphosphonates. Diclofenac can help inflammation around calcinotic deposits, and flucloxacillin can treat secondary infection that may prolong or worsen calcinosis. Topical tacrolimus (0.1 %) or topical corticosteroids may help localised skin disease [19]. However, expert opinion suggests that resistant skin disease reflects on-going systemic disease and should be treated by increasing systemic immunosuppression. JDM rashes can be triggered by ultraviolet light and adequate sun protection should be prescribed. Decreased bone mineral density is common in systemic rheumatic diseases and calcium/ vitamin D supplements, with or without bisphosphonates, may be required.

Steroid dose should be weaned as a patient shows clinical improvement. There is no high level evidence of when to stop therapy but consideration may be given to withdrawing treatment if a patient has been off steroids and in remission on MTX (or alternative disease modifying anti-rheumatic drug) for a minimum of 1 y.

Exercise for rehabilitation is extremely important to improve and maintain range of movement of the joints, muscle strength/ stamina and aerobic fitness [4, 19]. It should start at the time of diagnosis and form part of the treatment regime. A holistic approach is needed to deal with emotional and functional disease burden. Age appropriate patient reported outcome measures can be used to measure activity, participation and quality of life.

Outcomes

Over the last few decades, prognosis has significantly improved for JDM, but the disease continues to be associated

Table 3 Treatment options for JDM

Drug	Frequency of use, shown in registry data / cohort studies	Evidence base for use	Indication in clinical practice
Corticosteroids	Used in 95–98.5 % of cases. Intravenous pulses used in approximately 50 % of cases in addition to oral corticosteroids [5–7].	Mortality rates pre- steroid (one-third of cases) compared to post-steroid era (<10 %) prove efficacy. Early use of high dose corticosteroids for adequate duration associated with better functional outcome compared to low dose [19].	Use systemic corticosteroids at disease onset and disease flares; high dose oral (2 mg/kg/d) or intravenous pulses (particularly if concern about absorption). Wean dose slowly (over at least 1–2 y) as disease improves.
Methotrexate (MTX)	Used in 56–92.5 % of cases, with increased use in recent years [5–7].	Shown in case–control studies / case series to reduce muscle inflammation, reduce rate of complications including calcinosis and allow steroid reduction with fewer side effects [19]. RCT shows time to inactive disease shorter when MTX used with prednisolone *vs.* steroids alone [20].	First line treatment for JDM in combination with corticosteroids. Should be started at time of diagnosis at a dose of 15–20 mg/m^2 once weekly, preferably by subcutaneous administration.
Cyclosporin A	Used in 10–21 % of patients. Less frequently used since 2000 when MTX has become more popular [5–7].	Efficacy supported by several small case series and a recent RCT; time to inactive disease shorter when cyclosporin A used in combination with prednisolone *vs.* steroid alone, but safety profile favours methotrexate over cyclosporine [19, 20].	Can be used with steroids alone or in combination with MTX. Frequently leads to hypertension or hirsuitism in JDM.
Intravenous immunoglobulin (IVIG)	11–48 % of patients. Widely used in severe or refractory disease, especially when skin features are prominent [5–7].	Retrospective case series show clinical improvement and ability to markedly reduce steroid treatment with addition of IVIG [19].	Beneficial adjunctive treatment, particularly if poor response to first line therapy. Used for skin and muscle disease.
Hydroxychloroquine	15–60 % of patients; usually used in mild disease, most commonly in combination with prednisolone and MTX [5–7]	Small case series have shown that patients may respond to hydroxychloroquine but evidence not convincing [19].	Can be used as an adjunctive therapy, particularly in those with marked cutaneous disease and is widely used, but likely that other treatments may be more efficacious.
Mycophenolate mofetil	16.7 % in a recent cohort [6]	Found in retrospective case series to lead to improvement in muscle strength and rash by 6 mo, with further improvement in skin rash by 1 y [19, 21]	May be useful for muscle and skin disease, including calcinosis and is an alternative option if MTX not tolerated or ineffective.
Cyclophosphamide	1.4–10.1 % [5–7]	Improved outcome in a retrospective case series (n=12) of patients with severe disease, refractory to combination of treatments [19]	Indicated for major organ involvement or ulcerative skin disease. Due to side effect profile, it tends to be reserved for severe disease
Azathioprine	9 % [5, 7]	Not specifically tested in JDM except in case series where used in combination with MTX and steroids.	Less commonly used over time but combination of mTX and azathioprine is an option in resistent disease / presence of calcinosis.
Tacrolimus	Not shown	Small retrospective case series [19]	May be a useful adjunct, particularly for cutaneous manifestations
Rituximab	2.7–6.2 % [6, 7]	RCT of rituximab for refractory IIM myositis failed to reach its primary or secondary endpoints, but overall response rate, steroid-sparing effect and re-treatment response suggest that rituximab has an effect	May be useful in refractory disease but can take up to 26 wk to work.
Anti-TNF therapies	2.7–10 % [5–7]	Infliximab shown to be beneficial in a retrospective case series (n=5) of patients with refractory disease [22] and updated case series from UK (presented in abstract) showed improvement in muscle strength, skin rash and calcinosis, but mixed results found in a case series (n=9) of etanercept in JDM [4]	May be useful in refractory muscle or skin disease, including calcinosis. Infliximab or adalimumab may be more efficacious than etanercept.

with significant mortality and morbidity in developing countries. Delayed or inadequate steroid dose is one of the most important factors associated with poor prognosis and increased risk of calcinosis [19]. Persistence of skin rash is associated with longer time to remission and should be treated aggressively. Important causes of death in JDM are vasculopathic complications, major organ involvement and infections [2]. Early recognition and aggressive treatment is the key to improving outlook. All children with suspected IIM should be referred to a specialist centre, particularly those at high risk due to young age, major organ involvement, skin ulceration or disease complications.

Myositis Overlap and Mixed Connective Tissue Disease

Inflammatory myopathy may overlap with other autoimmune diseases in 3–11.2 % of cases [4, 8, 12]. The most common overlap is with scleroderma, but others include arthritis, lupus, or Sjögren's. Patients are more likely to have Raynaud's phenomenon, sclerodactyly, ILD, arthritis and gastro-intestinal symptoms than children with JDM [12]. ANA titres tend to be higher and anti-PM-Scl, anti-Ro, anti-La, anti-Sm or anti U1-RNP may be positive [12].

RNP positive mixed connective tissue disease (MCTD) is rare in children [23]. It has a female predominance. Features evolve over time; rashes of JDM / systemic lupus erythematosus (SLE), swollen hands, polyarthritis (frequently RF positive) and Raynaud's phenomenon are common at onset, whilst scleroderma is more common later [23]. Vasculitis or vasculopathy can be severe. Hematological complications, such as resistant thrombocytopenia, are frequent. Sicca syndrome occurs in one-third of cases. Nephritis, seen in 25 % of patients is less severe than in SLE. Subclinical myositis is recognised. PFT abnormalities are common and can be asymptomatic. Cardiopulmonary disease and esophageal dysmotility are infrequent. Treatment should be directed towards the main symptoms. Long-term outlook is varied and unpredictable. Sclerodermatous features (sclerodactyly, vasculopathy and esophageal disease) can be resistant to treatment [23].

Juvenile Scleroderma

Juvenile scleroderma encompasses a spectrum of autoimmune diseases where chronic inflammation within the skin and subcutaneous tissues leads to fibrosis [24]. In children, localised scleroderma ismore common (93 %) than systemic scleroderma (7 %) [25]. Although the diseases share similar skin biopsy findings, fibrosis in localised scleroderma is limited to skin and subcutaneous tissues whereas organ fibrosis also occurs in systemic scleroderma.

Juvenile Localised Scleroderma

Juvenile localised scleroderma (JLS) subtypes include morphea (plaque, deep, pansclerotic or generalised) and linear scleroderma (affecting limbs and/or head). Atrophy of the skin and soft tissues is a complication. In growing children this can lead to joint contractures, limb length discrepancy and facial atrophy, which can have a marked psychological and functional effect (Fig. 2).

Epidemiology

The reported incidence of JLS is 3.4 per million children per year, with two thirds of children having the linear subtype [25]. With female predominance, mean age of onset is 7.3 y [26]. There is often a significant delay in diagnosis of around one year and many cases are misdiagnosed initially [27, 28].

Clinical Features

Many children do not report symptoms but itching or abnormal sensation within the affected skin may suggest on-going disease activity. A thorough skin examination should be performed, preferably in natural light, to delineate extent of disease. New or extending lesions, induration, erythema or violaceous edge suggest active disease. Lesions can become tethered with dermal atrophy (skin may appear shiny, show visible vessels or cliff-drop sign) and subcutaneous atrophy (flattened or concave appearance) or may appear waxy and white. Hyper or hypopigmentation can occur.

Plaque morphea is characterised by round circumscribed areas of induration. Lesions may be superficial or deep with underlying subcutaneous fat atrophy. Generalised morphea has 4 or more large plaques involving two or more anatomical areas. Linear scleroderma presents with linear distribution of

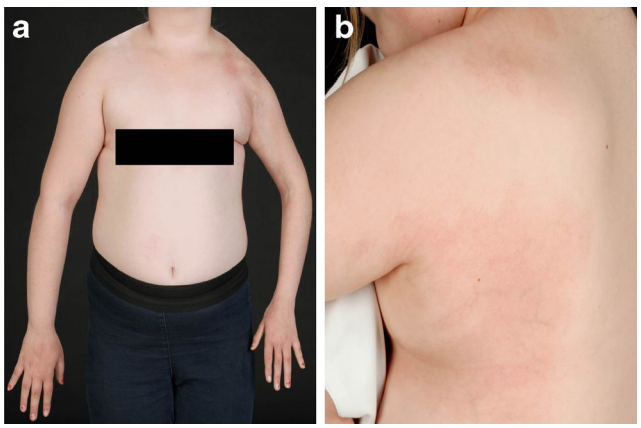

Fig. 2 Child with JLS: **a** Linear scleroderma lesions affecting *left arm* leading to atrophy, limb length discrepancy and joint contracture (shown by asymmetry with non-affected *right arm*). **b** Same patient with patch of active morphea on *left back* with erythema and induration

lesions that may extend from skin to subcutaneous tissues, muscle and bone. Linear lesions on the face can present as progressive facial hemiatrophy (also known as Parry Romberg Syndrome) or *en coup de sabre* lesions. Scalp lesions typically show loss of hair over affected skin and there may be loss of eyebrows/lashes. The temporomandibular joint and mouth should be examined for orthodontic abnormalities; with dental review if indicated.

In non-facial linear disease, the patient should be carefully assessed for gait disturbances, limb length discrepancy, differences in hand/foot size, joint contractures and associated arthritis.

Approximately one-fifth of patients with JLS have extra-cutaneous manifestations, which can be distant from the site of affected skin, most commonly articular, neurological and ocular [29]. The latter are more common in head and face lesions.

Investigations and Monitoring Disease Activity

Most children have normal inflammatory markers. ANA can be positive but is not diagnostically or prognostically useful [26]. Skin biopsy is unnecessary in most patients unless there is diagnostic uncertainty [30]. MRI and plain X-ray can help define depth of disease and associated bony changes. Serial photographs of skin lesions help monitor progression and response to treatment.

Because of the association with brain abnormalities, all children with head/facial lesions should have a baseline MRI brain [30]. Risk of uveitis in this group remains undefined but uveitis screening should be considered.

Many outcome measures have been studied in JLS but application in routine clinical practice is limited by availability *e.g.,* thermography and laser Doppler [31, 32]. The Localised Scleroderma Cutaneous Assessment Tool (LoSCAT) is validated in JLS and is a useful, widely available tool [33]. It scores different anatomical areas based on clinician skin examination, with activity and damage indices.

Management

Children should be managed within a specialist team with expertise in JLS; joint clinics with pediatric rheumatologists and dermatologists are ideal.

There have been limited therapeutic trials within JLS with only one randomised placebo-controlled trial of systemic treatment. In this study, all children received oral prednisolone for 3 mo with either MTX or placebo. At 1 y, disease relapse occurred in 32.6 % of the MTX group compared to 70.8 % of the placebo group ($p<0.005$). Use of other disease modifying anti-rheumatic drugs (DMARDs) in JLS is limited to a case series of MMF ($n=10$) that appeared to be effective and well-tolerated. To date there are no published uncontrolled trials or case series of other DMARDs or biologics in JLS, although in

Table 4 Clinical features seen in JSSc at presentation and during follow-up in a large international cohort of JSSc where mean follow-up time was 3.9 y (range 0.2–18.8). Organ-specific investigations/assessments and treatment are detailed in columns 4 and 5

Clinical feature	Frequency [40]		Investigations and/or assessment of clinical manifestation	Treatment [44]*
	At diagnosis	At follow-up		
Raynaud's phenomenon	75 %	84 %	Nailfold capillaroscopy, presence of digital ulcers, pitting scars, tissue loss	**Calcium channel blockers, iloprost or other prostanoids** (sildenafil)
Nailfold capillary changes	25 %	52 %		
Digital pitting	28 %	38 %		
Skin thickening	74 %	76 %	Modified Rodnan skin score	**Methotrexate** (mycophenolate mofetil, azathioprine, cyclosporin)
Lung fibrosis	12 %	29 %	HRCT thorax, PFT with DLCO	**Cyclophosphamide**
Pulmonary hypertension	1 %	7 %	ECHO, Cardiac catherisation	**Bosentan, sildenafil, sitaxentan, continuous IV epoprostenol**
Dysphagia	10 %	24 %	Barium swallow, Video fluoroscopy, pH study, GI endoscopy	**For gastro-esophageal reflux proton pump inhibitors. Prokinetics in dysmotility**
Gastro-esophageal reflux	8 %	30 %		

HRCT High resolution computerised tomography; *PFT* Pulmonary function tests; *DLCO* Diffusion lung capacity for carbon monoxide; *ECHO* Echocardiogram; *GI* Gastrointestinal

*Treatments in bold represent EULAR recommendations, treatments not in bold have lower level evidence to support their use [44]. This is not an exhaustive list of treatments

practice these are used in refractory disease [34, 35]. Within the United Kingdom and United States of America, most pediatric rheumatologists use MTX and/or corticosteroids (oral or intravenous) as first line treatment [34, 36]. Topical therapies (*e.g.*, corticosteroids, vitamin D analogues and tacrolimus) can be helpful adjuncts. Ultra-light therapies have also been used [37].

Physiotherapy and occupational therapy input is vital in children with functional impairment.

Outcomes

Studies of adults with childhood onset disease show persistent disease activity, although patients may experience long periods of disease inactivity [38, 39]. In one study, 56 % had permanent sequalae with 89 % having ongoing disease activity as adults [38], whereas in another study, 31 % of patients reported active disease after 10 y, with all but one patient having aesthetic sequelae and 38 % reporting functional limitations [39].

Juvenile Systemic Scleroderma

Juvenile systemic scleroderma or sclerosis (JSSc) is a rare and potentially life threatening disease. The hallmark features are inflammation, fibrosis and microvascular disease.

Epidemiology

The reported incidence of JSSc is 0.27 per million children per year [25]. Female to male ratio is approximately 4:1 [40, 41]. Mean age at onset in an international cohort was 8.1 y (range 0.4–15.6), although Indian children were older at 12 y with a longer time from onset to presentation (median 4 y) [40, 42].

Clinical Features

JSSc is characterised by skin induration that does not spare the fingers. Widespread and rapid skin thickening with early organ involvement is typical of diffuse cutaneous JSSc, whereas skin thickening is limited to distal extremities in limited cutaneous JSSc. Microvascular abnormalities manifest as Raynaud's phenomenon, nailfold capillary changes, digital ulcers, pitting scars and ischemia. Compared to adults, children more commonly have overlap features with diseases such as JDM and SLE, with muscle involvement in one-third [41]. Table 4 shows the frequency of manifestations [40].

Investigations

Children may have positive auto-antibodies, including ANA (80 %), ENA (42 %), Scl-70 (34 %) or anti-centromere (7 %) [40]. Investigations at baseline should aim to identify organ involvement to define therapeutic decisions. Although cardiac involvement is uncommon, occurring in 5–10 %, it was the leading cause of death in JSSc [43]. Children should have a baseline ECG and echocardiogram, with consideration of 24 h cardiac monitoring for arrhythmias and cardiac MRI if symptomatic. Effective treatments exist for cardiopulmonary complications, so screening is vital even in asymptomatic children and should as a minimum include echocardiogram, ECG, PFT with diffusion capacity for carbon monoxide (DLCO) every 6 mo in early disease and annually in later disease.

Treatment

There are no therapeutic trials in JSSc; evidence is extrapolated from adult studies. Evidence based recommendations highlight organ-specific treatments (Table 4) [44]. In severe rapidly progressing disease, intravenous cyclophosphamide should be considered although biologics such as rituximab, tocilizumab and abatacept may also have a role.

Outcome

JSSc has a significant mortality, reported as 12 % in one study; all patients had diffuse disease, characterised by rapid progression and major organ involvement [43]. Adult survivors of JSSc appear to have similar organ involvement and survival compared to those with adult-onset SSc [45].

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