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Ultrasonography, MRI and classic radiography of skin and MSK involvement in juvenile scleroderma

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Abstract

Scleroderma is a rare, autoimmune, chronic condition that affects the connective tissue by excessive collagen production. If diagnosed before the age of 16, it is referred to as juvenile scleroderma. There are two major types of the condition: localized and generalized scleroderma. Localized scleroderma has a much higher incidence than the generalized type which is extremely rare among children and affects mostly adults. In either case, imaging can prove to be useful in both the diagnosis and monitoring of the disease. In this article, we aim to review the imaging findings that can be present in juvenile scleroderma, focusing on ultrasonography, magnetic resonance imaging, and classic radiography. Ultrasound provides high-resolution images in real-time dynamic examination. With high-frequency transducers, it may provide a considerable input into the imaging of skin and musculoskeletal involvement. Several findings might be present when using B-mode or Doppler modalities such as thickening and hypervascularization of the cutis and subcutaneous tissue, synovitis and tenosynovitis, as well as small calcifications. Magnetic resonance imaging is also useful to evaluate inflammatory skin infiltration or skin atrophy, as well as deeply located structures, including fasciae, muscles and joints that might not be seen on ultrasonography. This modality is, however, expensive and time-consuming, and might require sedation in children. Classic radiology can show soft tissue calcifications, acroosteolysis, contractures, and subluxations. Computed tomography, which requires a high dose of radiation, is generally avoided in children, except in very specific cases.

Introduction

Scleroderma is a rheumatic disease that affects both children and adults, with the estimated annual incidence rate of 1.4–5.6 per 100,000 in adults, and 1–3 per 100,000 children^(1,2). Juvenile scleroderma (JS) is a rare, chronic disease with an autoimmune background that affects the connective tissue by excessive collagen production⁽³⁾. Girls are nearly 4 times more frequently affected than boys⁽⁴⁾. There are two main types of JS: juvenile localized scleroderma (jLS) and juvenile systemic scleroderma (jSSc),

which differ in clinical presentation, but share same pathophysiology including the inflammatory phase associated with endothelial dysfunction⁽⁵⁾. The two main types are further divided into more subtypes based on additional clinical findings (Tab. 1). There is a noticeable discrepancy in incidence between jLS and jSSc which is estimated up to be 2.7 cases per 100,000 per year in jLS, and 0.27 per 1,000,000 per year in jSSc. This is contrary to the adult population, where systemic scleroderma (SSc) is more frequent than localized scleroderma (LS)⁽²⁾. Arthritis and myositis, which can occur during the course of the disease, are

Tab. 1. Classification of juvenile scleroderma⁽⁷⁾

Juvenile systemic scleroderma	Juvenile localized scleroderma
Juvenile systemic sclerosis	Morphea
Diffuse cutaneous (dcSSc)	Plaque morphea
Limited cutaneous (lcSSc)	Keloidal morphea
	Generalized morphea
	Bullous morphea
Skin limited systemic sclerosis (CREST syndrome)	Linear scleroderma
	Linear morphea
	En coup de sabre
	Parry-Romberg syndrome – hemifacial atrophy
Overlap syndrome	Eosinophilic fasciitis

also more frequent in children. Raynaud's phenomenon and skin sclerosis may also be observed⁽⁴⁾. Racial predilection is evident in jLS, with up to 82% of children affected being Caucasians. JSSc does not follow this pattern⁽³⁾.

The diagnosis of jLS remains challenging. It is diagnosed by a rheumatologist or dermatologist based on the patient's history and physical examination. Clinical assessment of skin involvement is based on the modified Rodnan score. Multiple skin folds are assessed on a scale from 0 to 3, with 3 standing for immobile, rock-hard skin thickening⁽³⁾. A skin biopsy may also be done to confirm the diagnosis. There are no specific laboratory tests with diagnostic utility. RF and autoantibody profiles are performed mainly to exclude other autoimmune diseases. Up to 50% of patients may present with elevated levels of ANA, AHA, and anti-ssDNA⁽⁶⁾.

Imaging, although commonly used, is still not included in any diagnostic criteria and constitutes only an auxiliary tool. In this article, we aim to review the imaging techniques available for juvenile scleroderma including classic radiography (CR), ultrasonography (US), and magnetic resonance imaging (MRI). Computed tomography (CT), which requires a high dose of radiation, is rarely used in children. We will focus on each type of scleroderma separately, and describe imaging findings that can be seen in children affected.

Juvenile localized scleroderma

JLS is the most frequent subtype of scleroderma in children. Excessive collagen production leads to thickening and hardening of limited areas of the skin and subdermal tissues. The manifestation of the disease ranges from very small superficial plaques involving only the skin to extensive lesions causing significant functional and esthetic deformity due to bone undergrowth secondary to skin fibrotic changes following active inflammation (Fig. 1)⁽⁸⁾. Extracutaneous involvement can also occur, with the musculoskeletal system (MSK) being the most commonly affected⁽³⁾. It is important to take that fact into account, as Adrovic *et al.* demonstrated that up to 25% of patients with jLS complained of musculoskeletal complications⁽⁷⁾.

Clinical manifestations of jLS

JLS presents in various patterns of skin involvement, and includes several subtypes classified by the size and localization of skin changes (Tab. 1). The most common is linear scleroderma, followed by plaque and generalized morphea. Other subtypes, such as deep and bullous morphea, are very rare⁽⁸⁾. *En coup de sabre* is a characteristic location of linear scleroderma affecting the head and face, but underlying structures including the skull, eyes, and central nervous system may be also involved. It resembles a saber or a knife cut, and hair loss is typically found in the area affected⁽⁹⁾. The esthetic impairment is the most severe in this type, and may negatively impact the child's quality of life. Neurological symptoms might be reported, with seizures being the most frequent, and other complications comprise headaches, neuropathy, and ocular findings. MRI or CT should always be considered in all patients with this type of localized scleroderma, even those without any symptoms. The evolution of jLS is slow, and the initial symptoms are often underestimated and considered a bruise or an injury, which may cause a significant delay in the diagnosis. Early active lesions are characterized by erythema and violet color. Over time, the skin thickens and becomes shiny with visible veins, and hair loss and cliff-drop atrophy follow⁽⁷⁾. Although internal organ involvement in LS is rare, nearly 25% of patients complain of musculoskeletal complications, such as arthralgia, arthritis, joint contractures, myositis, myalgia, muscle spasm, and hemiatrophy⁽⁷⁾. Bone underdevelopment occurs secondary to soft tissue involvement, and may become a serious problem esthetic but also motoric (e.g. facial deformity, shorter extremities).

Imaging findings in juvenile localized scleroderma

There are a number of pathologies that occur in jLS and can be observed in ultrasonography, MRI or classic radiography.

Ultrasonography

When examining the skin or other superficial structures by ultrasound, high-frequency transducers must be used. Thickening and hypervascularization may be found in B-mode and Doppler studies of the cutis and subcutaneous tissue (Fig. 1). In 2009, Li *et al.* conducted a study on Doppler ultrasound utility in patients with LS. Their findings indicated that hyperemia of subcutaneous tissue might be used as a disease activity monitoring tool⁽¹⁰⁾. This suggests that Doppler US could aid treatment decisions. Porta *et al.* performed a study on changes in skin thickness during steroid and methotrexate treatment. The study also indicated that ultrasound might help to identify disease activity earlier than the clinical examination, and confirmed the role of US in the investigation of not only the skin but also the subcutaneous tissues⁽¹¹⁾.

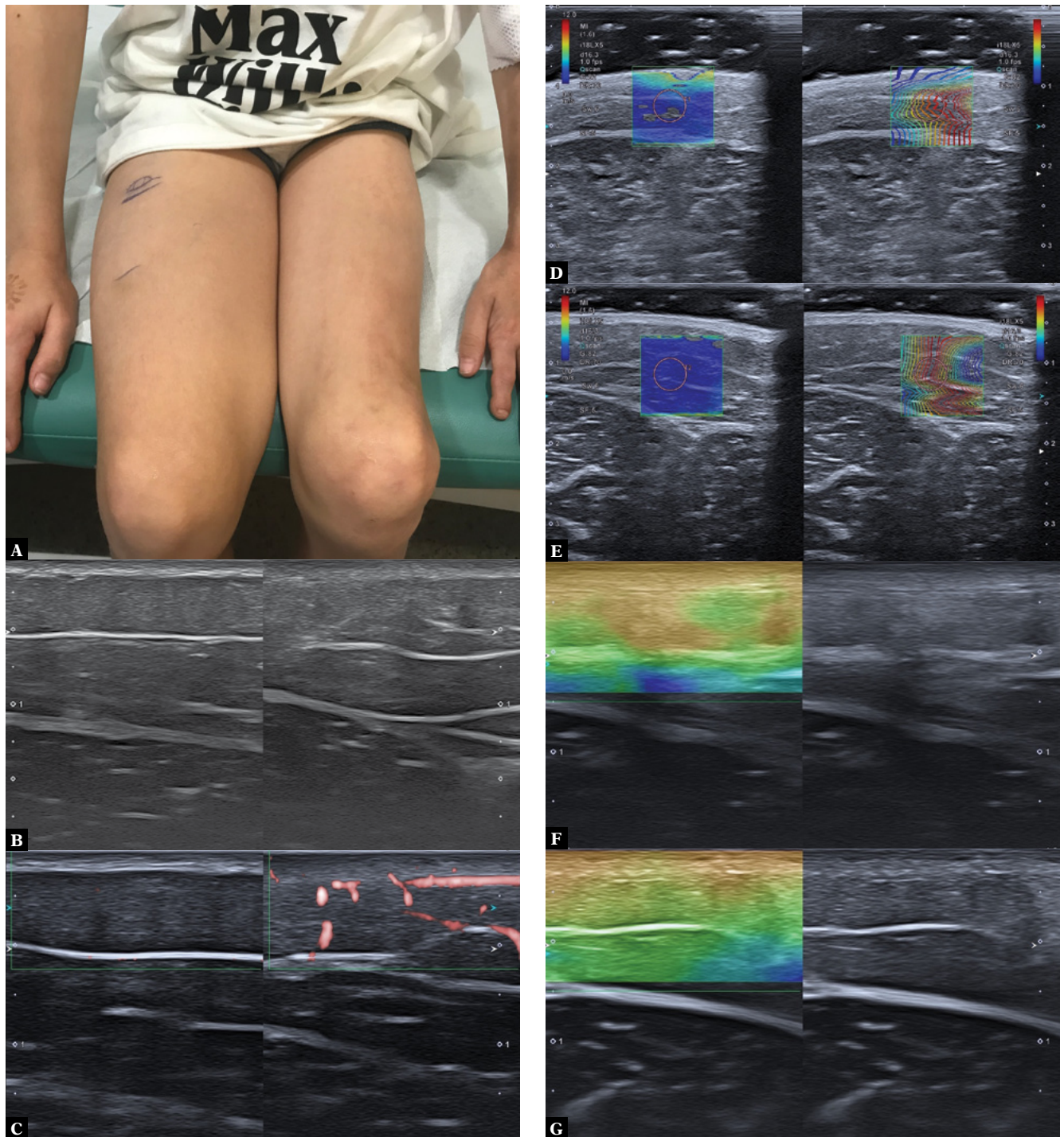


Fig. 1. 13 y.o. boy with jSS and developmental disorders of the left thigh, left forearm and hand. **A.** Clinical presentation; **B.** Gray-scale B-mode with 24 MHz probe shows ill-defined border between the cutis and subcutaneous tissue, their thickening and increased echogenicity, comparing to the contralateral healthy side (left part of the image). **C.** The affected side shows increased vascularity in SMI comparing to the avascular healthy side. **D.** Shear wave (SW) elastography on 18 MHz transducer with propagation map taken from the affected area in the subdermal tissue of the thigh and the corresponding contralateral healthy side show an average speed in this area 1.91 m/s with standard deviation (SD) 0.71 m/s. **E.** SW elastography on the contralateral healthy side was 1.18 m/s and SD 0.18 m/s. **F.** Strain elastography shows lower tissues elasticity of the affected side. **G.** Strain elastography on the healthy side, for comparison

Constant development of ultrasonography has resulted in even higher than 18 MHz transducers used for MSK diagnosis (up to 32 MHz), with more sensitive Doppler options, such as superb microvascular imaging (SMI), and more

accurate shear wave elastography on these high frequency transducers (Fig. 1). Although more research is needed, these technological achievements might have potential in terms of following up disease activity, recognizing low

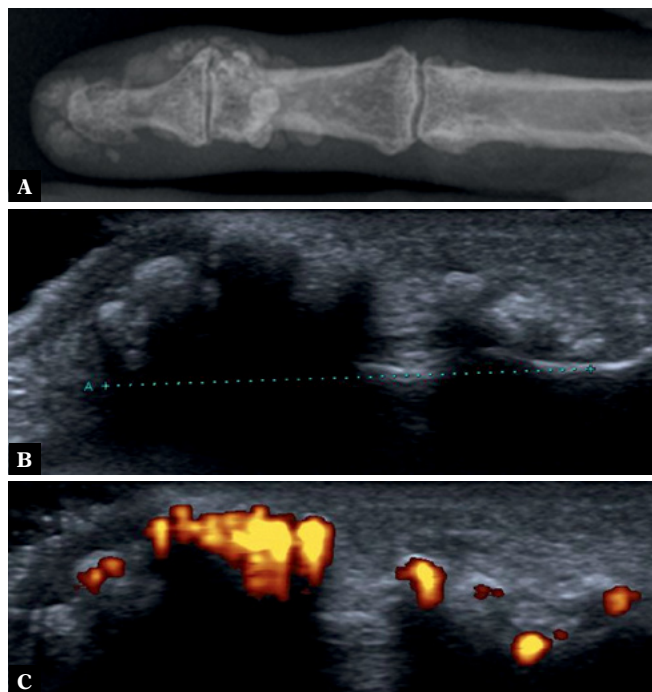


Fig. 2. Calcifications in scleroderma. Plain film radiography (AP projection) reveals a collection of calcifications in the soft tissue at the distal phalanx (A), ultrasonography confirms calcification in this location (B) with twinkling artefact on PD (C) Courtesy of Pracoń *et al.*¹⁴

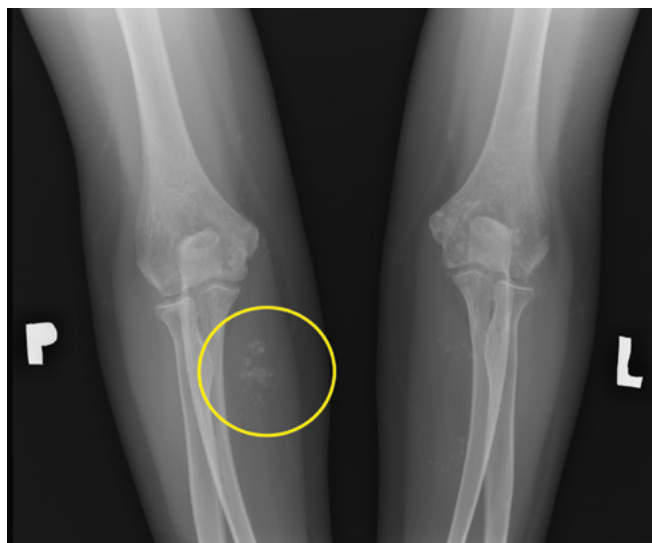


Fig. 3. Calcinosi cutis in a 15-year-old male patient with scleroderma

activity, or fibrosis of affected tissues. Such information would be highly appreciated by pediatricians.

Regarding MSK involvement, synovitis and tenosynovitis are the most frequent pathologies in jLS⁽¹²⁾. The disease rarely leads to destructive lesions. In a series of 190 children with jLS studied by Osimina *et al.*, the vast majority of surveyed patients had linear scleroderma of the limbs, generalized morphea (including unilateral form) and pansclerotic scleroderma. Ultrasound showed synovitis or tenosynovitis in up to 65.7% of cases⁽⁵⁾.

Tenosynovitis and skin atrophic changes may lead to flexion contractures which are most characteristic in the metacarpophalangeal (MCP) and interphalangeal (IP) joints⁽¹³⁾. As this can result in disability, monitoring affected joints by US seems to be very beneficial.

Finally, soft tissue calcifications, which are typical in scleroderma, are by far best seen on radiographs or CT. However, the Doppler modality also enables visualization of those small calcifications, as the twinkling artifact is present (Fig. 2). It is a phenomenon observed on color and power Doppler examination right behind stationary echogenic surfaces. It detects minute calcific deposits before their size is capable of eliciting an acoustic shadow. It is worth bearing in mind, though, that this artifact can mimic blood flow or inflammation⁽¹⁴⁾. Modern MicroPure option can be useful in detecting clustered microcalcifications that are not seen in B-mode imaging⁽¹⁵⁾. This modality is also useful in ruling out the presence of calcifications.

Classic radiography

Radiography may visualize several types of lesions in jLS. Bone resorption of the distal phalanges (acroosteolysis) is the most specific one. As mentioned before, soft tissue calcifications such as calcinosi cutis and subcutaneous calcification are also frequently seen and very well visualized (Fig. 3). Contractures and subluxations seen on CR are results of tendons, fascia and bursal fibrosis. Joint space narrowing, erosions, or bone atrophy are very rare signs⁽¹⁶⁾. In the study mentioned before performed by Osimina *et al.*, which focused on articular involvement in children with jLS and included 190 patients, radiograph abnormalities were seen in the knee, hip, ankle and wrist joints in 14 patients. Among those patients, 8 suffered from linear jLS, 5 from unilateral generalized morphea, and 1 from pansclerotic morphea. In 12 children, joint space narrowing was detected, only in 2 articular erosions occurred. Patients with articular erosions had a prolonged disease duration (more than 7 years) and were treated inadequately. Avascular osteonecrosis of the tibia was present in 1 girl with unilateral scleroderma⁽⁵⁾.

Magnetic resonance imaging

MRI can show abnormalities of the skin, and subcutaneous and deep tissues. It is a modality of choice and gold standard in many musculoskeletal entities. Thanks to the lack of ionizing radiation and high soft tissue contrast MRI is a valuable tool in the diagnosis of juvenile scleroderma, however long acquisition time and the necessity of sedation in younger children are among the disadvantages of this option. Examination of specific anatomical regions or whole-body MRI may be performed. Inflammatory infiltration and atrophy of subcutaneous fat are the most common MRI findings in jLS⁽¹⁵⁾. In linear scleroderma “en coup de sabre”, in addition to band-like sclerotic lesions typically involving the fronto-parietal regions of the scalp, children often present with neurologic symptoms. Muscle inflammation (Fig. 4), fascial involvement and bone marrow edema

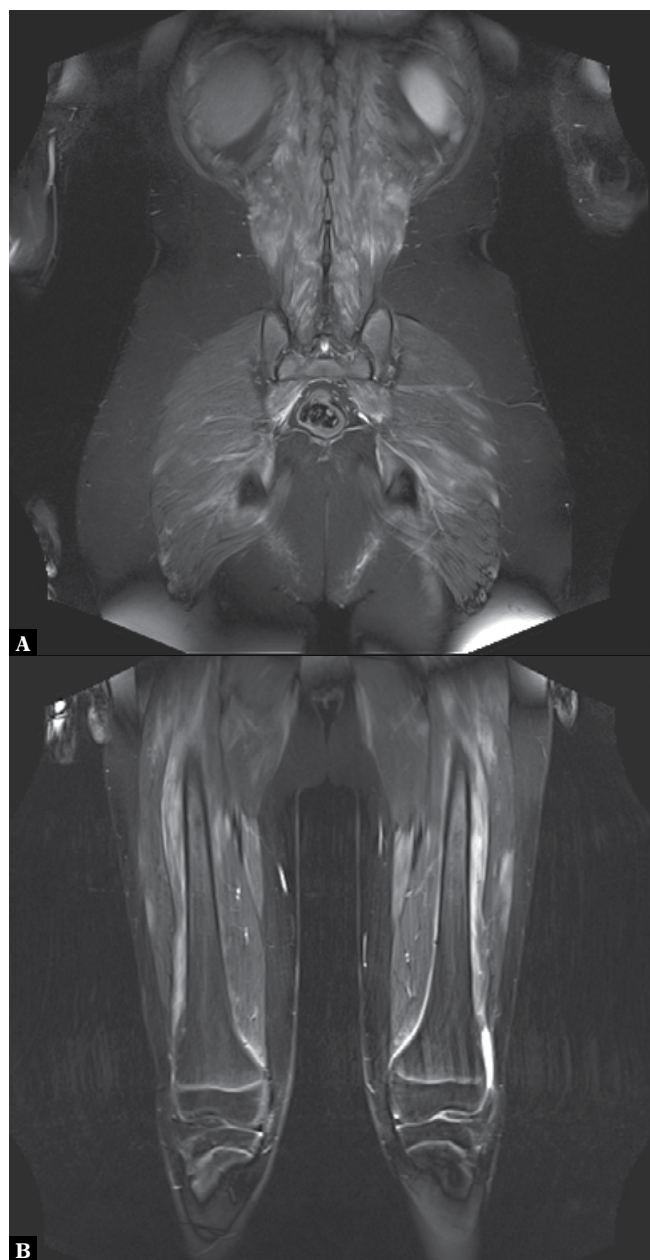


Fig. 4. Whole body MRI in PD FS sequence, coronal views in a juvenile with scleromyositis: **A.** increased signal of paravertebral and gluteal muscles, **B.** increased signal of thigh muscles bilaterally (arrows)

are less frequent, but can be found in MRI images in jLS, the last is exclusively seen on MRI. MRI may especially be needed in the overlapping syndromes, which most commonly concern scleroderma and dermatomyositis (scleromyositis); MRI is the imaging modality of choice for the latter (Fig. 4).

Juvenile systemic scleroderma

JSSc is extremely rare in children. It is associated with fibrous changes in internal organs which can lead to

pulmonary, cardiovascular, gastrointestinal, renal, neurological, musculoskeletal and ocular complications. Therefore, this type of scleroderma has a poorer prognosis⁽¹⁷⁾.

Clinical manifestations of jSSc

Just like in jLS, the skin and musculoskeletal system are the most frequently affected in JS. However, the main prognostic factor in this disorder is the involvement of the cardiopulmonary system. In this scenario, interstitial lung disease may develop, leading to pulmonary hypertension, and ultimately resulting in heart failure. Pulmonary fibrosis is considered to be the main cause of mortality in adults, while cardiac failure is the leading cause of death in the juvenile population⁽¹⁸⁾.

Some of the major clinical manifestations are Raynaud's phenomenon (RP) and skin changes affecting the hands. RP is a vasospasm of the peripheral arteries and arterioles which leads to a triphasic color change of the hands: first pallor, then blue, and at the end red with swelling and pain. RP is quite common in jSSc and according to Scalpina *et al.* it affects 74% to 100% of patients⁽¹⁹⁾. Cutaneous manifestations are often subtle and insidious at the beginning, and children may fail to communicate them to their parents or caretakers. Initial cutaneous signs include edema of the skin followed by palpable skin thickness and fibrosis. Other skin findings include calcinosis, telangiectasias, and dyspigmentation⁽²⁰⁾.

Internal organ involvement in children is not as common as in adults. According to Scalpina *et al.* in a study that included 111 patients with childhood onset of SSc gastrointestinal symptoms like reflux, dysphagia, esophagitis, bloating are the most common and occur in approximately half of the children⁽¹⁹⁾. Lung and cardiac involvement were rare in the pediatric population. Those were, however, a major cause of SSc-related mortality in children. Lung involvement presented with interstitial lung disease and pulmonary arterial hypertension. Cardiac manifestations included pericarditis, cardiomyopathy and arrhythmias. Renal involvement is rarely seen in childhood. Renal crisis has been described, with a frequency of less than 5% in children⁽²¹⁾.

Compared to the adult onset, MSK involvement is more common in juvenile SSc. The most prevalent manifestations are arthralgia, arthritis and myalgia. Approximately 25% to 40% children experience arthritis⁽¹⁾. Foeldavi *et al.*, in a prospective study including 80 children, investigated the difference in manifestations of limited cutaneous juvenile systemic sclerosis (lcSSc) and diffuse cutaneous juvenile systemic sclerosis (dcSSc) subtypes. Musculoskeletal involvement was present in 58% in dcSSc and 73% in lcSSc group. In both subsets, joint contractures dominated, with 42% in dcSSc and 55% in lcSSc ($p = 0.542$), while swollen joints were rarely observed. Similarly to adults, there was a female dominance (the female-to-male ratio 4.8:1 in the dcSSc, and 3.4:1 in the lcSSc group).

Male patients, however, tended to suffer a more severe course of the disease⁽²²⁾.

Ultrasonography

Similarly to jLS, high-frequency ultrasonography can be used to evaluate and monitor skin thickness and echogenicity. In the case of jSSc, skin thickness was associated with greater disease severity, and was shown to predict the extent of visceral involvement, and patient prognosis and survival. Likewise jLS, excessive collagen production and subsequent fibrosis of the skin lead to increased skin stiffness which nowadays can be measured during ultrasound examination using shear wave elastography. Stiffness is coded in appropriate colors in the elastography box which is usually superimposed on B-mode gray-scale presentation. A very high sensitivity, specificity and reliability of shear wave elastography in the assessment of SSc skin involvement was confirmed in a study by Yang *et al.*⁽²³⁾. A later study, conducted by Aryan, on the effectiveness of elastosonography to differentiate scleroderma lesions from other skin lesions considering tissue elasticity also concluded that elastography is useful for skin assessment in scleroderma which would be helpful for disease evaluation in its clinical course⁽²⁴⁾. Nevertheless, their studies were limited by a small number of enrolled patients due to low general prevalence of the disease.

Classic radiography

Radiographs in jSSc may show bone resorption of the distal phalanges (acroosteolysis) with periarticular calcification and atrophy at the tips of the fingers. Bone loss and subcutaneous calcification are additional findings that might be seen. Resorption of the first carpometacarpal joint (CMC) with radial subluxation is a characteristic feature on radiographs of the hands. Shortening of long bones is possible due to soft tissues fibrosis. Dilatation of the esophagus in the most typical sign, along with gastro-esophageal reflux due to reduced sphincter tone⁽¹⁶⁾.

Magnetic resonance imaging

MRI, as far as systemic sclerosis is concerned, plays an important role in the diagnosis of brain abnormalities which are, fortunately, extremely rare. Brain calcifications and hyperintense white matter signals can be seen on MRI⁽¹⁷⁾. It is also useful as an additional diagnostic tool when internal organ involvement is suspected.

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Computed tomography

CT is rarely performed in children, as it requires a high dose of radiation. It is, however, the main tool for the assessment of interstitial lung disease which is the main cause of mortality in children with jSSc.

Conclusion

Juvenile scleroderma is a chronic disease with no cure. The treatment focuses on the management of inflammation of specific organs affected. Juvenile localized scleroderma, despite having a much better prognosis than juvenile systemic scleroderma, with almost no mortality, has a poorer prognosis when diagnosed in childhood. Due to the fact that the condition affects children during their intensive growth period, it may cause significant functional deformities such as extremity length differences, joint contractions, and growth retardation. This is why a quick diagnosis and appropriate treatment at the early stage of jLS are crucial. Imaging, especially new high-frequency ultrasonography, shear-wave sonoelastography, and MRI, may provide early diagnosis and good monitoring of the disease. They are essential tools for the treatment because immunosuppressive therapy is effective only in the active, but not the sclerotic phase of the disease. Due to a limited population of patients, studies of juvenile scleroderma are very few and insufficient. Imaging techniques, as well as the quality and protocols of imaging, vary across different centers. Further research needs to be done to standardize those protocols. In addition, scleroderma belonging to the group of diffuse rheumatoid connective tissue disorders, may occur with another disease simultaneously, creating what is called an overlap syndrome – a term used to define the coexistence of more than one connective tissue condition. Precise diagnosis in these cases is very demanding, especially in children⁽²⁵⁾. Since imaging techniques are constantly being developed, the implementation of new technologies, software and protocols may help in the diagnosis, monitoring and treatment of rare systemic diseases such as juvenile scleroderma. This is a crucial aspect, as treatment decisions and prognostic assessment are directly related to imaging results along with clinical findings.

Conflict of interest

The Authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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