Review Article on Pediatric Pulmonary Hypertension

Systemic sclerosis-associated pulmonary arterial hypertension in children

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Abstract: Systemic sclerosis (SSc) is a rare disease in childhood and is characterized by a combination of vasculopathy, inflammation, autoimmunity, and fibrogenesis with individually varying expression pattern. Pulmonary arterial hypertension (PAH) is a serious complication of SSc and affects approximately 10% of SSc patients. SSc-PAH is complex and difficult to diagnose, as symptoms are non-specific and may be complicated by other SSc-associated diseases such as interstitial lung disease or left heart disease. SSc-PAH patients can deteriorate rapidly, and disease progression can occur even in patients with mild PAH symptoms at diagnosis. Therefore, interdisciplinary care of SSc patients is essential, and treating physicians must be aware of the association between SSc and PAH. In order to detect PAH early, children with SSc should be regularly screened for PAH by pediatric cardiologists. If PAH is detected, a systematic diagnostic approach by trained PH specialists including careful phenotyping of PAH is required. Relevant interstitial lung disease and left heart disease should be ruled out in the differential diagnosis of SSc-PAH before starting any targeted therapy. Due to the progressive character of SSc-PAH known from adult studies, it appears appropriate to initiate targeted PAH-therapy in juvenile SSc-PAH early. Adapted from adult treatment algorithms, combination therapy regimens (addressing at least two pathophysiological pathways) are increasingly used for pediatric PAH patients, and there is growing evidence to support this approach also in SSc-PAH patients.

Keywords: Pediatric pulmonary hypertension; pulmonary vascular disease; pediatric cardiology; pediatric rheumatology; systemic sclerosis (SSc); cardiac catheterization

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Systemic sclerosis (SSc) usually presents with a combination of vasculopathy, inflammation, autoimmunity, and fibrogenesis that can individually vary (*Figures 1-3*) (1). Major complications can include digital vasculopathy, gastrointestinal complications, cardiac and pulmonary fibrosis, scleroderma renal crisis, digital contractures, calcinosis, and acro-osteolysis (2).

The etiology and pathogenesis of SSc is largely unknown. There is evidence of multifactorial genesis with interacting genetic, vascular, autoimmunological and metabolic factors (3,4). Genome-wide analysis showed a significant association of SSc with modifications of the fibrillin-1 gene and other genes involved in collagen metabolism. In skin and lung fibroblasts, collagen production is activated by transcription. Other candidate genes relate to HLA molecules and inflammation mediators, especially transforming growth factor β (TGF-β) and connective tissue growth factor (CTGF). Furthermore, a disturbed expression of metalloproteinases and their inhibitors has been described. An increased expression of cytokines and chemokines (IL-1, IL-4, TNF-α, IL-17, IL-21, MCP-1, MCP-2) can lead to an increased presence of immunological effector cells in the

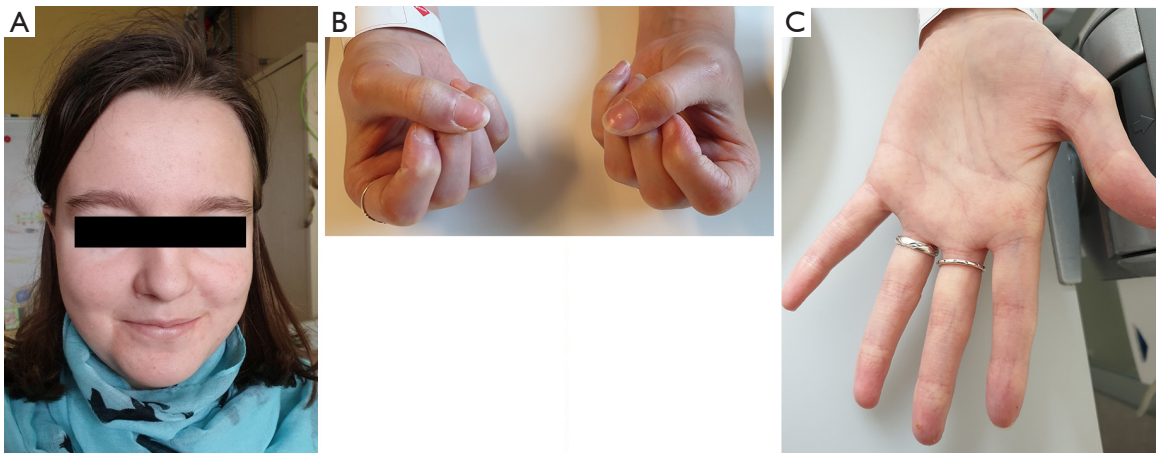

Figure 1 Typical clinical findings of systemic sclerosis in a teenaged girl who presented with evidence of PAH at echocardiographic examination and an elevated NT-pro BNP level of 1,286 ng/L (normal: <97 ng/L). She reported of general weakness, painful knee and wrist movement, paleness of fingers, loosing of hairs, and difficulties in swallowing resulting in weight loss of 5 kg in 6 weeks. (A) Symmetrical facial skin tightening; (B) painful limitations of motion in both wrists and flexion contractures in all metacarpophalangeal and proximal interphalangeal joints; (C) Raynaud's phenomenon.

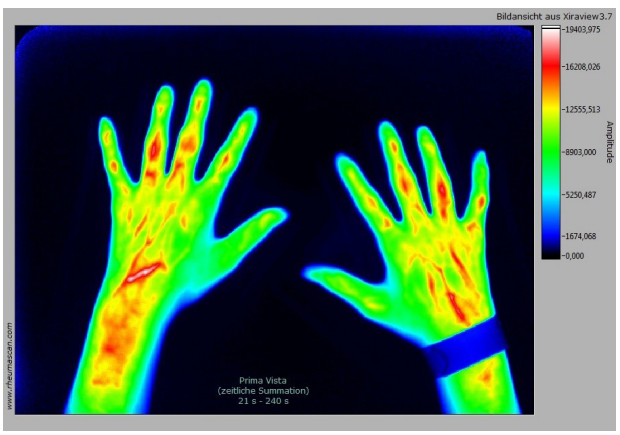

Figure 2 Fluorescence optical imaging of the same patient as in *Figure 1* revealing active polyarthritis.

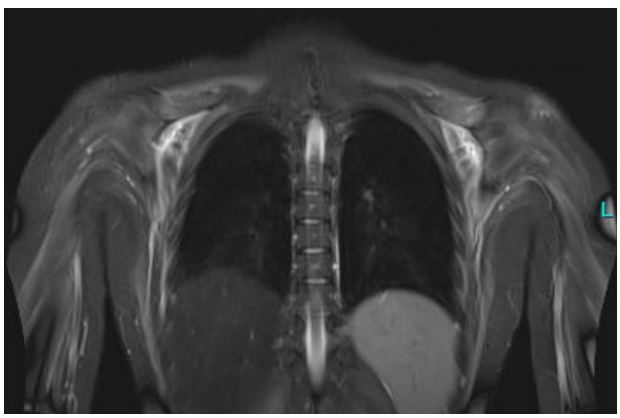

Figure 3 Magnetic resonance imaging of the upper torso and upper extremities in the same patient as in *Figure 1* showing diffuse myositis.

target organ. Lymphocytes may be sensitized to components of the connective tissue and stimulate fibroblasts to increase collagen production. Further evidence of autoimmunity in SSc results from the detection of antinuclear antibodies and an association with HLA class I and II antigens (HLA-B8, –DR3, –DR5) (4).

SSc is rare in children with a reported annual incidence of 0.27 to 0.5 per million children age <16 years (5,6), and a prevalence of 3 per million (7,8). Characteristic skin changes were the most common feature reported in the largest series of 153 patients with juvenile SSc, followed by Raynaud's phenomenon, musculoskeletal and cardiopulmonary symptoms (9). Approximately 10% of adult patients with SSc are affected by pulmonary arterial hypertension (PAH). Corresponding data in children with SSc is rare, however PAH appears to be similar frequently in juvenile and adult SSc (4,9-12).

In adult patients, PAH associated with connective tissue disease (CTD-PAH), including SSc, is the most commonly identified type of disease-associated PAH (13). According to

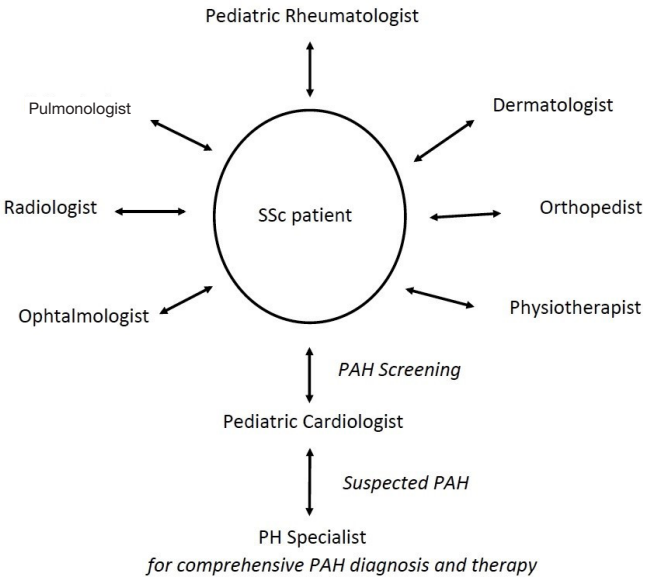

Figure 4 Schematic presentation of the interdisciplinary team involved in the medical care for SSc patients. If PH is suspected, further specific diagnosis and treatment should be performed by trained PH experts.

data of the largest pediatric PH registry, the global TOPP-registry (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension), CTD-PAH affected 3% of 362 registered children with invasively confirmed pulmonary hypertension (14).

Pulmonary arterial hypertension in SSc

PAH is a progressive disease of the pulmonary vessels that eventually leads to right ventricular failure and death if left untreated. PAH is a serious complication of many connective tissue diseases (CTD), including SSc, systemic lupus erythematosus, mixed CTD, and, to a lesser extent, dermatomyositis, and Sjögren's syndrome (15).

The prognosis of CTD-PAH patients is affected by the underlying CTD etiology and disease severity, but it is known from adult data, that patients with SSc-PAH might have poor prognosis (16,17). While children with SSc usually have better outcome compared to adult SSc due to lower frequency of severe organ involvement (18,19), PAH is still one of the leading causes of morbidity and mortality in patients with SSc (19-22).

A lack of awareness of SSc-PAH related symptoms among treating physicians and patients can cause delays in diagnosis and therapy. However, while SSc-PAH can progress rapidly, early detection and treatment is essential (23,24). Therefore, regular screening for PAH of SSc patients in an interdisciplinary setting is considered to play an important role in the disease management (*Figure 4*). In adults, annual PAH-screening of SSc patients is recommended (15), and there is growing evidence to support this approach also in pediatric SSc patients.

Patients with SSc-PAH frequently present with non-specific symptoms, therefore it is reasonable to have a high index of suspicion in this at-risk population. Red-flag findings for the presence of SSc-PAH should optimally be recognized and seeked for, such as decreased diffusing capacity of the lung for carbon monoxide (D_{LCO}), increased ratio of forced vital capacity to D_{LCO}, and an abnormal antinuclear antibody pattern (25). In contrast to adult SSc-PAH, presence of anti-centromere antibodies does not seem to be appropriate for PAH screening in children with SSc, as they can be found only rarely in childhood, and no correlation could be detected between anti-centromere antibodies and the manifestation of PAH in juvenile SSc (18,26).

Transthoracic echocardiography is a recommended assessment tool for PAH-screening of patients with SSc (15). A tricuspid valve regurgitation Doppler velocity >2.8 m/sec is regarded as suspicious of the presence of PAH. If no tricuspid valve regurgitation is available, indirect markers of evidence for possible PAH include right ventricular dilatation, right ventricular dysfunction, systolic flattening of the interventricular septum, and Doppler abnormalities of pulmonary arterial blood flow (increased acceleration time, systolic notch).

Additional screening options include pulmonary function tests, exercise stress testing, and measurement of cardiac biomarkers, i.e., brain natriuretic peptide (15,27).

Composite screening algorithms can increase the sensitivity and negative predictability of testing compared to single screening methods alone.

Importance of a systematic diagnostic approach

It has to be considered that pulmonary hypertension in SSc can present with varying features of precapillary (pulmonary vascular disease), intrapulmonary (due to interstitial lung disease) and postcapillary (as a consequence of left ventricular myocardial dysfunction) disease.

A precise differential diagnosis of PAH is often challenging (15,28), but careful phenotyping of PAH in SSc

patients, usually including systematic invasive evaluation by cardiac catheterization, is critical to allow prognostic assessment and targeted treatment (29,30).

PH due to interstitial lung disease (ILD, group 3 PH) often has worse prognosis than SSc-PAH (31). PAH-specific therapies have not shown to improve symptoms and outcome in ILD, and may even cause an increased risk of hypoxia in SSc patients with ILD and PH (30).

Post-capillary PH can be due to myocardial fibrosis and resulting left ventricular dysfunction (group 2 PH) (30). There is no clear evidence that PAH-specific therapies are able to improve outcome in SSc patients with left heart disease (32). Additional pulmonary veno-occlusive components can also complicate SSc-PAH, and are associated with worse survival and increased risk of pulmonary edema if PAH therapies are initiated.

Therefore, relevant interstitial lung disease and left heart disease should be ruled out in the differential diagnosis of SSc-PAH before starting any targeted therapy.

Treatment of SSc-PAH

The following targeted drugs are meanwhile available for specific therapy of PAH addressing three pathophysiologic pathways (nitric oxide, endothelin, and prostacyclin pathways): the phosphodiesterase-5 (PDE-5) inhibitors (Sildenafil and Tadalafil); Riociguat, a soluble guanylate cyclase stimulator; the endothelin receptor antagonists (ERA) (ambrisentan, bosentan and macitentan), the prostacyclin analogues iloprost (inhalation), epoprostenol, treprostinil (subcutaneous and intravenous), and the prostacyclin (IP) receptor agonist Selexipag (33,34). Owing to the rarity of the disease in children, and the lack of randomized controlled clinical studies, the majority of these drugs is used off-label, only Sildenafil and Bosentan are currently approved by the European regulatory agency (EMA) for specific therapy of children with PAH beyond infancy (33,34).

Due to the progressive character of SSc-PAH known from adult studies, it appears appropriate to initiate targeted PAH-therapy in juvenile SSc-PAH early. If left untreated, the prognosis for SSc-PAH might be quite poor with reasonable mortality, similar to other progressive forms of PAH (i.e., idiopathic or heritable PAH).

Recently, adult registries have demonstrated, that the emergence of new treatments and use of combination therapy has improved survival for SSc-PAH patients (32). Both, the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) and 2017 European League Against Rheumatism (EULAR) guidelines therefore recommend that adult patients with SSc-PAH should be treated according to evidence-based treatment algorithms (32,35). Growing evidence has established initial double combination therapy as a key strategy for treating adult patients with PAH, including those with SSc-PAH. The 6th WSPH proceedings recommend initial monotherapy only in a minority of PAH patients (32). A structured follow-up, particularly early after treatment initiation, should allow for the identification of early signs of disease progression to intensify treatment. Recently, corresponding recommendations for PAH in children adapted from adult treatment algorithms became available (36,37). Dual combination therapy regimens (i.e., ERA and a PDE-5 inhibitor) are increasingly used for patients with a low- or intermediate-risk status (36), and there is growing evidence to support this approach in CTD-PAH patients (38,39).

In SSc-PAH, the targeted PAH-therapy is usually combined with immunomodulatory/immunosuppressive drugs to control the inflammatory process and slow the progression towards fibrosis (i.e., cyclophosphamide, mycophenolate mofetil) (40).

Concluding remarks

PAH is a serious complication in children with SSc associated with a high risk to deteriorate and increased morbidity and mortality. Therefore, treating physicians must be aware of the association between SSc and PAH, and interdisciplinary care of SSc patients is essential. Regular screening by pediatric cardiologists may enable early diagnosis, which should be followed by structured diagnostic testing and comprehensive PAH-targeted treatment by PH specialists.

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