Respiratory System Involvement in Collagen Vascular Disease in Childhood

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Summary
The collagen vascular diseases (CVD) constitute a group of autoimmune disorders whose common denominator is damage to components of connective tissue at a variety of sites in the body. This term encompasses a number of distinct clinicopathologic disease entities, each of which is characterized pathologically by cellular inflammation and fibrotic changes, and clinically by the types of alteration produced and by the locations of the affected tissues. For the purpose of this short review, we will focus on CVD most frequently presenting involvement of the respiratory system in paediatric patients.

Introduction
Collagen vascular diseases (CVD) represent a heterogeneous group of immunologically-mediated inflammatory disorders affecting a variety of organs, including the respiratory system [1]. Airways, vessels, parenchyma, pleura and respiratory muscles may all be involved as a result of specific manifestations of the immune processes, but also of opportunistic infections and of toxicity of drugs used to treat patients [1,2]. The respiratory system is a particularly vulnerable target because of both its abundant vasculature and its large content of connective tissue which are frequently involved in CVD. The frequency of involvement varies according to the type of underlying disorder but also whether clinical, physiologic, roentgenographic, or histologic criteria are used to detect the abnormalities [1-3]. The lesions may be morphologically characterized by interstitial inflammation and fibrosis, granulomatous reaction, primary vasculitis, reflecting the different pathogenetic mechanisms involved [4]. Prognosis and response to therapy vary, depending on the pattern of involvement as well as on the underlying connective tissue disorders [5]. The subject of this short review is to describe the most frequent type of respiratory system disorders observed in paediatric patients affected by the major CVD, i.e. systemic scleroderma, systemic lupus erythematosus and juvenile dermatomyositis.
Systemic scleroderma

Systemic scleroderma (SSc) is a progressive, multi-system disorder of connective tissue characterized by deposition of excessive extracellular matrix and vascular inflammation and obliteration in many organs, including the skin, the lung and the kidney [6]. As for the other CVD, the aetiology of SSc is unknown, but the current concepts recognize that in response to unknown initiating factor(s), endothelial and/or epithelial injury may precede inflammation and fibrosis. The pathophysiologic features that follow the initial injury include immunologic and inflammatory responses in a profibrogenic microenvironment [6-8]. Respiratory involvement is frequent, being described in 50 to 90% of the affected children and it may be the presenting feature of the disease and accounts for significant morbidity and mortality [8-10]. Pulmonary abnormalities in SSc include: a) chronic interstitial lung disease; b) pulmonary arterial hypertension, c) aspiration pneumonia.

Chronic interstitial lung disease (ILD) associated with SSc is morphologically indistinguishable from idiopathic pulmonary fibrosis (IPF) and classified in different histopathologic subsets termed diffuse alveolar damage (DAD), desquamative interstitial pneumonitis (DIP), non specific interstitial pneumonitis (NSIP), bronchiolitis obliterans organizing pneumonia (BOOP) [also termed cryptogenic organising pneumonia (COP)] and lymphocytic interstitial pneumonitis (LIP) [6,7,11]. Although it was suggested that these subsets may account for some of the difference in outcome for patients with SSc-ILD, a recent report on adult patients indicated that survival was linked more strongly to disease severity at presentation, i.e. pulmonary function impairment, than merely to histopathologic findings [11]. High resolution computed tomography (HRCT) findings include ground glass opacification, subpleural micronodules, linear opacities and honeycombing, frequently seen in association with thin-walled cysts/bullae and large cystic airspace (figure 1A) [6-8,12]. There is usually no clear correlation between the duration of illness and the severity of interstitial/destructive changes [12]. Pulmonary function tests may show in a high proportion
(≥50%) of patients a restrictive ventilatory defect with alveolar–capillary diffusion abnormality, demonstrated by low values of carbon monoxide diffusing capacity (DLCO) [6-8]. Airflow obstruction may also be present [6-8].

**Pulmonary arterial hypertension** (PAH) occurs frequently in patients with SSc and is an important cause of mortality [5-8,13]. It may be seen as a primary (primary pulmonary arterial hypertension or PPAH), or as a secondary phenomenon, related to the underlying interstitial fibrotic changes [13]. Symptoms are non-specific and can be ascribed to other features of the disease, so it is often under-recognized until the late stages. Although systolic pulmonary artery pressure evaluation remains the diagnostic gold standard for the diagnosis of PAH, abnormal pulmonary function, and particularly a disproportionate fall in DLCO, can identify patients in the early stages of PAH. Earlier treatment with new agents is associated with better treatment outcomes.

**Aspiration pneumonias** of various degrees is not uncommon in patients with SSc, as a result of regurgitation and gastroesophageal reflux due to the typical esophageal and gastric dysmotility or because of oropharyngeal dysphagia [14]. Indeed, a small oral aperture, secondary to facial skin thickening and tightness, can inhibit normal eating and interfere with oral hygiene, while low saliva flow, due to salivary gland involvement, may cause difficulty swallowing in addition to delayed neutralization of refluxed gastric content. Symptoms may include the sense of food sticking in the mouth or coughing on swallowing [14].

### Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of autoantibodies against various nuclear antigens and multiple systems and organs involvement [4]. At respiratory level pleural effusions, pneumonitis, diaphragmatic dysfunction and shrinking lung syndrome, alveolar haemorrhage, ILD, bronchiolitis obliterans (with or without organising pneumonia) can all be observed, in addition to opportunistic pulmonary infections or drug toxicity from immunosuppressive therapy [4,15]. Although involvement of the respiratory system in
children is infrequent, it may either be an initial or a late life-threatening complication [15-17]. Pulmonary function tests in patients with SLE often show a moderate to marked functional restrictive ventilatory defect with low DLCO values despite a normal radiologic appearance of the lungs [15-18]. HRCT may show the presence of ground-glass attenuation and consolidation, reflecting the presence of acute lupus pneumonitis, alveolar haemorrhage, while the diagnosis of ILD is supported by the demonstration of a reticular pattern, with interlobular septal thickening, irregular linear hyperattenuating areas and architectural distortion, involving mainly the lower lung zones. Such abnormalities are usually mild and focal and honeycombing is uncommon [18].

Pleural involvement is the most common thoracic manifestation of SLE, in the form of pleuritic chest pain, with or without pleural effusion [16]. Pleuritis can be unilateral or bilateral and may occasionally be the initial manifestation of the disease, the effusions are usually of small volume and rarely require chest tube drainage [17]. Non-inflammatory pleural effusions may also be observed, as in the case of nephrotic syndrome, and are usually asymptomatic [16].

Acute lupus pneumonitis is characterized by alveolar wall damage and necrosis, inflammatory cell infiltration, haemorrhage, oedema, and hyaline membrane formation. Large vessel vasculitis and thrombosis of small vessels have rarely been detected. Presenting symptoms comprise cough, dyspnoea, pleuritic chest pain, hypoxemia and fever, no or minimal haemoptysis and possible presence of pulmonary arterial hypertension. Chest radiographs and HRCT will reveal atelectasis and bibasilar infiltrates [16-18].

Diffuse alveolar haemorrhage (DAH) is characterized by diffuse alveolar infiltrates, haemoptysis, and a drop in haematocrit/haemoglobin levels (figure 1B) [15-18]. It can mimic congestive heart failure and pneumonitis, or present with sudden pallor, and tachycardia. Pathologically, neutrophilic vasculitis of the capillaries and venules, bland haemorrhage, or diffuse alveolar damage with haemorrhage can all be seen [19]. A reversible rise in DLCO per unit alveolar volume (DLCO/VA) at pulmonary function tests can be detected, reflecting active intrapulmonary haemorrhage [20].
**Shrinking lungs syndrome** (SLS) is one of the uncommon manifestations of SLE. It is characterised by tachypnea and the use of accessory respiratory muscles, hypoventilation on both pulmonary bases and a restrictive defect at spirometry [21]. Some patients may present pleuritic chest pain. Chest x-ray and HRCT scan can demonstrate the presence of linear atelectasis and elevated hemidiaphragms [21,22]. The processes leading to SLS are unknown but the existence of a dysfunction of the respiratory muscles, detected in affected patients, or a restriction in the expansion of the chest wall of unknown origin could be the cause for the decrease of pulmonary volumes [21].

**Juvenile Dermatomyositis**

Juvenile Dermatomyositis (JDM) is an autoimmune inflammatory myopathy characterized by acute or chronic non-suppurative vascular inflammation of the striated muscles, skin and various other organs and clinically by cutaneous changes, proximal muscle weakness and laboratory evidence of myositis [23]. Involvement of the respiratory system is commonly in the form of: a) ILD; b) aspiration pneumonia secondary to pharyngeal dysmotility (probably the most common pulmonary complication) (figure 1C); c) hypoventilation, hypercapnic respiratory failure and hypostatic pneumonia, as a result of respiratory muscle weakness; d) primary pulmonary hypertension, related to fibro-proliferative processes involving the arterioles and small muscular pulmonary arteries [23]. Lung function tests may demonstrate restrictive lung disease and decreased DLCO [24]. The frequency of radiographic abnormalities is low, the most common being a symmetric, predominantly basal reticular pattern that may progress to honeycombing, or bilateral areas of consolidation usually corresponding to aspiration pneumonia or organizing diffuse alveolar damage [25]. Functional or radiographical findings of interstitial lung involvement may also be found in asymptomatic patients [25, 26].

**Interstitial lung disease** associated with polymyositis or dermatomyositis has a wide spectrum of histopathologic features but three major groups can be identified: non specific interstitial
pneumonitis (NSIP), diffuse alveolar damage (DAD), bronchiolitis obliterans organizing pneumonia (BOOP) [23-27]. In contrast with patients BOOP, those with DAD or NSIP have a poor prognosis. BOOP is characterized histologically by intra-alveolar and small airways buds of granulation tissue, consisting of intermixed myofibroblasts and connective tissue and chronic inflammation in the walls of surrounding alveoli with preserved lung architecture [27]. BOOP was reported in association with various systemic disorders, including infections, drug reactions and collagen vascular diseases, such as polymyositis/dermatomyositis, rheumatoid arthritis, SLE and mixed connective tissue disease [27-29]. It is rare in children [28,29] and, in contrast with the other ILD histopathologic subsets, the intra-alveolar and small airway fibrotic changes, are in general dramatically reversible with corticosteroid treatment [27].

**Conclusion**

Different types of respiratory tract involvement may be present in several forms of CVD also in childhood. The clinical presentation, prognosis and response to therapy may vary depending on the underlying CVD but also on the histological pattern of the respiratory tract manifestations reflecting different pathogenetic mechanisms or stage of the disease.

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