Editorial

Juvenile-onset systemic sclerosis: children are not small adults

The majority of childhood-onset rheumatic diseases differ markedly in presentation and management from their equivalent adult conditions, and juvenile-onset systemic sclerosis (JSSc) is no exception. Chronic illness from any cause in childhood impacts heavily, not only on physical growth and development, but also in terms of social, educational and psychological development. Even localized scleroderma, the most common spectrum in children, which is not associated with the internal organ complications that account for the majority of mortality and morbidity in both juvenile and adult systemic disease, has profound effects on limb growth and development that cause major morbidity compared with the adult disease.

SSc is the most serious form of scleroderma and is much rarer in children than adults. In the past, lessons from adult SSc have been extrapolated to JSSc but this is potentially misleading. In the present issue, Martini et al. [1] present the most recent of a series of reports examining clinical features and outcomes of JSSc in retrospective cohorts, and indirectly help to identify the characteristics of juvenile-onset disease that differentiate it from the adult condition [1–3]. The clinical heterogeneity of SSc remains one of the most challenging aspects of adult disease, but both the limited and diffuse subsets do tend to follow recognizable disease courses, in which genetic, environmental and autoantibody profiles appear to play a pathophysiological role. This study, along with those performed previously, reveal a disease that differs in terms of epidemiology, clinical characteristics, immunology and outcomes, and does not clearly follow any of the defined pathways seen in adult disease [4]. Even in late-stage disease, within an adult SSc cohort, patients with juvenile-onset disease continue to remain distinct in terms of clinical features and outcomes [5].

Incidence and prevalence of JSSc is somewhat difficult to determine, with incidence quoted between 3 and 10% of adult disease. This difficulty arises from a lack of clear definition in juvenile-onset CTDs. These present as overlap syndromes far more commonly than adult-onset disease, and so Martini et al. [1], by applying ACR preliminary classification criteria for SSc in adults, may exclude many overlap syndromes with features of SSc and a proportion of those with limited cutaneous disease. Additionally, the scleroderma research community depends heavily on the modified Rodnan skin score as a primary or secondary outcome measure in clinical trials but this measure has not been validated in JSSc. A preliminary system for diagnosis and classification of JSSc has now been agreed between PRES, EULAR and ACR to endeavour to standardize clinical research, therapeutic trials and other studies [6].

Notwithstanding these caveats, the present study again confirms the clinical suspicion that diffuse disease is more common in JSSc; in this study, 122/134 patients had diffuse disease. In adult cohorts, the majority of cases are the limited subset; for instance in our centre, only one-third of the patients under follow-up have the diffuse subset [7]. Perhaps unsurprisingly, the hallmark autoantibody of limited disease, ACA, is extremely rare in childhood disease, carried by just one patient in this cohort. Autoantibodies carried in cases of JSSc are less specific than adults in any case. Interestingly, the higher incidence in females, even prior to puberty, again challenges the dogma that oestrogens are solely responsible for the increased autoimmune propensity in females, with X-inactivation chimerism cited as an alternative mechanism.

While the overall mortality of juvenile-onset disease is lower, those with a poor outcome tend to progress more rapidly than their adult counterparts. Cardiac disease in adults is rarely the primary cause of death, whereas this study supports findings from previous studies that most juvenile deaths occur due to cardiac disease, excluding right heart failure for pulmonary arterial hypertension—25% in this study and over 50% in previous studies. Remembering the increased incidence of overlap syndromes in children, this may be accounted for by an increased vasculitic or inflammatory serosal component to this disease compared with adults. An alternative explanation arises from both animal and clinical research in adult SSc, where a secondary insult obtained over time in a susceptible individual may result in a particular pattern of disease, whether that be epithelial injury as a cause for lung fibrosis or hypertension or steroid use triggering renal crisis. With the relative absence of long-term comorbidities or exposures to epithelial injury, and less specific auto-antibody profiles in children, these adjuvant factors may be less prominent resulting in the apparent overrepresentation of cardiac disease in this cohort. In adults, primary cardiac disease in SSc can involve any of the cardiac structures, and hence can present diversely as pericardial effusions, inflammatory myocarditis, diastolic dysfunction, conduction defects and restrictive or dilated cardiomyopathy. The most commonly cited cause of death in juveniles was heart failure, which often occurred in the context of multi-organ involvement. Pericardial effusion is a common finding in SSc, usually without haemodynamic significance. The stronger association of mortality and pericardial effusion in juvenile-onset disease suggests a less benign mechanism for this particular clinical finding.

Interestingly, clinical or radiological evidence of pulmonary fibrosis at presentation was associated with increased mortality, though this is not reflected in the causes of death, with 2 of 16 patients dying as a result of respiratory failure. Indeed, raised creatinine levels are also strong predictors, though unlike the adult context, hypertensive renal crisis is less likely to be the cause, as vasculitic processes and hypoperfusion due to primary cardiac disease are more prevalent in the juvenile cohort.

Treatment of JSSc is especially challenging. Treatment of organ-specific disease is similar to adults, with the use of endothelin receptor antagonists or phosphodiesterase inhibitors followed by intravenous prostanoids for pulmonary arterial hypertension, cyclophosphamide and steroid for pulmonary fibrosis, ACE-inhibitors and prostacyclin for hypertensive crises and vasodilators and prostacyclin (with a putative role for endothelin receptor antagonists or phosphodiesterase inhibitors) in digital vasculopathy. Again, perhaps as a reflection of the increased incidence of overlap syndromes and diffuse disease in the young, immunosuppression with MTX, cyclophosphamide or mycophenolate mofetil is central in the overall management of JSSc. Special consideration of the long-term impact of such therapies on fertility and risks of malignancy is vital in this cohort.
Long-term outcomes (average 10-yr follow-up in this cohort) are, in general, favourable in terms of mortality. Newer therapeutic vascular and immunosuppressive agents have become available within that period, which gives us hope that, like adult patients, the long-term outlook will continue to improve in this devastating disease.

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