Raynaud's syndrome in children: systematic review and development of recommendations for assessment and monitoring

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ABSTRACT

Objective. *To develop recommendations for investigation and monitoring of children with Raynaud's syndrome, based on paediatric evidence collated by a systematic review.*

Method. *A systematic review was undertaken to establish the paediatric evidence for assessment and monitoring of Raynaud's syndrome. An expert panel including members of the Paediatric Rheumatology European Society (PRES) Scleroderma Working Group, were invited to a consensus meeting where recommendations were developed based on evidence graded by the systematic review and where evidence was lacking, consensus opinion. A nominal technique was used where 75% consensus was taken as agreement.*

Results. *The expert panel recommended testing anti-nuclear antibody (ANA), more specific antibodies associated with connective tissue disease and nail-fold capillaroscopy in all children presenting with Raynaud's syndrome as data suggests these can be risk factors for evolution into a connective tissue disease. The frequency of follow-up recommended depends on presence of these risk factors with the aim to detect evolving connective tissue disease early in high risk individuals. Those with no abnormalities on capillaroscopy and negative autoantibodies were deemed low risk of progression, whereas those with ANA positivity, specific autoantibodies and/or nailfold capillary changes were deemed high risk and more frequent follow-up was recommended.*

Conclusion. *Recommendations, primarily based on consensus opinion, were agreed regarding investigation and monitoring of children who present with Raynaud's syndrome. Further prospective studies are needed to better define the risk factors for progression to connective tissue disease.*

Introduction

Raynaud's syndrome or phenomenon is an episodic response to cold or emotional stress causing colour change and associated symptoms such as numbness, pain and tingling in the extremities (1). Primary Raynaud's syndrome occurs due to functional changes in blood vessels and does not lead to irreversible tissue damage (2). Secondary Raynaud's syndrome (for example due to systemic sclerosis (SSc) and diseases of the scleroderma spectrum) can lead to tissue loss, digital ulcers and gangrene and most importantly is characterised by specific nailfold capillaroscopic abnormalities (SSc pattern) and serum biomarkers such as autoantibodies (3-5).

In addition, Raynaud's syndrome can be the presenting feature of juvenile systemic sclerosis (JSSc), juvenile systemic lupus erythematosus (JSLE) or other connective tissue disease (6, 7).

A prospective study in adults with Raynaud's syndrome without other features of connective tissue disease, identified specific nailfold capillary changes and autoantibodies as independent predictors of progression to SSc (8, 9). Such large scale prospective studies are lacking in children. There are currently no guidelines on how to assess children with Raynaud's syndrome, what prognostic markers suggest progression to development of a connective tissue disease, how frequently children should be assessed to identify early evolution of systemic disease or how to treat

Raynaud's syndrome in this age-group. A consensus meeting was organised within the framework of the PRES scleroderma working group. Our aims were to develop recommendations for assessment, monitoring and treatment of children with Raynaud's syndrome based on the available evidence and where this was lacking, expert opinion.

Objectives

To perform a systematic review of the paediatric evidence for assessment and monitoring of Raynaud's syndrome.

To develop recommendations based on paediatric evidence (identified in the systematic review) and where this was lacking consensus opinion, for the assessment and monitoring of children with Raynaud's syndrome.

Materials and methods

Systematic literature review

A systematic literature review was performed (CP, TC) to answer three specific questions which were identified as key to allow the evidence-based development of recommendations for the management of children with Raynaud's syndrome. Literature searches were designed for the three questions. However, due to perceived lack of paediatric data, searches were wide and included randomised control studies, controlled clinical trials, cohort studies (prospective and retrospective), case-control and case series with no restriction on sample size. All searches were limited to children up to 18 years of age although studies which also included young adults over 18 years of age were not excluded if subgroup analysis of paediatric data was performed. Review articles and conference abstracts were excluded. The searches were completed in PubMed (1966 to 31.10.2012) using relevant keywords (see supplementary appendix 1 for search strategies).

Studies were independently reviewed by CP and TC. References of relevant studies were also searched. Studies which addressed the three specific aims of the literature search were shared with the expert panel. Level of evidence was initially graded by CP and TC; this was confirmed by the other members of the expert panel.

The systematic review was designed to identify paediatric evidence to answer the three following questions:

1. What is the prevalence of Raynaud's syndrome in children and young people?
2. How many children and young people with Raynaud's syndrome develop a connective tissue disease over time?
3. What are the risk factors for progression to a connective tissue disease in children with Raynaud's syndrome?

Recommendation development

Members of the PRES scleroderma working group were invited to participate in the consensus meeting in Hamburg on 9th December 2012. A paediatric dermatologist and adult rheumatologists were also invited to participate. The expert panel consisted of 8 paediatric rheumatologists (CP, TC, IF, NT, MM, DP, NAA, DN), 3 adult rheumatologists with expertise in nailfold capillaroscopy and systemic sclerosis (CIK, MC, VS) and a paediatric dermatologist with an interest in SSc (PH). The results of the systematic review were presented at the consensus meeting. The expert panel discussed the development of recommendations for assessment and monitoring of children with Raynaud's syndrome using the available evidence and consensus opinion. A nominal group technique was used. 75% consensus was defined as agreement.

In 2016, an updated literature search was performed in PubMed from 1.11.2012 to 31.3.2016 using the same search strategy to identify any recent publications. Studies were independently reviewed by CP and TC. Studies which addressed the three specific aims of the literature search were shared with the expert panel and the initial recommendations made in 2012 were reviewed in light of new evidence.

Results

Systematic review

1. What is the prevalence of Raynaud's syndrome in children?

A study in 720 school children aged 12-15 years in the United Kingdom, identified Raynaud's symptoms in 15% of children (18% in girls; 12% in boys) via the use of a validated questionnaire (10). The occurrence of Raynaud's syndrome increased with age and is similar to rates reported in adults (1). The reviewers did not identify any studies examining prevalence rates in younger children or prevalence rates of secondary Raynaud's syndrome.

2. How many children with Raynaud's syndrome develop a connective tissue disease over time?

Raynaud's syndrome is reported as the first sign of disease in 61-70% of patients with JSSc (6, 7). During follow-up studies the numbers of patients affected by Raynaud's increases to 72-84% (6, 7, 11, 12), approaching almost 100% by adulthood (13, 14). The rates of Raynaud's symptoms in other paediatric connective tissue diseases have been reported as follows: mixed connective tissue disease 58% at disease onset (15), juvenile dermatomyositis 16% in all patients rising to 56% in those with overlap features (16). No studies were identified exploring rates of Raynaud's symptoms in JSLE. Data do not exist on the time period between onset of Raynaud's symptoms and development of other systemic features of connective tissue disease.

There have been two studies performed which have elucidated to the rates of progression from Raynaud's syndrome to connective tissue disease in children (17, 18).

A prospective study of 250 children and young people with Raynaud's syndrome aged 10–20 (44% aged 10–16 yrs) followed up patients 6 monthly with history, examination and nailfold capillaroscopy examination, for 1-6 years after first capillaroscopy was performed (18). At the end of follow-up, 23.6% had evolved into a connective tissue disease (undifferentiated connective tissue disease 10.8%, SLE 3.6%, rheumatoid arthritis 4% (juvenile onset in 6 out of 10), and sclerodermatous spectrum 5.2%. The mean time to development of disease was 2.4 years. Those data are close to that observed in adult SSc patients (19, 20).

A retrospective cohort of 123 children with Raynaud's syndrome identified

Table I. Recommendations for investigation and follow-up of children with Raynaud's syndrome (75% consensus defined as agreement).

	Recommendation	Level of evidence	Strength of recommendation
At presentation:			
1	Patients who have additional symptoms and/or signs pointing to a definite connective tissue disease should be evaluated according to disease specific guidelines and potential organ involvement.	4	D
2	ANA testing should be performed on all patients	3,4	D
3	All ANA positive patients should be screened for SSc-specific antibodies (e.g. anti-Scl 70 and anti-centromere, anti-Th/To, anti-RNAP) and anti-ds DNA and ENA (extractable nuclear antigens)	3,4	D
4	All patients should be investigated by capillaroscopy. Capillaroscopy will be classified into "normal", "non-specific changes" or "SSc pattern"(28).	3,4	D
Follow-up:			
5	Patients who are ANA negative and have normal nail-fold capillaroscopy should be clinically assessed at least every 12 months	4	D
6	ANA positive patients without disease-specific antibodies and with normal nail-fold capillaroscopy findings should be followed up at least every 6 months	4	D
7	ANA and disease-specific antibody positive patients should have organ specific evaluation as clinically indicated; for example if SSc specific antibody identified with high index of suspicion of evolving JSSc, evaluate patient according to the juvenile systemic sclerosis inception cohort protocol (www.juvenile-scleroderma.com)	4	D
8	ANA and disease-specific antibody positive patients should be followed up 3 monthly irrespective of nail-fold capillary changes. However, the presence of both disease-specific antibodies and nail-fold capillary specific changes represents a high risk of development of connective tissue disease and therefore warrants increased surveillance.	4	D
9	ANA-positive patients, who have no disease specific antibody but have specific capillaroscopy results, should be followed-up at least every 3 months.	4	D
10	ANA-negative patients with abnormal nail-fold capillaroscopy (defined as non-specific or SSc pattern) should be followed-up at least every 6 months.	4	D

*ANA positivity was defined by the group as a repeatedly positive titre of at least 1:80 (samples at least 3 months apart). Although an ANA titre of 1:80 is deemed as borderline, for the purpose of these recommendations the members of the consensus agreed that a lower threshold for ANA positivity would be valuable to identify those patients with evolving CTD.

that 8 children initially diagnosed with primary Raynaud's syndrome (defined as episodic reversible colour change in the extremities without established or suspected CTD) developed a connective tissue disease during follow-up (1.8 years ± 2.7 SD), which equates to a rate of 8%(17). ANA negativity was not a pre-requisite in this study for primary Raynaud's syndrome.

3. What are the risk factors for progression to a connective tissue disease in children with Raynaud's syndrome?

A prospective study of 586 adults with Raynaud's syndrome and no identifiable secondary cause identified positive SSc-specific autoantibodies and SSc pattern on nail-fold capillaroscopy as independent risk factors for development of SSc (8). In the only paediatric prospective study, 10 patients out of 250 (4%) had SSc type changes in nailfold capillaries before progression to a connective tissue disease (8 developed scleroderma spectrum disorders, 1 undifferentiated connective tissue disease and 1 SLE) (18). Both studies defined SSc type changes as described by Maricq (21-23) and included decreases in capillary density and widened giant loops with avascular areas. The authors concluded that in a child with Raynaud's syndrome the presence of SSc type changes on nail-fold capillaroscopic examination is highly correlated with the future development of scleroderma spectrum disorders. In a retrospective study of children with Raynaud's syndrome (defined as episodic reversible colour change in the extremities without established or suspected CTD), the following were significantly associated with connective tissue disease compared to children with primary Raynaud's syndrome: positive antinuclear antibody (ANA) 85% *versus* 25% of those with primary Raynaud's syndrome ($p<0.001$), positive ENA screen (including anti-dsDNA, SSA/Ro, SSB/La, RNP, Sm (Smith), Scl-70) 67% *versus* 6% of those with primary Raynaud's syndrome ($p<0.001$) and abnormal or borderline nail-fold capillaries in 68% *versus* 23% ($p<0.001$). In this study nail-fold capillaries were examined with an ophthalmoscope and defined as normal, borderline or abnormal by clinician opinion only. It is unclear whether anti-centromere antibodies were routinely measured. Of those children with Raynaud's syndrome secondary to a connective tissue disease, 93% were either ANA positive and/or had nailfold capillary abnormalities as compared to 39% of those classified with primary disease. Age at onset, sex or number of

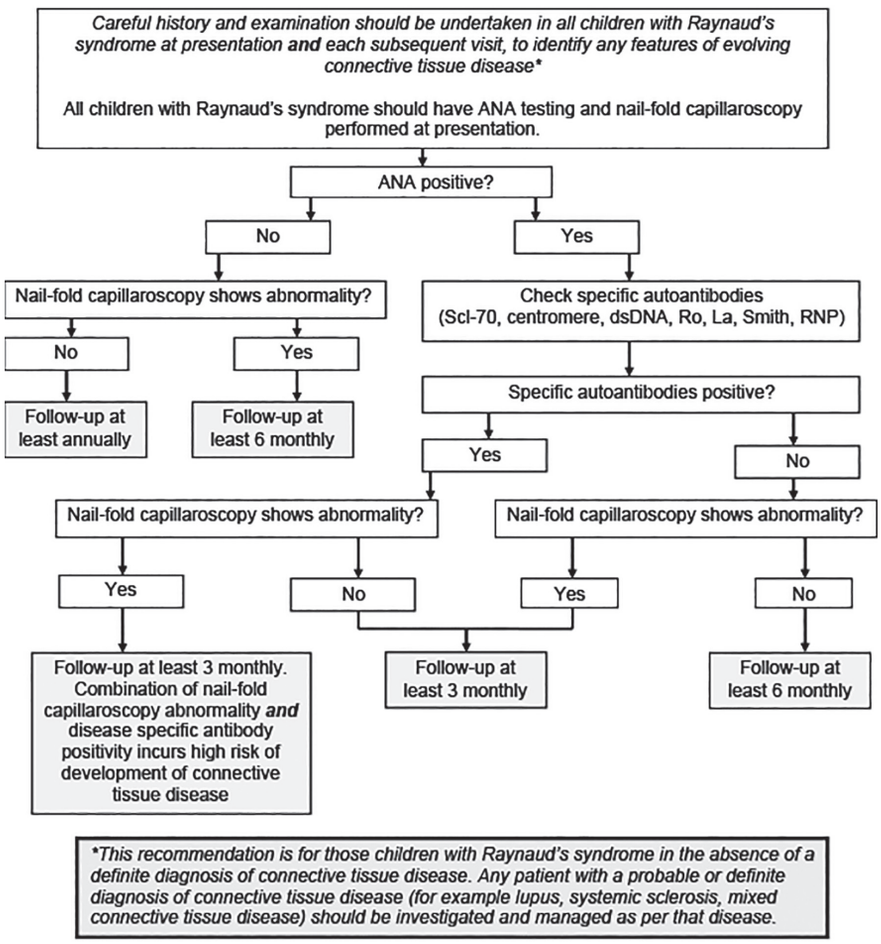

Fig. 1. Recommendations for investigations and frequency of follow-up for children with Raynaud's syndrome.

colour changes in extremities did not appear to differ between primary and secondary cases (17).

Characteristic nailfold capillaroscopic changes have been identified in children with connective tissue diseases such as juvenile dermatomyositis, JSLE, mixed connective tissue disease, undifferentiated connective tissue disease and of course JSSc. Non-specific microvascular abnormalities (such as tortuosity) have also been observed in healthy children and capillary density and width are age-related with younger children having wider and fewer capillaries than older children and adults (24, 25). Abnormalities (defined as changes in capillary density, length, shape (*e.g.* torturous, giant, bushy), disarrangement, avascular areas and haemorrhage) were significantly higher in mixed connective tissue disease (p=0.008), JSLE (p=0.0002) and juvenile dermatomyositis (p<0.0001) compared to healthy children. Five out of eight patients with JSSc showed SSc pattern, already at disease onset (26).

Results of consensus meeting

The following agreements (Table I and Fig. 1) were reached regarding development of recommendations for children with Raynaud's syndrome, where a consensus of 75% inferred agreement. Level of evidence and strength of recommendation is described according to European League Against Rheumatism (EULAR) standardised procedures where level 3 is evidence the panel considered from descriptive studies, such as comparative studies, correlation studies, or case-control studies and level 4 is where the recommendation was based on expert opinion of the panel only (27).

At initial presentation, the panel recommended that all patients should be carefully evaluated by history (including drug and where age-appropriate smoking history) and examination to establish any symptoms or signs suggestive of a more definite diagnosis of a connective tissue disease. If a specific disease such as JSSc or JSLE is likely, the patient should be evaluated as clinically indicated and may need organ-specific investigations as guided by assessment. The remaining recommendations for monitoring are for those children with Raynaud's syndrome only and exclude those with definite or probable connective tissue disease.

The expert panel agreed that all patients should have ANA checked at presentation. ANA positivity was defined by the panel as a repeatedly positive titre of at least 1:80 (on a minimum of two samples at least 3 months apart). If ANA was positive, more specific auto-antibody testing should be performed including SSc-specific antibodies (*e.g.* Scl-70 (anti-topoisomerase), anti-centromere, anti-Th/To, anti-RNA polymerase(8)), anti-double stranded (ds) DNA and extractable nuclear antibodies (to include ribonucleoprotein (RNP), SSA/Ro, SSB/La, Smith (Sm), Jo-1, Scl-70). Patients who are positive for specific auto-antibodies are likely to incur a higher risk of development to a connective tissue disease and therefore the expert panel agreed closer follow-up of this group was needed.

Agreement was reached that nailfold capillaroscopy should be performed in all patients with Raynaud's syndrome at presentation as there is evidence that children with specific abnormalities in nailfold capillaries are at higher risk of conversion to systemic disease. The panel recommended that capillaroscopy should be described as 'normal', 'non-specific' or 'SSc' pattern (28, 29) where SSc pattern may be defined into early, active and late. However, robust paediatric and age-specific definitions of such changes would need to be established in future work.

The combination of specific autoantibody positivity and nail-fold capillary specific changes (SSc pattern) was felt to represent the highest risk of development to a connective tissue disease and the panel recommended careful evaluation of the patient at least every

3 months. Patients who were neither ANA positive nor had nail-fold capillary changes were deemed lowest risk and a minimum of yearly evaluation was recommended. Appendix 1 shows a flow-sheet to identify the frequency of follow-up recommended as determined by ANA status, specific autoantibody status and nail-fold capillary examination (SSc pattern).

Additional evidence from literature review from 2012-2016

A revised literature review from 1.11.12 to 31.3.16 identified only two relevant papers published within this time period (see search strategy and results in supplementary data) (30, 31). A prospective study by Piotto *et al*. of 40 children with isolated Raynaud's syndrome without criteria for connective tissue disease showed that 14/40 (35%) presented with positive antinuclear antibodies and 5 (12.5%) had abnormal nail-fold capillaries examined by wide-field capillaroscopy (30). During repeat capillaroscopy (time interval 6 months to 2 years; mean 1.6 years) 3 children developed progressive changes with two developing SSc pattern (one developed mixed CTD and the other hypothyroidism with digital ulcers and puffy hands). However, of the 4 patients with non-specific changes initially, nail-fold capillaroscopy was entirely normal at follow-up. Some patients who were ANA positive also became negative on retesting. A retrospective study of 94 children and adolescents with Raynaud's syndrome showed that 8/94 (8%) developed a connective tissue disease over a 3 year follow-up period (31). Evolution of disease was associated with development of specific autoantibody profiles in several patients; three patients were diagnosed with SLE (positive anti-dsDNA and anti-Sm antibodies); three with SSc (all positive for anti-Scl-70), one with undifferentiated CTD and one patient with Sjogren's syndrome (anti-SSA/Ro and anti-SSB/La). This rate of progression to diagnosis of CTD is similar to that reported by Nigovic *et al*. (17).

All members of the original consensus group (n=12) were asked to review these two papers to evaluate whether the data presented in them would lead to a revision of the original recommendations. All 12 members felt that the data provided by these two studies supported the recommendations developed in 2012 for assessment and follow-up of Raynaud's in children (Table I). Agreement (12/12) was reached that there was no new evidence available to require revision of these recommendations.

Discussion

The panel developed recommendations for the initial investigation and subsequent follow-up of children with Raynaud's syndrome in whom a probable or definite diagnosis of connective tissue disease has not been made. The aim is that by standardising assessments and follow-up, this will facilitate collaborative working and the future development of multi-national prospective cohort studies of children with Raynaud's syndrome. The recommendations agreed by this consensus meeting were primarily based on expert opinion and limited evidence. Further prospective studies are essential to provide more robust evidence for prevalence of Raynaud's syndrome particularly in younger children, better understanding of risk factors for the development of connective tissue disease and the duration and frequency of follow-up. Through such recommendations we aim to produce clinical and research networks which will aide development of much needed studies and clinical trials for children with Raynaud's syndrome.

There are several limitations to our recommendations. Firstly, although we recommend examining nail-fold capillaries the panel did not agree on the capillaroscopic tool to be used. The published studies of nailfold capillaroscopy in children use several different tools including an ophthalmoscope at the bedside (17) to video capillaroscopy in a temperature controlled room (18). During the consensus meeting we discussed the need for a widely accessible bedside tool for determining capillary appearance. Further discussions are needed to clarify this and agree on standardised assessments (32). Secondly, the definitions of capillary appearances into 'normal', 'non-specific' and 'SSc pattern' are yet to be defined in the paediatric cohort. Several studies have looked at nail-fold capillary appearance in healthy children and there appear to be changes that occur with age which require further quantification to produce robust age-specific normative data (24-26, 33). Adult studies have defined capillaroscopic patterns in SSc into 'early', 'active' and 'late' and qualitative and semi-quantitative assessments have been used to predict SSc complications (34, 35). Nail-fold capillaroscopy has now been introduced in the 2013 American College of Rheumatology and EULAR classification criteria for adult SSc, since it increases significantly the sensitivity and specificity of the criteria (36, 37). Capillaroscopy is now widely used in adults and the authors conclude that there is considerable value in this tool for the diagnosis and management of SSc, whether performed with highly specialised equipment or with simple handheld tools such as a dermatoscope or ophthalmoscope. Validation of these criteria has not yet been performed in JSSc patients. However, the addition of capillaroscopy to these new criteria may encourage physicians caring for JSSc patients to perform this skill.

Data from the EUSTAR database indicates that early and active patterns are generally seen in adults with mild to moderate skin involvement and low organ involvement, whereas late patterns are associated more frequently with more severe skin and organ involvement (38). This needs to be studied in children as this may provide a useful tool for identifying children at risk of severe disease.

Prospective follow-up in the paediatric population with definitions used to assess morphology, density and diameter, as accepted for adult population, is required (28, 29).

The panel did not discuss how frequently or if at all, autoantibodies and nail-fold capillaries should be re-examined if initially negative and paediatric studies of Raynaud's syndrome do not appear to evaluate this in depth. The mean time from development of Raynaud's syndrome to a diagnosis of

a definite connective tissue disease was 2.4 years in one paediatric study (18). This may suggest that children only require a finite period of re-evaluation before their risk of evolution to a definitive connective tissue disease diminishes as suggested by adult studies (19). One prospective study evaluating nail-fold capillaroscopy in 40 children with Raynaud's syndrome highlighted that non-specific changes on nailfold capillaroscopy and ANA positivity can normalise on retesting (30). This highlights that repeat nailfold capillaroscopy and autoantibody assessment is important to detect significant changes and repeat nailfold capillaroscopy 6 monthly has been suggested (18, 30).

The studies identified in this review provide evidence for ANA positivity as a risk factor for evolution to CTD. Although, the published evidence was weaker for disease-specific autoantibodies, the opinion of the consensus group was that the presence of such antibodies incurred a higher risk of progression to a defined CTD and therefore warranted more frequent follow-up of patients (see Fig. 1).

A retrospective study identified positive anti-phospholipid antibodies in 36% (18/50) of children with primary Raynaud's syndrome (17). Of these 18, half became negative on repeat testing. There was no significant difference between children with primary and secondary Raynaud's syndrome with positive anti-phospholipid antibodies detected in 30% (7/23) of those with secondary Raynaud's syndrome; of which 6/7 had a diagnosis of SLE. Antiphospholipid antibodies can be transiently positive in children and such high frequency of positive testing has not been confirmed in other studies. A study of adults with SLE showed no positive association of anti-phospholipid antibodies with Raynaud's syndrome (39). The expert panel therefore agreed that there was not enough evidence to suggest routine testing of anti-phospholipid antibodies in children with Raynaud's syndrome, even in children who are ANA positive, unless in the context of suspected SLE.

The systematic review did not include adult studies and was limited to studies including children. However, the aim of the consensus meeting was to develop paediatric specific recommendations and to establish where paediatric evidence was lacking. The panel recognises that when paediatric studies are lacking, data from adult studies may provide useful evidence which may be applicable to children. The recommendations are in keeping with adult data, including a 20 year prospective study of patients with Raynaud's syndrome which showed that microvascular changes assessed by nail-fold capillaroscopy and SSc-specific antibodies were independent risk factors for the development of SSc (8).

Early detection of connective tissue diseases such as SSc which may present with Raynaud's syndrome as the first symptom would allow commencement of early treatment and ideally, better outcomes for children. In adult studies, the time from the onset of Raynaud's symptoms to first non-Raynaud's symptoms is a mean of 1.9 years in diffuse cutaneous SSc and a mean of 4.8 years in limited cutaneous SSc (40). Another study reported that 20% of patients initially diagnosed as having primary RP were found to have transitioned to either suspected secondary RP or secondary RP during the follow up period of 10 years (41).

The diagnosis of early and very early SSc aims to identify a patient in the time period where there may be a window of opportunity to treat aggressively and prevent internal organ involvement and marked skin fibrosis (42). Raynaud's syndrome is an integral part of the diagnosis of very early SSc together with puffy fingers (9), nail-fold capillary changes, ANA positivity and SSc specific auto-antibodies such as anti-centromere, anti-Scl 70, anti-Th/To and anti-RNAP (43). Available data suggests that identifiable risk factors for the progression of connective tissue disease such as autoantibody profile and nailfold capillary specific changes appear to be similar in children compared to adults. However, anti-centromere antibodies occur significantly less in children than in adults with SSc and 90% of children were classified as having diffuse disease (7). Further studies in children would aim to elucidate which children are at greatest risk of development of systemic disease. In JSSc, a subset of patients develop marked internal organ involvement very early in their disease course associated with a high mortality particularly from cardiac or pulmonary involvement (14, 44, 45). Identification of high risk patients would allow close surveillance to detect early internal organ involvement.

The authors accept that there is a paucity of evidence on many aspects of Raynaud's syndrome in children and that these recommendations are based largely on low-grade evidence and opinion of the expert panel. However, we hope that standardisation of practice, beginning with the formulation of recommendations will allow collaborative research to provide further evidence on management of Raynaud's syndrome in children. As new evidence becomes available these recommendations will require review and updating.

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