

JUVENILE SYSTEMIC SCLEROSIS

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Juvenile systemic sclerosis (jSSc) is a multisystem disease, meaning most of a child's organs can be involved. In many cases, jSSc often starts with Raynaud Phenomenon, an excessively reduced blood flow in response to cold or emotional distress, which causes discoloration of the fingers and toes, and occasionally other areas. Raynaud Phenomenon can be primary, where the cause is unknown and is not associated with a connective tissue disease, such as jSSc. It also can be secondary, where it is associated with a connective tissue disease, such as jSSc. In a U.K. cross sectional survey 15 percent of children ages 12 to 15-years-old's phenomenon, the rate increased with age. The presence of ANA positivity and nailfold capillaroscopy changes seem to be prognostic for secondary Raynaud's phenomenon and the development of a connective tissue disease.

Around 60 to 90 percent of children with jSSc have Raynaud Phenomenon before they develop other symptoms. In the course of the disease, most patients develop Raynaud Phenomenon. In the juvenile scleroderma inception cohort 90% are positive for Raynaud's phenomenon and around 10% of patients are still negative of Raynaud's Phenomenon after a mean follow up of 2.2 years. The symptoms of Raynaud Phenomenon can occur long before the onset of scleroderma, in the juvenile systemic scleroderma cohort (www.juvenile-scleroderma.com) the mean time between the occurrence of Raynaud's phenomenon and the occurrence of the first non-Raynaud presentation of jSSc is 0.7 years

In a process of a consensus conference organized by the Pediatric Rheumatology European Society (PRES) scleroderma working group⁽¹⁾ suggested that patients with Raynaud Phenomenon, antibody positivity and nail-fold capillary abnormalities should be followed at least every three months to be able to recognize the onset of the connective tissue disease quite early and to be able to prevent damage.

jSSc is an orphan disease. Orphan disease is defined, that the disease occurs in fewer than 1 in 1,500 persons in the United States, fewer

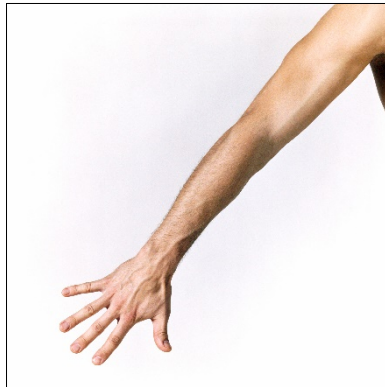
than 1 in 2,000 persons in the European Union. There is sparse data regarding the incidence (the number of patients who are diagnosed each year. One of the rare studies, which are looking at this issue was a prospective study to ascertain all newly diagnosed cases in the United Kingdom. It found an incidence (the number of newly diagnosed patients) of 0.27 per 1 million children⁽²⁾. This means less than 1 in one million children are diagnosed each year. A current publication looked in the US claim data base and found a prevalence of 3 children in 1 million children⁽³⁾. Prevalence means the number of patients who have a diagnosed disease in a year. The mean age at disease onset is about 8 years in most larger cohorts.

A unique characteristic of juvenile onset patients is that approximately 75% to 90% percent of them have the diffuse subtype^(4, 5). Diffuse subtype means that the skin proximal to the trunk, from knee and elbow is involved. Many patients have overlap features with other connective tissue diseases, such as dermatomyositis, systemic lupus erythematosus (SLE) or juvenile arthritis. Interestingly, the limited form of the disease, with skin involvement distal (more distant from the trunk) from knee and elbow, is rare. Overlap characteristics seem to be prognostically positive for the survival, as shown in the publication of jSSc patients in the adult cohort of the Royal free hospital⁽⁶⁾.

A new pediatric criteria, established in 2007, is used to diagnose jSSc. The disease is defined by one main criterion, which has to be fulfilled. This criterion is defined by hardening of the skin, or sclerosis, closest to the body from the most proximal finger joint (metacarpophalangeal) or the most proximal toe joint (metatarsophalangeal). There are also several minor criteria, which describe scleroderma-specific organ involvement. For a definitive diagnosis of jSSc, a patient has to fulfil one major and two minor criteria. [See: Figure 1] 2013 the adult criteria for systemic scleroderma was published (Arth Rheum 2013,65: 2737-47) where several characteristics of systemic scleroderma can add up to fulfil the criteria. These criteria are validated in the

frame of the juvenile scleroderma inception cohort ([juvenile-scleroderma.com](http://www.juvenile-scleroderma.com)) and all patients, who fulfil the pediatric criteria, do fulfil the adult criteria (Foeldvari et al abstract ACR 2015).

There are three large cohorts published of patients with jSSc, two of them were multinational surveys, and the patient populations of these two surveys overlap. These multinational



surveys were conducted by Foeldvari et al. and Martini et al. The top five organs involved in both surveys were skin, articular, gastrointestinal, pulmonary and cardiovascular. Interestingly, central nervous system involvement, including seizures, peripheral neuropathy and abnormal brain MRI, occurred in 16 percent of the patients in the cohort of Foeldvari et al., and 3 percent of patients in the cohort of Martini et al. Calcinosis, a deposit of calcium in the skin, occurred in about 20 percent of patients. The five-year survival rate of the Foeldvari cohort was 95 percent. This is significantly better than expected in a diffuse subset cohort. In adult cohorts, at the time of the survey, the five-year survival with diffuse subtype was about 78 percent. In the Martini cohort, an analysis of the risk factors for mortality (occurrence of death) was done. Patients with a fatal outcome had higher rates of pulmonary, gastrointestinal and cardiac involvement. Patients with fatal outcome also had a significantly shorter time until diagnosis, with 8.8 months compared to 23 months in the nonfatal group. In both cohorts, most patients died during the first five years of the disease. This means there is a group of patients that experience a very destructive disease during a very short period.

The Inception Cohort for Juvenile Systemic Sclerosis (www.juvenile-scleroderma.com), which I lead, collects data from jSSc patients with a standardized assessment of organ systems. Patients are included in this multinational multicentre cohort, if they developed they fulfill the adult SSc classification criteria under the age of 16 and

are under 18 at time point of the inclusion. Currently this project is supported from October 2017 for three years from the Joachim Herz Stiftung (Foundation). This project aims to learn more about the evolution of organ involvement, the prognosis of the disease and factors that influence prognosis. This is a very important issue, as early recognition of organ deterioration helps to guide the therapy. As with other autoimmune diseases, early intervention, using the therapeutic window of opportunity and prevention of damage to organ systems significantly improves survival. 2018 the first summary of the juvenile scleroderma inception cohort were published⁽⁴⁾. In these population around 75 % of the patients had diffuse subtype. Around 30% have in both subtypes anti-Scl70 positivity. Anticentromere positivity was 6% in the diffuse and 15% in the limited subset. Significant difference in the presentation of the two subtypes were observed in three organ involvements. We could show significant difference in number of active ulceration 29% in the diffuse and 0% in the limited group ($p=0.005$), the total pulmonary involvement was increased in the diffuse subtype (41% versus 22%, $p=0.009$), the total cardiac involvement was increased in the limited subtype (23% versus 3%, $p=0.015$). This is the first study which looked a patient and physician related outcomes. Physician related the global disease damage significantly higher in the diffuse subtype ($p=0.021$). This cohort has now over 120 jSSc patients and enrolling patients. This will make the data stronger regarding presentation and course of jSSc. As every patient counts, it would be great, if more U.S. centers would participate.

There are currently no controlled studies that explore the efficacy of certain medications in jSSc, but currently several medications are planned to be studied in jSSc. Establishing pediatric outcome measures, one of my main research interests, will enable us to conduct better prospective therapeutic trials for our patients. I have previously published information about the modified Rodnan skin score in children, which is a pivotal measure of jSSc outcomes. We are in the process to develop an adaptation of the paediatric "CRIS" (ref CRIS Khanna) score. This pediatric score should enable us to assess the effect of the medications with better sensitivity in a future clinical trial.

There is an important question that remains to be answered: what is the long-term prognosis for patients with jSSc? Currently, we have only indirect data from adult patient cohorts, where juvenile onset patients have been incorporated. The jSSc patients, now at adult age in the EULAR Scleroderma Research and Trials (EUSTAR) Cohort, did not differ from the young adult SSc patients, who developed the disease between the ages of 20 to 40 years old. Approximately 40 percent of them had diffuse subtype. This subtype distribution has been confirmed in the Royal Free Hospital Cohort. In this cohort, 61 percent of patients had overlap features; this seemed to be a prospective prognostic factor. The low rate of anticentromere positivity, about 5 percent, persists into the adulthood for jSSc patients. But we have missing data between the juvenile cohorts and the adult cohorts, so we would like to follow these patients from the inception cohort after the transition into the adult care to close this gap.

In the future, I hope that jSSc will be a more controllable disease. Preliminary data is promising regarding the effectiveness of biologics and the use of autologous bone marrow transplantation to control and significantly improve the quality of life and life expectancy of the jSSc patients.

Dr. Ivan Foeldvari runs the Hamburg Center for Pediatric Rheumatology and is the secretary of the juvenile scleroderma working group (jSScWG) of Pediatric Rheumatology European Society (PRES). The jSScWG is composed of around 30 colleagues, pediatric rheumatologist mostly from Europe, but some from South America and Australia, who are dedicated to the care for children with jSSc.

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