SOCIEDADE BRASILEIRA DE REUMATOLOGIA

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Original article

Esophageal abnormalities in juvenile localized scleroderma: is it associated with other extracutaneous manifestations?

Clarissa C.M. Valões[a], *Glaucia V. Novak*[a], *Juliana B. Brunelli*[a], *Katia T. Kozu*[a], *Ricardo K. Toma*[b], *Clovis A. Silva*[a,c,*]

[a] *Universidade de São Paulo, Faculdade de Medicina, Unidade de Reumatologia Pediátrica, São Paulo, SP, Brazil*
[b] *Universidade de São Paulo, Faculdade de Medicina, Unidade de Gastroenterologia Pediátrica, São Paulo, SP, Brazil*
[c] *Universidade de São Paulo, Faculdade de Medicina, Divisão de Reumatologia, São Paulo, SP, Brazil*

ARTICLE INFO

Article history:
Received 17 March 2016
Accepted 30 July 2016
Available online 17 October 2016

Keywords:
Juvenile localized scleroderma
Gastrointestinal
Esophagus
Methotrexate
Children

ABSTRACT

Objective: To assess esophageal involvement (EI) in juvenile localized scleroderma (JLS) population and the possible association between this gastrointestinal manifestation and demographic data, clinical features, laboratory exams, treatments and outcomes.
Methods: For a period of 30 years, 5881 patients with rheumatic diseases were followed in our Pediatric Rheumatology Division. EI was defined by the presence of symptoms (solid/liquid dysphagia, heartburn, esophageal regurgitation, nausea/vomiting and epigastralgia) and confirmed by at least one EI exam abnormality: barium contrast radiography, upper gastrointestinal endoscopy and 24-hour esophageal pH-monitoring.
Results: JLS was observed in 56/5881 patients (0.9%), mainly linear morphea subtype. EI was observed in 23/56(41%) of JLS patients. Eight(35%) of 23 EI patients with JLS were symptomatic and presented heartburn(5/8), solid and liquid dysphagia(3/8), nausea and epigastralgia(1/8). The frequency of any cumulative extracutaneous manifestations (calcinosis, arthritis/arthralgia, central nervous system, interstitial pneumonitis, mesangial nephritis and/or arrhythmia) was significantly higher in JLS patients with EI compared to those without this complication (56% vs. 24%, $p = 0.024$). No differences were evidenced in demographic data, JLS subtypes and in each extracutaneous manifestation in both groups ($p > 0.05$). The frequency of methotrexate use was significantly higher in JLS patients with EI compared to those without (52% vs. 12%, $p = 0.002$). Autoantibody profile (antinuclear antibodies, anti-SCL-70, rheumatoid factor, anticentromere, anti-cardiolipin, anti-Ro/SSA and anti-La/SSB) was similar in both groups ($p > 0.05$).
Conclusions: Our study demonstrated that EI was frequently observed in JLS patients, mainly in asymptomatic patients with linear subtype. EI occurred in JLS patients with other extracutaneous manifestations and required methotrexate therapy.

* *Corresponding author.*
E-mail: clovisaasilva@gmail.com (C.A. Silva).
http://dx.doi.org/10.1016/j.rbre.2016.09.011

Anormalidades esofágicas na esclerodermia localizada juvenil: associação com outras manifestações extracutâneas?

Palavras-chave:
Esclerodermia localizada juvenil
Gastrointestinal
Esôfago
Metotrexato
Crianças

RESUMO

Objetivo: Avaliar o envolvimento do esôfago (EE) na população com esclerodermia localizada juvenil (ELJ) e a possível associação entre essa manifestação gastrointestinal e dados demográficos, características clínicas, exames laboratoriais, tratamentos e desfechos.

Métodos: Durante 31 anos, 5.881 pacientes com doenças reumáticas foram acompanhados em nossa Divisão de Reumatologia Pediátrica. O EE foi definido pela presença de sintomas (disfagia para sólidos/líquidos, azia, regurgitação esofágica, náuseas/vômitos e epigastralgia) e confirmado com pelo menos um exame que revelou EE: radiografia contrastada com bário, endoscopia digestiva alta e pHmetria esofágica de 24 horas.

Resultados: Observou-se ELJ em 56/5.881 pacientes (0,9%), principalmente do subtipo morfeia linear. O EE foi observado em 23/56 (41%) dos pacientes com ELJ. Oito (35%) dos 23 pacientes com ELJ com EE eram sintomáticos e apresentavam azia (5/8), disfagia para sólidos e líquidos (3/8), náuseas e epigastralgias (1/8). A frequência de quaisquer manifestações extracutâneas cumulativas (calcinose, artrite/artralgia, envolvimento do sistema nervoso central, pneumonite intersticial, nefrite mesangial e/ou arritmias) foi significativamente maior em pacientes com ELJ com EE em comparação com aqueles sem essa complicação (56% vs. 24%, p = 0,024). Não foi evidenciada diferença nos dados demográficos, subtipos de ELJ e quaisquer manifestações extracutâneas entre os grupos (p > 0,05). A frequência de uso de metotrexato foi significativamente maior em pacientes com ELJ com EE em comparação com aqueles sem EE (52% vs. 12%, p = 0,002). O perfil de autoanticorpos (anticorpos antinucleares, anti-SCL-70, fator reumatoide, anticentrômero, anticardiolipina, anti-Ro/SSA e anti-La/SSB) foi semelhante nos dois grupos (p > 0,05).

Conclusões: Este estudo demonstrou que o EE foi frequentemente observado em pacientes com ELJ, principalmente naqueles assintomáticos com o subtipo linear da doença. O EE ocorreu em pacientes com ELJ com outras manifestações extracutâneas e exigiu tratamento com metotrexato.

Introduction

Juvenile scleroderma is a rare autoimmune disease, characterized by skin inflammation and fibrosis lesions, and occurs before the age of 18.[1–4] This condition comprises two major types in children and adolescents: juvenile localized scleroderma (JLS) and juvenile systemic sclerosis (JSS).[1,5,6]

Manifestations are mainly limited to the skin and subdermal tissues in JLS patients, whereas internal organs are frequently affected in JSS patients.[1,5] Extracutaneous manifestations have been reported in up to 25% of JLS patients and are mainly characterized by musculoskeletal involvement, particularly arthritis and tenosynovitis.[7]

Esophageal involvement (EI) has been described as frequent extracutaneous manifestations in JSS.[7–10] This involvement has been studied in children and adolescents with JLS, however it is usually limited to case reports or case series.[5–12] To our knowledge there are no studies that evaluated solely JLS patients comparing patients with and without EI.

Therefore, the aim of this study was to assess the prevalence of EI in JLS population, and the possible associations between this gastrointestinal manifestation and demographic data, clinical features, laboratory exams, treatments and outcomes.

Methods

This was a retrospective study carried out at the Pediatric Rheumatology Unit of a tertiary University Hospital, Sao Paulo city, Brazil. For a period of 31 years (1983–2014), 5881 patients with pediatric rheumatic diseases were followed up in the Pediatric Rheumatology Unit. The inclusion criteria were consecutive patients with JLS diagnosis followed from 1986 to 2014. Overlap syndromes with other autoimmune diseases were systematically excluded.

Demographic data and clinical features were collected from medical charts. The clinical JLS subtypes were defined according to Padua criteria 2004, and classified in 5 subtypes: circumscribed morphea, linear scleroderma, generalized morphea, pansclerotic morphea and mixed morphea.[4]

EI was defined by the presence of gastrointestinal symptoms (solid/liquid dysphagia, heartburn, esophageal regurgitation, nausea/vomiting and epigastralgia) and confirmed by at least one laboratory test abnormality: barium contrast radiography, upper gastrointestinal endoscopy and 24-h esophageal pH-monitoring. Extracutaneus manifestations related to JLS, such as calcinosis, articular, central nervous system, pulmonary, cardiac and renal involvements, and treatments were also systematically recorded.

Table 1 – Demographic data, clinical JLS subtypes and other extracutaneous manifestations in 56 JLS patients with and without esophageal involvement.

Variables	JLS with esophageal involvement ($n = 23$)	JLS without esophageal involvement ($n = 33$)	p
Demographic data			
Age at JLS onset, years	3.5 (2.8–7.4)	5.0 (3.0–9.8)	0.255
Age at diagnosis, years	5.6 (3.7–9.7)	7.15 (5.3–10)	0.253
Time between JLS onset and diagnosis, years	1.3 (1.0–4.0)	1.0 (0.4–2.0)	0.204
Female gender	19 (83)	28 (85)	1.000
JLS subtypes			
Circumscribed morphea	3 (13)	5 (15)	1.000
Linear scleroderma	15 (65)	22 (67)	1.000
Generalized morphea	3 (13)	3 (9)	0.600
Mixed morphea	2 (9)	3 (9)	1.000
Cumulative extracutaneous manifestations			
At least one	13 (56)	8 (24)	0.024
Raynaud phenomenon	0 (0)	0 (0)	1.000
Calcinosis	1 (4)	0 (0)	0.400
Arthritis/arthralgia	7 (30)	5 (15)	0.190
CNS involvement	1 (4)	1 (3)	1.000
Interstitial pneumonitis	3 (13)	1 (3)	1.000
Mesangial nephritis	0 (0)	1 (3)	1.000
Cardiac involvement	1 (4)	0 (0)	0.400

Results are presented in median (range) and *n* (%).
JLS, juvenile localized scleroderma; CNS, central nervous system.

The serum antibody profile included antinuclear antibody (ANA, including assessment of anticentromere antibody, by indirect immunofluorescence), anti-SCL-70 [DNA-topoisomerase1 by Enzyme Linked Immuno Sorbent Assay (ELISA)], rheumatoid factor (RF, by immunonephelometry), anticardiolipin antibodies (ACL IgM and IgG by ELISA), anti-Ro/SSA and anti-La/SSB (by ELISA), and anti-RNP by ELISA. Nail fold capillaroscopy was also performed at JLS diagnosis.

Statistical analysis

Results were presented as number (frequency) and median (range) or mean ± standard deviation. JLS patients were divided according to the presence or absence of EI, and categorical variables were compared using Fisher's exact test and continuous variables using Mann–Whitney *U*-test or t-test, as indicated. The statistical significance was set at $p < 0.05$.

Results

JLS was observed in 56/5881 (0.9%). EI was evidenced in 23/56 (41%) of JLS patients. EI was observed in 6/23 (26%) before one year of JLS diagnosis and 17/23 (74%) after one year of JLS diagnosis. EI was present in 16/23 (69%) before two years of JLS diagnosis and 7/23 (30%) after two years of diagnosis.

EI was diagnosed by upper gastrointestinal endoscopy in 4/23 (17%), barium contrast radiography in 20/23 (87%) and 24-h esophageal pH-monitoring in 0/1 (0%) of JLS patients. Gastroesophageal reflux diagnosis was performed by radiographic barium swallow in 16/23 (69%) of JSL patients. Fifteen of 23 EI patients with JLS (65%) were asymptomatic. Heartburn and esophageal regurgitation was only observed in 1/15 patient (previously asymptomatic) after two years of follow-up.

Eight (35%) of 23 EI patients with JLS were symptomatic and presented heartburn (5/8), solid and liquid dysphagia (3/8), and nausea and epigastralgia (1/8). Vomiting was not reported by any of the patients. Proton pump inhibitors were used in 4/8 JLS patients, histamine-2 receptor antagonist in 3/8 and prokinetic drugs in 4/8.

Regarding outcomes, esophageal imaging abnormalities were revaluated in 17/23 JLS patients with EI after one year of the previous exam, and 12/17 had maintenance of esophageal imaging. None of them required surgical intervention. None of them presented esophagus stenosis, neither Barrett's esophagus nor esophageal adenocarcinoma.

Demographic data, clinical subtypes and extracutaneous manifestations in JLS patients with and without EI are shown in Table 1. The frequency of any cumulative extracutaneous manifestations was significantly higher in JLS patients with EI compared to patients without this complication (56% vs. 24%, $p = 0.024$). No differences were evidenced in each extracutaneous manifestations in both groups ($p > 0.05$). The median age of diagnosis and disease duration were similar in both groups, as well as the frequency of circumscribed morphea, linear scleroderma, generalized morphea and mixed morphea ($p > 0.05$, Table 1).

Laboratory exams and treatments in JLS patients with and without EI are shown in Table 2. The frequency of methotrexate use was significantly higher in JLS patients with EI compared to patients without this complication (52% vs. 12%, $p = 0.002$). The median of blood eosinophils was similar in both groups ($p > 0.05$), likewise the frequency of autoantibody profile (ANA, anti-SCL-70, RF, anticentromere, ACL IgG and IgM, anti-Ro/SSA, anti-La/SSB and anti-RNP) ($p > 0.05$, Table 2).

Skin lesion biopsy was performed in 38/56 (68%) of JLS patients and revealed lymphohistiocytic inflammatory infiltrate with fibroblasts or fibrosis in dermis substituting

Table 2 – Laboratory exams and treatments in 56 JLS patients with and without esophageal involvement.

Variables	JLS with esophageal involvement ($n = 23$)	JLS without esophageal involvement ($n = 33$)	p
Laboratory exams at diagnosis			
ESR, mm/1st h	11 (6.5–19.5)	17 (8.7–30.2)	0.173
Blood eosinophils, mm^3	279 (200–350)	196 (106.5–478.5)	0.314
Cumulative autoantibodies			
ANA	8/22 (37)	9/29 (31)	0.760
Rheumatoid factor	1/10 (10)	1/14 (7)	1.000
Anti-SCL 70	1/20 (5)	1/19 (5)	1.000
Anti-centromere	0/22 (0)	0/29 (0)	1.000
Anti-Ro/SSA	1/9 (11)	1/9 (11)	1.000
Anti-La/SSB	2/9 (22)	0/9 (0)	0.470
Anti-RNP	1/16 (6)	0/26 (0)	0.381
Anticardiolipin IgM/IgG	0/10 (0)	0/15 (0)	1.000
Normal capilaroscopy	5/5 (100)	4/4 (100)	1.000
Cumulative treatment			
Methotrexate	12 (52)	4 (12)	0.002
Oral corticosteroid	5 (22)	2 (6)	0.110
Colchicine	7 (30)	6 (18)	0.340
D-penicillamine	4 (17)	3 (9)	0.420

Results are presented in median (range) and n (%).
JLS, juvenile localized scleroderma; ESR, erythrocyte sedimentation rate; ANA, antinuclear autoantibodies; CRP, C reactive protein.

adipose panicle compatible with scleroderma histology in all 38 patients.

Discussion

Our study demonstrated that EI was frequently observed at diagnosis in JLS patients. EI occurred in JLS patients with other extracutaneous manifestations and required methotrexate therapy. This gastrointestinal manifestation was observed mainly in asymptomatic patients with linear subtype.

The advantage of the present study was the inclusion of a JLS population of a University Hospital using standardized definition of these localized scleroderma subtypes.[8] In addition, JLS patients followed in our service had been submitted to a periodic exams evaluation annually, which included screening for esophageal, pulmonary and heart involvements. Indeed EI was observed in one third of our JLS patients two years after diagnosis, reinforcing the relevance of this longitudinal assessment.

EI has been rarely studied in JLS patients.[5–12] Guariso et al.,[5] reported EI in 8/14 (57%) of JLS patients, where only three of them were asymptomatic, contrasting with our study that almost two thirds were asymptomatic. Zulian et al.,[7] reported gastroesophageal reflux (preferably assessed by barium contrast radiography or 24-h intraesophageal pH monitoring) in 1.6% of JLS patients. In this study the diagnosis of gastroesophageal reflux was performed only in symptomatic patients.

Barium contrast radiography was used to exclude esophageal anatomic abnormalities, however this exam cannot differentiate between non-pathological gastroesophageal reflux and gastroesophageal reflux disease.[13] In our study none of our JLS patients were infants, suggesting that this abnormality may be related to the scleroderma, as also previously reported.[7]

An international study reported extracutaneous manifestations in 22% of JLS patients, and multiple extracutaneous involvements (more than one) in 4% of these patients. In this multicenter study, the main extracutaneous manifestations were articular (47%), neurologic (17%), and gastrointestinal (6%) and respiratory (3%) involvements that were rarely reported.[7] The high frequency of extracutaneous manifestations (31/56 – 55%), mainly EI, arthritis/arthralgia and interstitial pneumonitis observed in this study, may be related to the fact that our Hospital usually follows-up patients with moderate/severe chronic diseases.

Blood eosinophils count and autoantibody profile did not allow differentiating between JLS patients with and without EI. Additionally, the most frequent autoantibodies in our JLS patients with esophagus involvement was ANA, as also previously reported.[4,5,7,8]

The treatment of general EI, that involves gastroesophageal reflux disease and esophagitis, includes lifestyle changes, pharmacologic therapies and surgical intervention[13] and seem not to be different from systemic sclerosis in adults with EI.[14,15] In our cohort, standard therapy was introduced for symptomatic patients with adequate response and without esophagus complications. Furthermore, recent studies reported that use of methotrexate was beneficial for JLS therapy.[4,8] The high frequency of this immunosuppressive agent used in our JLS patients with EI may be due to the disease severity observed herein.

The main limitation of this study was the retrospective design with possible missing data, and the employment of different treatments in JLS patients throughout the years. Currently, impedance pHmetry is considered to be the gold standard for the diagnosis of gastroesophageal reflux disease.[13] However, impedance pHmetry and esophageal manometry were not performed in all of our patients, since these exams were made available at our service only recently.

In conclusion, EI was frequently observed in the first two years in JLS patients, mainly asymptomatic patients with linear scleroderma subtype. EI occurred in JLS patients with other extracutaneous manifestations and required methotrexate therapy. This study reinforces the need to screen for other organs and systems involvements in JLS patients periodically.

Funding

This study was supported by grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 303422/2015-7-level 1A to CAS), Federico Foundation (to CAS) and by Núcleo de Apoio à Pesquisa "Saúde da Criança e do Adolescente" da USP (NAP-CriAd) to CAS.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

Our gratitude to Ulysses Doria-Filho for the statistical analysis.

REFERENCES

1. Zullian F, Giorgio C, Sperotto F. Scleroderma in children: an update. Curr Opin Rheumatol. 2013;25:643–50.
2. Giacomin MF, França CM, Oliveira ZN, Machado MC, Sallum AM, Silva CA. Generalized morphea in a child with harlequin ichthyosis: a rare association. Rev Bras Reumatol. 2016;56:82–5.
3. Couto SB, Sallum AM, Henriques LS, Malheiros DM, Silva CA, Vaisbich MH. Nephrotic syndrome as the first manifestation of juvenile systemic scleroderma. Rev Bras Reumatol. 2017;57:613–5.
4. Laxer RM, Zullian F. Localized scleroderma. Curr Opin Rheumatol. 2006;18:606–13.
5. Guariso G, Conte S, Galeazzi F, Vettorato MG, Martini G, Zullian F. Esophageal involvement in juvenile localized scleroderma: a pilot study. Clin Exp Rheumatol. 2007;25: 786–9.
6. Foeldvari I. New developments in juvenile systemic and localized scleroderma. Rheum Dis Clin N Am. 2013;39:905–20.
7. Zullian F, Vallongo C, Woo P, Russo R, Ruperto N, Harper J, et al. Localized scleroderma in childhood is not just a skin disease. Arthritis Rheum. 2005;52:2873–81.
8. Zullian F, Athreya H, Laxer R, Nelson AM, Oliveira SKF, Punaro MG, et al. Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. Rheumatology. 2006;45:614–20.
9. Flick JA, Boyle JT, Tuchman DN, Athreya BH, Doughty RA. Esophageal motor abnormalities in children and adolescents with scleroderma and mixed connective tissue disease. Pediatrics. 1988;82:107–11.
10. Weber P, Ganser G, Frosch M, Roth J, Hülskamp G, Zimmer KP. Twenty-four hour intraesophageal pH monitoring in children and adolescents with scleroderma and mixed connective tissue disease. J Rheumatol. 2000;27:2692–5.
11. Birdi N, Laxer RM, Thorner P, Fritzler MJ, Silverman ED. Localized scleroderma progressing to systemic disease. Case report and review of the literature. Arthritis Rheum. 1993;36:410–5.
12. Diaz-Perez JL, Connolly SM, Winkelmann RK. Disabling pansclerotic morphea of children. Arch Dermatol. 1980;116:169–73.
13. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49:498–547.
14. Carlson DA, Hinchcliff M, Pandolfino JE. Advances in the evaluation and management of esophageal disease of systemic sclerosis. Curr Rheumatol Rep. 2015;17:475.
15. Wipff J, Allanore Y, Soussi F, Terris B, Abitbol V, Raymond J, et al. Prevalence of Barrett's esophagus in systemic sclerosis. Arthritis Rheum. 2005;52:2882–8.