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Original article

Incidence and prevalence of systemic sclerosis in Campo Grande, State of Mato Grosso do Sul, Brazil



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ABSTRACT

Introduction: Systemic sclerosis is an autoimmune disease which shows extreme heterogeneity in its clinical presentation and that follows a variable and unpredictable course. Although some discrepancies in the incidence and prevalence rates between geographical regions may reflect methodological differences in the definition and verification of cases, they may also reflect true local differences.

Objectives: To determine the prevalence and incidence of systemic sclerosis in the city of Campo Grande, state capital of Mato Grosso do Sul (MS), Brazil, during the period from January to December 2014.

Methods: All health care services of the city of Campo Grande – MS with attending in the specialty of Rheumatology were invited to participate in the study through a standardized form of clinical and socio-demographic assessment. Physicians of any specialty could report a suspected case of systemic sclerosis, but necessarily the definitive diagnosis should be established by a rheumatologist, in order to warrant the standardization of diagnostic criteria and exclusion of other diseases resembling systemic sclerosis. At the end of the study,

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15 rheumatologists reported that they attended patients with systemic sclerosis and sent the completed forms containing epidemiological data of patients.

Results: The incidence rate of systemic sclerosis in Campo Grande for the year 2014 was 11.9 per million inhabitants and the prevalence rate was 105.6 per million inhabitants. Systemic sclerosis patients were mostly women, white, with a mean age of 50.58 years, showing the limited form of the disease with a mean duration of the disease of 8.19 years. Regarding laboratory tests, 94.4% were positive for antinuclear antibody, 41.6% for anti-centromere antibody and 19.1% for anti-Scl70; anti-RNA Polymerase III was performed in 37 patients, with 16.2% positive.

Conclusions: The city of Campo Grande, the state capital of MS, presented a lower incidence/prevalence of systemic sclerosis in comparison with those numbers found in US studies and close to European studies' data.

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Incidência e prevalência de esclerose sistêmica em Campo Grande, Estado de Mato Grosso do Sul, Brasil

R E S U M O

Palavras-chave:

Esclerose sistêmica
Esclerodermia
Incidência
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Brasil

Introdução: A esclerose sistêmica (ES) é uma enfermidade autoimune, extremamente heterogênea na sua apresentação clínica e segue um curso variável e imprevisível. Embora algumas discrepâncias nas taxas de incidência e prevalência entre regiões possam refletir as diferenças metodológicas na definição e verificação dos casos, elas também podem refletir as verdadeiras diferenças locais.

Objetivos: Conhecer a prevalência e incidência da ES na cidade de Campo Grande, capital do Estado de Mato Grosso do Sul (MS), Brasil, de janeiro a dezembro de 2014.

Métodos: Todos os serviços de saúde de Campo Grande (MS) que tinham atendimentos na especialidade de reumatologia foram convidados a participar do estudo por meio de ficha padronizada de avaliação clínica e sociodemográfica. Médicos de qualquer especialidade poderiam reportar um caso suspeito de ES, mas obrigatoriamente o diagnóstico definitivo deveria ser feito por um reumatologista, para garantir a padronização dos critérios diagnósticos e excluir outras doenças que se assemelham à ES. No fim do estudo 15 reumatologistas relataram ter atendido pacientes com diagnóstico de ES e enviaram os formulários preenchidos com os dados epidemiológicos dos pacientes.

Resultados: A taxa de incidência de ES em Campo Grande em 2014 foi de 11,9 por milhão/habitantes e a de prevalência foi de 105,6 por milhão/habitantes. Os pacientes com ES eram principalmente mulheres, da cor branca, média de 50,58 anos, forma limitada da doença e tempo de evolução médio da doença de 8,19 anos. Em relação aos exames laboratoriais, observou-se a positividade de 94,4% para o ANA, 41,6% para ACA e 19,1% para anti-Scl70, o anticorpo anti-POL3 foi feito em apenas 37 pacientes, com positividade de 16,2%.

Conclusões: A capital do Estado de Mato Grosso do Sul, Campo Grande, apresentou dados de incidência e prevalência de ES inferiores aos encontrados em estudos americanos e próximos aos dados observados em estudos europeus.

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Introduction

Systemic sclerosis (SSc) is an autoimmune disease of the connective tissue, extremely heterogeneous in its clinical presentation, with the involvement of multiple systems and that follows a varied and unpredictable course.¹ Its etiology remains unknown; a multifactorial cause was suggested, possibly triggered by environmental factors in a genetically predisposed individual.²

The classification of SSc patients takes into account the extension of skin involvement and the presence of overlapping with certain characteristics of other autoimmune rheumatic diseases.³⁻⁵

In the United States, the reported prevalence rate for SSc was 1-5 per 1000 inhabitants. Two prevalence studies conducted in England found a similar value, about 1 per 1000 inhabitants.⁴ Regarding the incidence of SSc, an annual rate of 0.6-19 new cases per million inhabitants was estimated.⁵ Steen et al. found an incidence rate of SSc in 3.8-13.9 new

cases per million inhabitants per year.³ A study in a southern state in Australia reported an annual incidence of 22.8 new cases of SSc per million inhabitants and a prevalence of 233 cases per million inhabitants in 1999, with values similar to those in American studies conducted in the same period.⁶

More recently, a systematic review study reported similar prevalences of SSc observed in the UK and Japan, with 31 and 38 cases per million inhabitants, respectively.⁷ It is noteworthy that, in addition to regional genetic variations, environmental exposures can also have an effect on the prevalence and incidence rates. For example, silica exposure appears to increase the risk of developing SSc; however, this triggering action is only important to a small proportion of male patients.⁷

Interestingly, there has been an increase in SSc incidence rates in different geographical regions,^{6,8} possibly due to an earlier diagnosis and also to the use of new classification criteria. For example, in the United States, the rate for new cases increased from 0.6 cases per million in 1947 in Tennessee to 19.0 cases per million in 1991 in the Detroit area.⁹ Likewise, the prevalence and incidence of SSc appear to be larger in populations of European ancestry, and lower in groups of Asian descent.⁷ In Taiwan, the incidence and prevalence rates were 10.9 and 56.3 cases per million cases/inhabitants, respectively.¹⁰

In epidemiology studies of SSc, different results are observed in different regions of the world, and this also occurs in one same country or city.^{6-8,10} SSc prevalence data in a multi-ethnic French district suggested that the disease appears to be more frequent and severe in a population of non-European origin, which speaks in favor of the idea that the race could influence the susceptibility to the development of SSc, and also the clinical profile.¹¹ In this same line, the European group of SSc research pointed out that geographical variations in patients with SSc may also have an influence with regard to antibody associations and in the rate of occurrence among women and men, but no associations between races were found.¹²

There are no published data on the prevalence and incidence of SSc in the Brazilian population, since this is a rare condition. Thus, due to the scarcity of national studies and the high degree of miscegenation found in the Brazilian population¹³ we aimed to study the prevalence and incidence of systemic sclerosis in the city of Campo Grande, the state capital of Mato Grosso do Sul, Brazil, during the period from January to December 2014.

Objectives

To determine the prevalence and incidence of systemic sclerosis in the city of Campo Grande, Mato Grosso do Sul, Brazil, during the period from January to December 2014.

Methods

All health care services in Campo Grande – MS with Rheumatology specialty participated in this prospective observational study.

The Rheumatology units in the city are distributed among the Medical School Teaching Hospital of the Universidade Federal de Mato Grosso do Sul, the Regional Hospital of Mato Grosso do Sul, Santa Casa de Campo Grande, the outpatient clinic of the Medical Specialties Center of the Municipality of Campo Grande, outpatient clinics of the Medical Specialties Center of Anhanguera-Uniderp Medicine School, outpatient clinics of the Caixa de Assistência dos Servidores de Mato Grosso do Sul, and several private Rheumatology clinics.

Prior to starting this study, all rheumatologists were informed by e-mail and phone call about the procedures for data collection and objectives of this research. Periodically, we asked (by e-mail or phone call) to all involved doctors to complete a standardized form for collecting demographic and laboratory data of all patients diagnosed with systemic sclerosis and evaluated during the study period, regardless of whether they were new or old cases. Any doctor could report a suspected case of SSc (general practitioner, dermatologist, vascular surgeon, gastroenterologist, pulmonologist, etc.), but the definitive diagnosis necessarily should be established by a rheumatologist, in order to ensure the standardization of diagnostic criteria and to rule out other diseases resembling SSc, for example, mixed connective tissue disease (MCTD).

At the end of the study, 15 rheumatologists reported patients with SSc, and sent the completed forms with epidemiological data of their patients; verbal or written consent from all patients was requested. The reasons for other MS rheumatologists did not report cases were: they did not examine patients with SSc in the period, or the patients seen did not live in Campo Grande – MS or the patients had already been reported by another colleague (patient's duplicity). To avoid data redundancy in the event that an individual patient had been assessed by more than a rheumatologist, these patients were identified by the initials of their names and their date of birth.

Patients diagnosed with SSc and non-residents of Campo Grande – MS were not considered for incidence and prevalence estimates.

To be selected, patients with SSc should meet the following criteria:

- Meet the 2013 classification criteria of the ACR/EULAR for SSc¹⁴;
- In the case of absence of skin thickening, patients should meet the 2001 criteria of LeRoy and Medsger for early SSc.¹⁵

State of origin, provenance, age, gender and race/color data, and time elapsed from first symptoms to diagnosis, disease duration, and clinical form of SSc were collected, and laboratory tests such as antinuclear antibody (ANA) anti-DNA topoisomerase I antibody (anti Scl70), anticentromere antibody (ACA) and anti-RNA polymerase III (anti-RNAP III) also were conducted.

The methods used in autoantibody survey were, respectively:

- a. Antinuclear antibodies (ANA) survey
Immunofluorescent antibody test for ANA, with HEp2 cells as a substrate (Faar technique), according to the II

Table 1 – Comparison of incidence and prevalence rates of patients with systemic sclerosis (SSc) in several geographical regions.

Publication	Geographical region	Period of study	Prevalence per million inhabitants	Incidence per million inhabitants
Horimoto et al.	Campo Grande – Brazil	2014–2015	105.6	11.9
Rosa et al. ²⁶	Buenos Aires – Argentina	1999–2004	296	21.2
Mayes et al. ²⁸	Detroit – USA	1989–1991	242	19.3
Lo Monaco et al. ³⁷	Ferrara – Italy	1999–2007	254	32
Alamanos et al. ²⁹	Greece	1981–2002	154	11
Thompson et al. ³⁰	Australia	1993–2002	232.2	20.4
Tamaki et al. ³⁵	Tokyo – Japan	1987–1988	38	7.2
Kuo et al. ¹⁰	Taiwan	2002–2007	56	10.9

The results are shown in number of cases per million inhabitants per year.

Brazilian Consensus on Antinuclear Factor in Hep-2 cells (2003) criteria¹⁶ for the interpretation of results.

Sera were considered positive with a titer $\geq 1/160$, with dilution a negative fluorescence.

- b. Anticentromere survey – Indirect immunofluorescence technique with HEp2 cells as a substrate, according to the II Brazilian Consensus on Antinuclear Factor in Hep-2 cells (2003) criteria¹⁶ for the interpretation of results.
- c. Anti-DNA topoisomerase I (anti Scl70) survey – Immunoassay technique¹⁷; the sample was considered nonreactive with values <20 units, weakly reactive between 20 and 39 units, moderately reactive between 40 and 80 units and strongly reactive (higher values) with values >80 units.
- d. Anti-RNA polymerase III Antibody survey – ELISA technique¹⁸; the sample was considered negative with values <20 units, weakly reactive between 20 and 39 units, moderately reactive between 40 and 80 units, and strongly reactive (higher values) with >80 units.

Statistical analysis

IBGE data¹⁹ with estimates of the resident population in Brazil and in Units of the Federation and with a reference date of July 1, 2014, were considered for the calculation of the incidence and prevalence of SSc.

Data is presented in absolute and relative frequencies, means and standard deviations, and with a confidence interval of 95% and statistically significant values for $p < 0.05$.

Results

During 2014, a total of 166 patients with scleroderma or systemic sclerosis were treated in various outpatient clinics and Rheumatology Units in the city of Campo Grande – MS. Eighty-nine patients who lived in the city had a definitive diagnosis of systemic sclerosis and were clinically examined in that city during the study period.

Of this total, 10 were new cases of SSc diagnosed during the year 2014 and 79 patients had already been previously diagnosed. Therefore, the incidence rate of SSc in the city of Campo Grande – MS during the year 2014 was 11.9 per million inhabitants and the prevalence rate was 105.6 per million

inhabitants. The data are presented in Table 1, which also lists comparisons with incidence and prevalence rates in other countries and regions.

Results observed in systemic sclerosis

Among the 89 patients with SSc, 86 were women (96.6%) and 3 were men (3.4%) with a mean age of 50.58 ± 13.85 years (mean \pm standard deviation).

Thirty-one patients (34.8%) with SSc were born in the city of Campo Grande; 31 patients (34.8%) were born in the countryside of MT, and 27 patients (30.4%) were born in other states.

Of the 89 patients with SSc, 58 patients (65.2%) reported being white, 20 patients (22.4%) had a brown color, 8 patients (9.0%) were black and 3 patients yellow (3.4%).

Regarding clinical forms of SSc, 38 patients (42.7%) showed the limited form, 24 patients (27.0%) exhibited the diffuse form, 17 patients (19.1%) show overlapping with other collagen diseases, 6 patients (6.7%) exhibited the *sine scleroderma* form and 4 patients (4.5%) had the early form. Among the 17 patients with the overlapped form, 8 patients (47.1%) concomitantly had systemic lupus erythematosus, 5 patients (29.4%) had rheumatoid arthritis, and 4 patients (23.5%) had their SSc associated with inflammatory myopathies.

Patients with SSc were already presenting symptoms for 4.74 ± 5.01 years before their diagnosis, and the disease duration, in general, was about 8.19 ± 7.40 years.

ANA was positive in 84 patients with SSc (94.4%), and the main patterns found in these patients were: fine speckled nuclear pattern (30 patients – 36.6%), centromeric pattern (29 patients – 35.4%) and quasi-homogeneous nuclear pattern, with metaphase plate staining for 5–10 points (12 patients – 14.6%). Among all patients, 37 (41.6%) had positive ACA, 17 (19.1%) were positive for anti-Scl70 and 1 patient (1.1%) was simultaneously positive for both autoantibodies. On the other hand, the anti-RNAP III was performed in only 37 patients, being positive in 6 of these (16.22%).

The characteristics of the epidemiological profile of patients with SSc and the results observed in laboratory tests for autoantibodies of the same patients are shown respectively in Tables 2 and 3.

Table 2 – Distribution of patients evaluated in this study and results of epidemiological data in patients with systemic sclerosis (SSc).

Variable	Results
Epidemiological data	
Age	50.58 ± 13.85
Gender	
Male	3 (3.4)
Female	86 (96.6)
Race	
White	58 (65.2)
Brown	20 (22.4)
Black	8 (9.0)
Yellow	3 (3.4)
Disease duration	
<5 years	33 (37.1)
Between 5 and 10 years	31 (34.8)
>10 years	25 (28.1)
Duration of symptoms before Dx	4.74 ± 5.01
Duration of symptoms after Dx	8.19 ± 7.40
Clinical form	
Limited	38 (42.7)
Diffuse	24 (27.0)
Overlap	17 (19.1)
Sine scleroderma	6 (6.7)
Early	4 (4.5)
Dx, diagnosis. The results are presented as mean ± standard deviation or as absolute frequency (relative frequency).	

Table 3 – Results of autoantibodies in patients with systemic sclerosis (SSc).

Variable	Results
ANA	
Positive	84 (94.4)
Negative	5 (5.6)
ANA pattern (n = 84)	
Nuclear fine speckled	30 (35.7)
Centromeric	29 (34.5)
Nuclear quasi homogeneous	12 (14.3)
Others	13 (15.5)
Anti-Scl70	
Positive	17 (19.1)
Negative	72 (80.9)
ACA	
Positive	37 (41.6)
Negative	52 (58.4)
anti-RNAP III (n = 37)	
Positive	6 (16.2)
Negative	31 (83.8)
ANA, antinuclear antibody; Scl70, anti-DNA topoisomerase I antibody; ACA, anti-centromere antibody; anti-RNAP III, anti-RNA polymerase III antibody. The results are presented in absolute frequency (relative frequency).	

Discussion

In this study, an unprecedented and representative sample of the Midwest of Brazil was defined, having been characterized by a heterogeneous group of patients with various spectra of disease and different stages of clinical manifestations and activities of the disease, but that is very similar to what occurs in other populations of patients in this country and even from other locations.^{3,13,20-23}

A systematic review of 32 articles published from 1969 to 2006 indicated that the incidence rate for SSc varied from 0.6 to 122 cases per million inhabitants; on the other hand, the prevalence rate for the same disease ranged from 7 to 489 cases per million inhabitants,⁹ which is consistent with the rates observed in our study. Several geographical variations were observed, with a higher prevalence of SSc in the United States (276 cases per million inhabitants) and Australia (233 cases per million inhabitants) versus Japan and Europe, where one still observed a north-south variable gradient, with lower prevalence rates in northern European countries.^{9,12}

The rates found for SSc in our study (incidence of 11.9 per million inhabitants and prevalence of 105.6 per million inhabitants) are more similar to those for European countries. For example, the prevalence of SSc in a French multi-ethnic district was 158.3 cases per million inhabitants in 2001¹¹; in the north of England a prevalence of 88.0 cases per million inhabitants in 2000 was found.²⁴ A peculiarity of the city of Campo Grande – MS is that its population was mainly composed of national immigrants and foreigners, who came mainly from the states of Minas Gerais, Rio Grande do Sul, Parana, and Sao Paulo, and from countries like Germany, Spain, Italy, Japan, Paraguay, Portugal, Syria and Lebanon.²⁵

There are no Brazilian studies published on the incidence or prevalence of SSc. In South America, the incidence and prevalence of SSc observed in Buenos Aires – Argentina were 21.2 cases and 296 cases per million inhabitants, respectively.²⁶ In the Caribbean, a lower incidence was observed, with a total of 17 cases of SSc observed in the Afro-descendant population of Barbados during an observation period of 10 years (1996–2006).²⁷ In North America, the incidence and prevalence of SSc observed in the United States were higher, respectively 19.3 and 242.0 cases per million inhabitants.²⁸

Although some discrepancies in the incidence and prevalence of SSc between regions may reflect methodological differences in the definition and verification of cases, they can also reflect true local differences. These regional differences could occur due to the diverse genetic susceptibility to the development of SSc, or to different degrees of exposure to environmental factors incriminated in the pathogenesis.⁶

In Brazil, as in all regions of the world, there were some differences in the rate of women affected by SSc compared to men, and female predominance has been observed in all studies.^{6,7,10,11,13,20,23,26-38} While there is an agreement between the results of our study and those in the literature, a high female/male ratio of 28.6:1 in SSc was observed. For example, national data for SSc inform a variable rate of 7.7–32 women for every affected man^{13,18,23,37}; in South America (Argentina), the rate is 17:1²⁶; in Caribbean countries

(Barbados and Puerto Rico), the rates are respectively 26:1²⁷ and 23:1³³; in North America (US and Canada), the rates are respectively 6.1:1⁸ and 7.6:1³⁴; in Asia (Taiwan and Japan), the rates are respectively 3.5:1¹⁰ and 14:1³⁵; in the Middle East (Iraq), the rate is 8.3:1³⁶; and in Europe (Italy, Germany, France and England), the rates are respectively 9.7:1,³⁷ 5:1,²¹ 11.5:1,¹¹ and 5.2:1.²⁴

Regarding other demographic data found, the mean age of our patients with SSc (50.5 years) was almost consensus among the various studies in Brazil and overseas,^{6,11,13,20-24,28-31,33,34,36,37} with the diagnosis established between the fourth and fifth decades of life; only the African-Caribbean population²⁷ had a younger mean age at diagnosis (37.3 years). With regard to the race informed by the patient, there was a prevalence of white color in our patients with SSc; however, one does not rule out the possibility of a bias of racial classification, due to the high degree of miscegenation found in the Brazilian population.¹³ In the South²⁰ and Southeast²³ of this country, there was a higher prevalence of white people with SSc. On the other hand, in the Northeast³⁸ region, a high prevalence of mulattoes and blacks was observed, probably because the study was conducted in a state with a known predominance of Afro-descendants (Bahia).

In this same vein, the European research group on SSc (EUSTAR) pointed out that geographical variations in patients with SSc may also have an impact with regard to antibody associations and in the rate of occurrence between women and men,¹² but this, as well as another study, found no association between races.^{12,39} In this study, most patients with SSc were born in the same state (73.4%), and the remaining patients were from different locations, but mainly from the states of São Paulo (13.44%) and Paraná (5.04%).

In this study, the limited clinical presentation of SSc showed a slight predominance of the diffuse form, in accordance with other descriptions in the country^{13,20,23,37} and in most other populations.^{11,21,22,24,28,33,36} However, there are descriptions in which the diffuse form is more common in populations of Blacks vs. Caucasian populations,^{11,28,38} including, in this case, those of African-Caribbean descent, in which a predominance of diffuse (63%) over the limited (37%) form was observed.²⁷

Regarding the laboratory tests performed in patients with SSc, antinuclear antibody (ANA) was present in 94.4% of patients – a similar result to most national studies^{13,20,23,37} and in other regions.^{11,21,28,36,40-42} The main patterns observed were: fine speckled nuclear, centromeric, and quasi-homogeneous nuclear patterns. Bernstein et al. described ANA positivity in 97% of patients with SSc, mainly represented by fine speckled and centromeric patterns, besides the observation of an association with the nucleolar (speckled and homogenous) pattern in 33% of patients.⁴² Hesselstrand et al. reported ANA positivity in 84% of patients with SSc, and the most observed patterns were: fine speckled (41%), homogeneous (25%), nucleolar (24%) and centromeric (18%) patterns.⁴⁰

Regarding specific antibodies for SSc observed in this study, anti-centromere (ACA), anti-DNA topoisomerase I (anti Scl70) and anti-RNA polymerase III (anti-RNAP III) positivity was observed in 41.6%, 19.1% and 16.2% of patients, respectively, and the percentages were comparable to those in two studies

conducted in Southern Brazil,^{13,20} although Müller et al. had found surprisingly high levels of anti-RNAP III (41.18%).²⁰ In this study, 60 of 89 patients (67.4%) were positive for at least one of those three specific autoantibodies to SSc (anti-Scl70, ACA, or anti-RNAP III).

The literature reports that the prevalence of highly specific autoantibodies associated with SSc or with overlap syndromes with SSC features is high in patients with SSc, primarily represented by ACA and anti Scl70,⁴⁰⁻⁴² here including the Brazilian population with SSc.^{13,20} Although the studies report that the coexistence of these specific autoantibodies is rare in patients with SSc (1.6%),⁴⁰⁻⁴² in this study, we observed two patients (2.2%) that were concomitantly positive for specific autoantibodies: one patient with the diffuse form presented concomitant positivity for anti Scl70 and ACA, and another patient also with the diffuse form had concomitant positivity for anti Scl70 and anti-RNAP III.

Our conclusion is that the city of Campo Grande, the state capital of Mato Grosso do Sul, presented lower incidence and prevalence of SSc versus those found in American studies and similar to those observed in European studies. This incidence, however, may still be underestimated, especially in patients with the limited form of SSc, because in these individuals only the Raynaud's phenomenon is apparent for many years, with little systemic involvement; thus, they may not seek medical attention. We suggest that epidemiological surveys in SSc are conducted in other Brazilian cities, in order to reflect possible regional differences and environmental influences in the development of both diseases.

Conflict of interest

The authors declare no conflicts of interest.

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