Osteonecrosis of the jaw on imaging exams of patients with juvenile systemic lupus erythematosus

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ABSTRACT

Objective: The objective of the present study was to evaluate radiographic changes of the temporomandibular joint (TMJ) in patients with juvenile systemic lupus erythematosus (JSLE) and a control group. **Patients and Methods:** Panoramic radiographies of the TMJ of 26 JSLE patients and 28 healthy individuals were evaluated. Multislice computed tomography (MCT) was performed on those patients who presented flattening and/or destruction of mandibular condyles. Demographic data, oral health indices, clinical manifestations, laboratorial exams, and treatment were evaluated. **Results:** Important radiographic changes consistent with osteonecrosis of the mandible, confirmed by MCT of the TMJ, were observed in 2/26 (8%) JSLE patients *versus* 0% in the control group (P = 0.22). Mild clinical dysfunction and abnormal TMJ mobility were observed in 67% and 54% of the patients, respectively. Age of onset, disease duration, and current age were similar in JSLE patients with and without severe radiographic changes of TMJ (9.3 *versus* 10.8 years, *P* = 0.77; 3.3 *versus* 2 years, P = 0.63; 12.6 *versus* 13.5 years, P = 0.74, respectively). Significant differences in gender, socioeconomical status, oral health indices, clinical manifestations, laboratorial exams, and treatment were not observed between both subgroups (P > 0.05). Both JSLE patients with osteonecrosis of the mandible had active chronic disease, used corticosteroids for a prolonged period, and had mild TMJ dysfunction. Antiphospholipid antibodies were not observed in those two patients, and neither one had been treated with bisphosphonate. **Conclusions:** Osteonecrosis of the mandible with mild TMJ dysfunction was observed in some of the patients, demonstrating the importance of odontological assessment during clinical follow-up.

Keywords: juvenile systemic lupus erythematosus, children, mandible, temporomandibular joint, osteonecrosis.

INTRODUCTION

Juvenile systemic lupus erythematosus (JSLE) is an autoimmune disorder affecting several organs and systems, with a wide range of manifestations that can involve the masticatory system and oral mucosa.[1,2]

Orofacial involvement in JSLE has not been the focus of a large number of studies. In a recent study, we evaluated 48 patients with JSLE *versus* 48 age- and gender-matched healthy individuals, and we identified higher incidence of bacterial plaque and gingival bleeding in lupus patients.[3] Orofacial involvement has also been evaluated in a study with patients with juvenile idiopathic arthritis (JIA). A study undertaken by our department observed precarious oral hygiene, higher incidence of cavities, and involvement of the temporomandibular joint (TMJ) in JIA patients when compared to the control group.[4]

Radiographic evaluation and osteonecrosis of the TMJ in adult patients with SLE and JSLE have rarely been reported. In 1986, Szántó *et al*. reported a case of an adult patient with SLE who developed osteonecrosis of the mandibular

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condyle.[5] On the other hand, osteonecrosis has been observed in SLE and JSLE, associated, especially, with disease activity, antiphospholipid antibodies, and corticotherapy.[6,7]

The lack of systematic studies evaluating radiographic changes and TMJ osteonecrosis in children and adolescents with JSLE stimulated the present study.

The objectives of this study included the evaluation of radiological changes in JSLE patients and their correlation with demographic data, oral health indices, clinical manifestations, disease activity, cumulative damage, and treatment.

PATIENTS AND METHODS

JSLE patients and healthy controls

Twenty-six consecutive JSLE patients, diagnosed according to the classification criteria of the American College of Rheumatology (ACR), [8] were evaluated at the Pediatric Rheumatology Unit of the Children's Institute (ICr, from the Portuguese) of the Hospital das Clínicas (HC) of the Medical School of Universidade de São Paulo (FMUSP). The control group was composed of 28 age- and gender-matched healthy children and adolescents undergoing routine dental treatment at the Odontology Department of HC-FMUSP. Patients with JSLE and children and adolescents in the control group did not present local comorbidities or other systemic disorders with dental or articular repercussions. Patients were included in the study after the patient or guardian signed an informed consent. This study was approved by the Ethics on Research Committee of HC-FMUSP (CAPPesq 014/03).

Radiographic and orofacial assessments

Radiographic evaluation consisted of orthopantomographic (panoramic) X-rays assessing the facial skeleton, teeth, periodontium, and TMJ. Changes of the mandibular condyles were classified in four degrees: grade 0 (absence of radiographic abnormalities), grade 1 (discrete irregularities of the borders of the condyle), grade 2 (erosions and/or flattening of the condyle), and grade 3 (complete destruction of the condyle).[9] Assessment was carried out by three different examiners, who were specialist on TMJ and/or radiologists.

Patients whose panoramic X-ray was compatible with osteonecrosis (grades 2 or 3) were submitted to computed tomography (CT) of the TMJ with thin slices. The Light Speed-Multislice – General Electric, Wisconsin, USA – was used for the CTs.

Plaque index (PI) and gingival bleeding index (GBI)[10] were used for oral and gingival assessments. Plaque index was used to evaluate oral hygiene. This index was calculated by the number of dental surfaces stained by plaque disclosing tablets multiplied by 100 and divided by the total number of surfaces. The presence of gingival inflammation (gingivitis) was assessed by the GBI, which was determined by the number of bleeding surfaces after the use of the periodontal probe multiplied by 100 and divided by the total number of surfaces. The number of teeth with cavities, missing teeth, and number of fillings (DMF-T) were also evaluated.[11]

Helkimo's index[12] was used for the clinical evaluation of the TMJ: clinical mandibular dysfunction index (CMDI) and mandibular mobility index (MMI). The clinical mandibular dysfunction index evaluates five clinical signs of dysfunction [pain on palpation of mastication muscles, pain on palpation of the TMJ, pain during mandibular movements, TMJ dysfunction (articular deviation or noise), and abnormal MMI], and each item receives scores ranging from 0 to 5, according to the severity, for each item, and the final result is composed by the sum of those scores (maximal CMDI of 25). A CMDI of 0 indicates the absence of clinical TMJ dysfunction, 1-4, mild dysfunction, 5-9, moderate dysfunction, and 10-25, severe dysfunction. The MMI evaluates the amplitude of four mandibular movements [maximal oral opening (normal $\geq$ 40 mm), left and right mobility (normal $\geq$ 7 mm), and protrusion (normal > 7 mm)], and each receives scores ranging from 0 to 5, depending on severity, and the final result is the sum of all scores (maximal MMI of 20). A mandibular mobility index of 0 indicates normal mandibular mobility, 1-4, mild dysfunction, and 5-20, severe dysfunction.

Demographic data, clinical manifestations, laboratorial tests, JSLE activity, cumulative disease damage, and treatment

Socio-demographic data evaluated included current age, duration of the disease, and gender. Clinical manifestations were determined at the time of the orofacial evaluation, including: cutaneous involvement (malar erythema, oral ulcer and/or vasculitis), arthritis, nephritis (hematuria, leukocyturia, cylindruria, and proteinuria, and systemic hypertension), neuropsychiatric involvement (according to the criteria of 19 SLE-related syndromes proposed by the ACR in 1999),[13] serositis (pleuritis and/or pericarditis), and hematologic involvement (hemolytic anemia, leucopenia, and/or thrombocytopenia).

Laboratorial tests included: serum complement levels (C3 and C4), and anti native or double strand DNA antibodies (evaluated by indirect immunofluorescence using *Crithidia lucillae* as substrate). Antiphospholipid antibodies were evaluated by at least

two mensurations: anticardiolipin antibodies [by enzyme-linked immunosorbent assay (ELISA) using the commercial Hemagen anticardiolipin kit®)], and lupus anticoagulant (detected by three methods: activated partial thromboplastin time, dilute Russell's viper venom, and kaolin clotting time).[14]

Activity of juvenile systemic lupus erythematosus, cumulative damage, disease course, and treatment (corticosteroids, antimalarials, intravenous cyclophosphamide, methotrexate, and azathioprine) were determined at the time of radiographic and oral evaluations.

The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[15] was used to quantify disease activity. SLEDAI scores greater than or equal to four were, arbitrarily, considered an indication of active disease. The Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR-DI)[16] was used to evaluate the cumulative damage of JSLE. SLICC/ACR-DI scores greater than or equal to one, after a 6-month period of disease activity, was interpreted as a sign of the presence of some cumulative damage.

The course of the disease was divided in three types: long quiescent (characterized by absence of disease activity for at least one year), relapsing-remitting [characterized by periods of disease activity intercalated with periods of inactivity (during one year in two or more consultations)], and chronic active (persistent active disease for at least one year).[17]

Statistical analysis

Results are presented as median (variation), for continuous parameters, and numbers (%), for categorical parameters. Fisher's exact test or the Mann-Whitney test were used to compare significant radiographic TMJ changes (grades 2 or 3) between JSLE patients and the control group, as well as for comparison between JSLE patients with significant radiographic changes of the TMJ (grades 2 or 3) and JSLE patients without changes or with mild changes (grades 0 or 1). $P < 0.05$ was considered statistically significant.

RESULTS

Mild radiographic changes (grades 0 or 1) of the TMJ were observed in 24/26 and in all 28 individuals of the control group ($P = 0.22$). Significant TMJ changes (grades 2 or 3) were not observed in the control group. However, two out of 26 (8%) JSLE patients presented radiographic changes in the mandibular condyles compatible with grade 3. Those two patients underwent CT of the TMJ, which showed osteonecrosis of the TMJ.

Tables 1 and 2 show the comparison between JSLE patients with significant radiographic TMJ changes (Group A) and those with mild or no changes (Group B). Statistically significant differences in demographic data, oral health indices, clinical manifestations, and laboratorial tests were not observed between both groups ($P > 0.05$, Table 1). Besides, disease activity, cumulative damage, chronically active disease, and treatment were similar in both groups ($P > 0.05$, Table 2).

Both JSLE patients with osteonecrosis of the TMJ are also described:

Case 1

This is a female patient from São Paulo. In 2001, at the age of 12 years and 6 months, the patient presented acute oligoarthritis of the ankles, malar erythema, and oral ulcer. Fifteen days later, the patient developed dyspnea and orthopnea progressing to restrictive cardiac failure secondary to pericardial effusion. Laboratorial exams revealed: hemoglobin 11.2 g/dL, hematocrit 35%, leucocytes 9,700/mm^3 (87% neutrophils, 10% lymphocytes, and 4% eosinophils), platelets 170,000/mm^3, antinuclear antibodies (ANA) 1/160, positive anti-double stranded DNA antibodies, C3 0.91 g/L (0.5-1.8 g/L), and C4 0.1 g/L (0.1-0.4 g/L). Physical exam revealed alopecia and purpuric vasculitis of the lower limbs. The diagnosis of JSLE was established according to ACR[8] criteria, and the patient was treated with prednisone, 25 mg/d, and hydroxichloroquine sulfate, 20 mg/d. At the age of 14 years, the patient underwent radiographic and orofacial evaluation, which showed an increase in orofacial indices (PI = 23, GBI = 41, DMF-T = 2, and Helkimo indices: CMDI = 1 and MMI = 1) without pain on palpation or with movements. Orthopantomographic X-rays of the face showed grade 3 changes. The CT scan of the TMJ showed bilateral asymmetry, more pronounced on the left, with flattened condyles, reduction of the articular space, discrete subchondral cysts, remodeling of the condyles, and marginal hypertrophic reaction compatible with osteonecrosis. At that time, laboratorial exams showed: hemoglobin 12.4 g/dL, hematocrit 37%, leukocytes 4,900/mm^3 (68% neutrophils and 24% lymphocytes), platelets 125,000/mm^3, ESR 15 mm in the first hour, CRP negative, ANA 1/320, anti-dsDNA antibodies negative, C3 0.99 g/L, C4 0.09 g/L, and negative antiphospholipid antibodies. The patient was treated with prednisone for 20 consecutive months. At the time of the evaluation, the patient was taking prednisone (10 mg/d) and hydroxichloroquine sulfate (250 mg/d). The patient had chronic active disease, SLEDAI of 2, and SLICC/ACR-DI of 0.

Table 1
Demographic and socio-economic-cultural data, oral health indices, clinical manifestations, and laboratorial exams of patients with juvenile systemic lupus erythematosus (JSLE) with significant radiographic changes of the TMJ (Group A) *versus* those with mild or no changes (Group B).

Parameters	Group A (n = 2)	Group B (n = 24)	P
Demographic and socio-economic-cultural data			
Age of onset of JSLE, years	9.3 (6-12.5)	10.8 (3-16.5)	0.77
Duration of JSLE, years	3.3 (1.6-5)	2 (0.33-8.6)	0.63
Current age, years	12.6 (11.3-14)	13.5 (7.3-18)	0.74
Female	1 (50)	22 (92)	0.22
Economic class (C or D)	2 (100)	15 (63)	0.53
Oral health indices			
Index of cavities, missed teeth, and fillings	4 (2-6)	3.5 (0-11)	0.88
Plaque index	61 (23-100)	66 (16-100)	0.85
Gingival bleeding index	47.6 (41-54)	27.7 (0-74)	0.08
Helkimo's clinical mandibular dysfunction index (CMDI)			
Mild clinical dysfunction (CMDI 1-4)	2 (100)	16 (67)	1.0
Altered mobility (MMI > 1)	2 (100)	13 (54)	0.49
Clinical manifestations			
Cutaneous involvement	2 (100)	22 (92)	1.0
Mucous ulcers	1 (50)	17 (71)	0.53
Arthritis	1 (50)	23 (96)	0.15
Nephritis	0 (0)	19 (79)	0.06
Neuropsychiatric involvement	0 (0)	7 (29)	1.0
Serositis	1 (50)	8 (33)	1.0
Hematologic involvement	1 (50)	21 (88)	0.29
Laboratorial exams			
Anti-dsDNA antibodies	1 (50)	23 (96)	0.15
Anticardiolipin antibody IgM > 20 MPL	0 (0)	7 (29)	1.0
Anticardiolipin antibody IgG > 20 GPL	0 (0)	8 (33)	1.0
Lupus anticoagulant	0 (0)	4 (17)	1.0
Decreased C3 and/or C4	2 (100)	21 (88)	1.0

Results expressed as n (%) or median (variation); TMJ: temporomandibular joint.

Case 2

This is a male patient from Pernambuco. In 1998, at the age of 4 years and 4 months, the patient developed auto-immune hemolytic anemia and arthritis of the proximal interphalangeal joints, knees, and tarsus, being treated, at another service, with prednisone, 7.5 mg/d, and methotrexate, 5 mg/week. Antinuclear antibodies and anti-dsDNA were negative. In 2000, at the age of 6 years, the patient was referred to the Children's Institute with a 15-day history of fever and arthritis of the left ankle. At that time, laboratorial exams showed: hemoglobin 13.2 g/dL, hematocrit 40%, leukocytes 8,100/mm^3 (60% neutrophils, 34% lymphocytes, 2% eosinophils), platelets 265,000/mm^3, ESR 33 mm in the first hour, ANA 1/320, positive anti-dsDNA, anti-Ro, anti-RNP, and anti-Sm antibodies, C3 1 g/L, C4 0.3 g/L, and red blood cells in the urine. Juvenile systemic lupus erythematosus was diagnosed, according to ACR criteria[8]; the patient was treated with methotrexate (10 mg/week), prednisone (1.0 mg/kg/d), and hydroxichloroquine sulfate (5 mg/kg/d). Orofacial assessment was undertaken when the patient was 11 years and 3 months old (PI = 100, GBI = 54, DMF-T = 6; and Helkimo's indices: CMDI = 1, and MMI = 1). Orthopantomographic

Table 2
Disease activity, cumulative damage, disease course, and treatment of patients with juvenile systemic lupus erythematosus (JSLE) with significant radiographic changes of the TMJ (Group A) *versus* those with mild or no changes (Group B).

Parameters	Group A (n = 2)	Group B (n = 24)	P
Disease activity and cumulative damage			
SLEDAI	2	2 (0-20)	1.0
SLEDAI > 4	0 (0)	11 (46)	0.49
SLICC/ACR-DI	0.5 (0-1)	1 (0-3)	0.16
SLICC/ACR-DI > 1	0 (0)	12/21 (57)	1.0
Disease course			
Chronic active	2 (100)	11 (46)	0.48
Treatment			
Prednisone	2 (100)	24 (100)	1.0
Chloroquine	2 (100)	21 (88)	1.0
Intravenous cyclophosphamide	0 (0)	2 (8)	1.0
Azathioprine	0 (0)	4 (17)	1.0
Methotrexate	0 (0)	2 (8)	1.0

Results expressed as n (%). TMJ: temporomandibular joint; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR-DI: Systemic Lupus International Collaborating Clinics/ACR Damage In.

X-rays of the face was consistent with grade 3. CT scan of the TMJ showed bilateral involvement with flattening of the mandibular condyles, reduction of the articular space, discrete subchondral cysts, remodeling of the condyles, and marginal hypertrophic reaction compatible with bilateral osteonecrosis of the TMJ (Figure 1). Laboratorial exams were as follow: hemoglobin 12.4 g/dL, hematocrit 35.8%, leukocytes 6,000/mm^3 (46% neutrophils, 40% lymphocytes, 6% eosinophils), platelets 240,000/mm^3, ESR 23 mm in the first hour, CRP negative, ANA 1/40, positive anti-dsDNA antibodies, negative antiphospholipid antibodies, C3 0,95 g/L, and C4 0.18 g/L. The patient was treated with prednisone for seven consecutive years. At this moment, the patient was on prednisone (5 mg/d) and hydroxichloroquine sulfate (180 mg/d). He had chronic active disease with SLEDAI for 2 and SLICC/ACR-DI of 1.

DISCUSSION

This is the first study to evaluate concomitantly radiographic changes of the TMJ and oral health parameters in JSLE patients. This study identified the presence of TMJ changes, such as osteonecrosis, usually asymptomatic, with discrete mandibular dysfunction, in a small number of patients.

The incidence of pediatric rheumatic disorders is low, but they have significant physical, emotional, and social impact. Although JSLE is a chronic disease with periods of activity and remission, the prognosis and survival of those patients has been increasing progressively in the last two decades and, therefore, orofacial evaluation is important. This involvement can change the quality of life of children and adolescents with JSLE. Orofacial pain, TMJ dysfunction, and oral infections can reduce school and work performance, and disrupt social relationships.[18]

Although panoramic X-rays of the mandible is not a precise exam, it allows visualization of the facial skeleton, including the TMJ, with good definition of the mandibular condyles. The advantages of panoramic X-rays include low cost, low level of radiation, and it is easy to execute. On the other hand, computed tomography and, especially, MRI show additional details necessary to evaluate the TMJ, which help the detection of early muscular, synovial, cartilaginous, and osseous changes of this joint. They also allow better identification of osteonecrosis.[18-20] In the present study, CT scan was performed only in patients with significant radiographic changes, confirming the diagnosis of

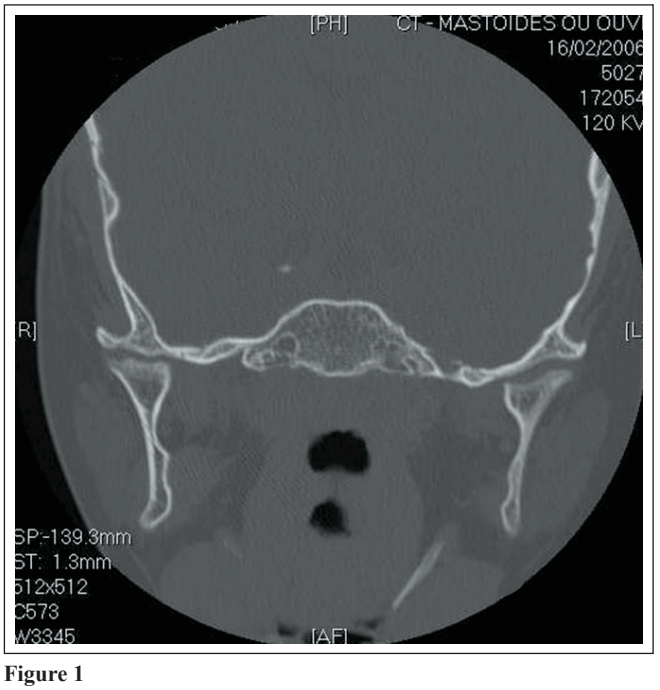

Figure 1
Multislice computed tomography shows bilateral involvement with flattening of madibular condyles, reduction of the joint space, subtle subchondral cysts, remodelation of the condyles, and bilateral marginal hypertrophic reactions, compatible with bilateral osteonecrosis of the temporomandibular joint.

osteonecrosis. Besides, patients did not have associated bacterial infections, such as osteomyelitis and septic arthritis or other mandibular comorbidities, indicating that the radiographic signs were compatible with avascular necrosis of the TMJ.

Osteonecrosis or avascular necrosis of the bone represents the death of bone cells secondary to ischemia due to interruption of the blood flow. It can be due to direct vascular damage (post-traumatic necrosis), or intraluminal or extraluminal obliteration of the bone marrow.[21] Non-traumatic causes are associated with multiple risk factors and systemic disorders, such as alcoholism, chronic use of corticosteroids and bisphosphonate, radiotherapy, hemoglobinopathies, bleeding disorders, and malignancies[22-24]. Among rheumatic diseases, SLE and JSLE, with or without associated antiphospholipid syndrome, can cause osteonecrosis.[6,7]

Avascular bone necrosis in adult patients with SLE, especially in the neck of the femur, can be related to disease activity and chronic use of corticosteroids. In a recent Brazilian study, in 2007, Fialho *et al*. observed that the activity of SLE in adult patients was the main independent risk factor for aseptic necrosis.[6]

Although statistically significant differences in disease activity, cumulative damage, and disease progression between both groups were not observed in the present study, both patients with osteonecrosis had chronically active disease and used corticosteroids for a prolonged period of time. Systematic studies on osteonecrosis in pediatric patients are not available, but we have observed a 2% incidence of coxofemoral osteonecrosis in our population of JSLE patients with anticardiolipin syndrome.[6]

Besides, osteonecrosis of the mandible frequently leads to articular collapse, bone destruction, and loss of function with varying clinical mandibular dysfunction. This manifestation can also be associated with poor oral hygiene, increasing the risk of oral infections and tooth extraction. It can also be associated with the use of bisphosphonate, such as alendronate, pamidronate, and zoledronate.[25] Those drugs were not used by the patients presented here.

Despite the small number of patients with osteonecrosis *versus* the elevated number of patients without osteonecrosis, the statistical tests used in the present study (Mann-Whitney and Fisher's exact tests) allow comparison of proportions and medians between both subgroups with different populations, which represents another relevant methodological aspect.[26]

To conclude, the present study demonstrated that osteonecrosis of the mandible with mild TMJ dysfunction can be observed in some JSLE patients, although without statistically significant differences between groups..It also shows the usefullnees of a multidisciplinary approach to evaluate this condition. Routine odontological evaluation should be part of the clinical follow-up of those patients, even those without radiographic changes.

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