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"We cannot forget that in the intricate web of human relationships there is a mass of feelings and emotions that influence our actions and our attitudes toward the world".

EDITORIAL

On the influence of a human being, or, the role of a doctor.

Every time we look back and analyze the path we have traveled, we tend to remind us of some remarkable personalities that we have met in our life. Some of them have advised us and encouraged us to follow ahead; others have offered barriers and led us astray. It seems that part of the responsibility of what we are or that we do belong to such people.

Indeed, no one is an island! We cannot forget that in the intricate web of human relationships there is a mass of feelings and emotions that influence our actions and our attitudes toward the world.

However, in a society like ours, oriented towards self-preservation, there is a great tendency to excessively emphasize the reflection of somebody's elses action over our behavior. We justify our failures and our inertia in terms of the action of others, rather than assuming full responsibility for what we are and what we do. " I did not do this because no one told me to."; " I did not know because no one taught me that."; "I thought I'd have done differently but all others advised me otherwise.", "I do so because everyone else does ..." How many times have we heard this or said this to ourselves?

I do not intend to preach individuality or isolation here. However I would like to reflect on two points that seem to be crucial in our country nowadays.

The first is about the need to understand that we are entirely responsible for ourselves. Although there are positive and negative external influences, if someone aims to be recognized as a human being, he or she should learn how to filter, analyze and accept or not these influences. The second is the need that we have to see the responsibility of our own influence on others.

Our society as a whole is deeply lacking responsible people. It seems like in the middle of the changes promoted by the modern world there is no time for personal growth. Amid so much rush, so many tasks, there is very little time for individual reflection, for critical analysis and even for time to acquire material and intellectual elements to learn how to judge correctly some situations. Swept away by "progress" and by the "I do what they expect me to do", we forget to ask: is this right? Is this really what I want to do with my life? Or, is what I'm doing contributing to a better world or to a fair society?

Of course, even when well-intentioned, we do not always have the necessary capacity or strength to achieve certain changes we think are appropriate. Society as a whole has a much larger force than the isolated subject. However, we are the society. If in the small position we occupy we are willing to act in a responsible and conscious way, maybe we can change this microenvironment.

The second point, about being responsible for the influence we exert on others, somehow refers to the first item of our discussion. If we accept the proposition of being faithful to our own principles whatever they are, the reflection we irradiate will be consistent with our philosophy of life. This is very clear when we observe the dissociation between speech and behavior that happens in our political scenario. How many words are used to claim honesty, involvement with the socially disadvantaged and so on? However popular wisdom tells us that "what we are, we do so loudly that no one listens to what we have to say..." The influence exerted is expressed not in words but in actions, in a way of life.

As physicians, we occupy a special point in the network of human relationships. We impact our patients and their families, younger colleagues and society in general. The very large contact we have with other people and the situation in which it takes place, gives us more responsibility. To reflect on our own way of life and what we do is important to contribute to build a responsible world.

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EDITORIAL

Fine-needle aspiration in the evaluation of thyroid lesions: difficulties in the interpretation of reports.

Thyroid nodules (TN) are very common lesions, and fine-needle aspiration (FNA) biopsy is considered the routine initial and the most cost-effective procedure in their evaluation. It is estimated that more than 300,000 thyroid FNA biopsies will be performed this year in the United States. FNA is a widely used technique for the diagnosis and triage of thyroid lesions. However, the accuracy of thyroid FNA interpretation is variable among different cytopathologists in academic versus community centers (1).

The diagnosis of TN by needle biopsy was first described by Martin and Ellis in 1930, and subsequently, cutting needle biopsy with Silverman or tru-cut needles were used for tissue examination however, unsuccessfully. In the 1960s Scandinavian investigators introduced the fine-needle aspiration biopsy of the thyroid, confering a widespread use of the technique in North America in the 1980s (2,3). There was a great concern in improving the cytological diagnosis of nodular thyroid lesions by introducing criteria for its diagnosis, in view that historically, terminology for thyroid FNA has varied from one laboratory to another, creating confusion and hindering the sharing of data among multiple institutions.

Despite the efforts of several groups to standardize thyroid cytopathology reporting, the management of TN remained without a standard universal thyroid cytophatologic reporting system for years. Currently, the Bethesda System has been considered the best thyroid cytopathology reporting system and has facilitated the clinical management of thyroid nodular diseases.

In order to adopt a terminology and to facilitate the communication among cytopathologists, endocrinologists, surgeons, radiologists and also to allow easy and reliable data sharing from different laboratories, the National Cancer Institute of the United States (NCI) hosted the "The NCI Thyroid Fine Needle Aspiration State of the Science Conference" in Bethesda, Maryland, which resulted in Bethesda Thyroid Atlas Project and formed the framework for The Bethesda System for Reporting Thyroid Cytology (4). Therefore, the Bethesda System for Reporting Thyroid Cytology improved and refined specific diagnostic cytologic criteria definitions to improve clinical and surgical management of thyroid nodules.

The introduction of Bethesda System has had a significant positive impact on thyroid FNA reporting, strengthening among different specialists mutual understanding in FNA role in the management of thyroid lesions.

In this edition of the *Revista de Endocrinologia & Diabetes Clínica e Experimental* a review article entitled "*Fine-needle aspiration biopsy in thyroid gland: cytological aspects of thyroid nodular lesions*" is presented describing the methodology for conducting FNA and the cytological aspects of nodular thyroid lesions.

We are honored to take part of this edition and to write this editorial. We would like to thank the editor-in-chief, Mirnaluci Paulino Ribeiro Gama, for her invaluable consideration with the authors. We hope this edition can represent an opportunity to update and to provide new information for our colleagues.

Luís Jesuíno de Oliveira Andrade e Mércia Margotto

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Cover: **"Basunga (3 weeks-old newborn with albinism) is happily sleeping with his cousin" Kinshasa, Congo Photo and caption by Patricia Willocq National Geographic**

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REVIEW
FINE-NEEDLE ASPIRATION BIOPSY IN THYROID: CYTOLOGICAL ASPECTS OF THYROID NODULAR LESIONS

PUNÇÃO ASPIRATIVA COM AGULHA FINA EM TIREÓIDE: ASPECTOS CITOLÓGICOS DAS LESÕES NODULARES TIREOIDIANAS

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Keywords: Cytodiagnosis, Thyroid, Aspiration biopsy, Nodule
Descritores: Citodiagnóstico, Tireóide, Biópsia aspirativa, Nódulo.

Abstract

Introduction: Thyroid nodule (TN) is an increasingly common problem in clinical practice and its prevalence is high in worldwide population. The prevalence of palpable TN ranges from 3 to 7%, being 10 times greater with the use of high-resolution ultrassonography (US). **Objective:** To describe the methodology for conducting fine-needle aspiration citology (FNAC) and cytological aspects of thyroid nodular lesions. **Method:** Literature review of the technical description of thyroid nodule FNAC and cytological diagnosis of thyroid nodular lesions. **Results:** The FNAC, especially when it is driven by US, has become a key diagnostic procedure for thyroid malignant nodules. However, the cytological diagnosis depends on appropriate and significant sample of cells, as well as the expertise of the cytopathologist. **Conclusion:** The use of FNAC significantly reduced the unnecessary thyroid surgery, and with modern techniques of molecular biology reliability in the method has increased. **Endocrinol diabetes clin exp 2015 1769 -1774.**

Resumo

Introdução: Nódulo de tireóide (NT) é um problema cada vez mais comum na prática clínica, sendo sua prevalência muito elevada na população mundial. A prevalência de NT à palpação cervical varia de 3 a 7% aumentando em 10 vezes com o uso da ultrassonografia de alta resolução (US). **Objetivo:** Neste artigo são descritos a metodologia para a realização da citologia por punção aspirativa com agulha fina (CPAAF) e os aspectos citológicos das lesões nodulares da tireóide. **Método:** Revisão da literatura, para descrição da técnica e diagnóstico citológico das lesões nodulares da tireóide. **Resultados:** A CPAAF, principalmente quando orientada por US, tornou-se um procedimento diagnóstico fundamental na identificação das lesões malignas e orientação na conduta a ser tomada. O diagnóstico citológico depende, entretanto, de uma amostra adequada e significativa de células, bem como da experiência do citopatologista. **Conclusão:** O uso da CPAAF reduziu significativamente as tireoidectomias desnecessárias, e com as modernas técnicas de biologia molecular têm-se aumentado a confiabilidade no método. **Endocrinol diabetes clin exp 2015 1769 -1774.**

INTRODUCTION

Thyroid nodules (TN) are a common problem increasingly in clinical practice, and it is highly prevalent in worldwide population. It has a prevalence of 3-7% on physical examination (1). It is believed that in goiter endemic areas, the prevalence can reach 10% of the population. With uneventful use of ultrasound (US) in the assessment of thyroid, considering that this method has a greater sensitivity in TN detection when compared to physical examination, the prevalence varies from 20 to 70% of population, especially in women with advanced age (2).

It is estimated that in the United States of America 300,000 new cases of TN are diagnosed each year, with a frequency of 0.1% per year (3). Thus, currently, due to its high prevalence, TN is a public health problem with controversial aspects on its clinical management (4).

Therefore, when dealing with a thyroid nodule, the most important is to differentiate whether this is benign or a malignant nodule. Thyroid lesions are usually investigated when greater than 1.0 cm whereas those lesser than 1.0 cm are oftenly submitted to FNAC when there are suspicious ultrasonographic features. Apart from the ultrassonographic features of thyroid nodules there are some clinical aspects that should call attention to proceed with clinical investigation of a certain thyroid nodule, ex., family history of thyroid cancer or multiple endocrine neoplasia, a rapidly growing nodule, fixation to adjacent structures, hardened nodules, vocal cord paralysis as well as regional lymphadenomegaly.

Ultrassonography is generally not indicated as a screening population exam due to its limitation in differentiating malignant thyroid nodules from benign lesions that would promptly require submitting patients to FNAC of thyroid lesions that are mostly benign and without clinical significance. Moreover, the risk of malignancy is similar in palpable nodules or in nodules incidentally detected by an imaging method. The risk of malignancy in an asymptomatic TN is 1-12 cases per 100.000 inhabitants (3).

The initial evaluation of a TN comprises measuring serum thyroid stimulating hormone (TSH), free thyroxine and anti-thyroid antibodies besides US and FNAC which is the method for assessing the need for surgical intervention.

The main indication of FNAC is to detect malignancy in a TN, because of its excellent accuracy. FNAC reduced to 85% the number of diagnostic surgeries (5). The use of US to guide FNAC and its correct technique practically exempt the method of complications (6).

This review presents the methodology aspects of thyroid FNAC and the cytological aspects of thyroid nodular lesions.

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2. METHODOLOGY OF SAMPLE COLLECTION AND BLADE PREPARATION

The obtainment of an adequate sample is one of most important factors for cytological exact evaluation. The puncture and the reading of a blade should be made preferably by a cytopathologist. An adequate sample when directed by US is simple and improves the quality of cleaned material and also allows the morphological evaluation of injury and its correlation with cytological aspect (7,8).

The TN must be identified by palpation or driven by US, and the cell sample should be obtained in at least three different areas with aspiration using a syringe of 10ml connected to a 25GI or 27GI needle. TN is immobilized with the index and middle fingers and the needle is inserted and moved back and forth successively, with fast and smooth movements (9). In most cases, the local anesthesia is not necessary however, some patients require topical anesthesia due to low threshold for pain. If the TN is vascularized, visualized by color Doppler ultrasound, the aspiration should be performed in about five seconds or just punctured without aspiration (6).

The criteria for a sample to be considered adequate for cytological diagnosis are variables according to each cytologist, that consider the suitability of the sample according to the number of visualized follicular cells (10). The Papanicolaou Society of Cytopathology Task Force on Standard of Practice does not indicate the appropriate number of cells to consider a sample as suitable (11). The rate of inadequate or insufficient samples described in the literature ranges from 2 to 21% with an average of 17% (12).

One of the limitations of cytologic diagnosis of TN by FNAC is the presence of malignant process with non-neoplastic process or multiple malignancies in the same gland, overlapping cytologic features between various neoplasms and overlapping neoplastic cytologic patterns with non-neoplastic cytologic patterns (13). However, the main limitation of FNAC is to be incapable to differentiate follicular neoplasms of the thyroid. FNAC alone can not distinguish between adenoma and follicular carcinoma, or between adenoma and carcinoma of oxyphilic cells (Hürthle cells). About 20% of follicular neoplasms are malignant (14).

The technical preparation of the slides require an appropriately smear of the aspirated material, dried to air or fixed with alcohol for microscopic reading. The blades can also be prepared by the cell block technique, in which the cellular architecture is preserved facilitating cytological diagnosis. Papanicolaou technique can be used for blades fixation, in which the fixing is done with ethyl alcohol or sprayed with fixative and placed in Carnoy solution by 3 to 5 minutes before coloration with the intent of removing the red blood cells of the sample. Papanicolaou technique best visualize nuclear details (11). Another method of coloring is Romanowsky technique in which the slide is air-dried and colored immediately because the delay in sample fixing combined with air results in artifacts presence with loss of cellular detail. Romanowsky technique best visualize cytoplasmic details (6). The concurrent use of both methods is recommended due to their complementarity (15).

3. CYTOLOGICAL CLASSIFICATION OF THYROID NODULAR LESIONS

In 2007 the National Cancer Institute of the United States discussed a review about the thyroid FNAC, establishing categorical cytological results to avoid interpretive confusion, resulting in Bethesda System for Reporting Thyroid Cytopathology publication, which classifies the samples into 6 categories : I- Nondiagnostic or Unsatisfactory, II- Benign, III- Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance, IV- Follicular Neoplasm or Suspicious for a Follicular Neoplasm, V- Suspicious for Malignancy and VI- Malignant (16,17).

3.1. Category I - Nondiagnostic or Unsatisfactory

In this category are included samples that present material difficult to evaluate, due to artifacts presence, blood or insufficient follicular cells or due to poor technical preparation (Figure 1) (18). The frequency of nondiagnostic or unsatisfactory samples varies from 2 to 20%, ideally should be no more than 10%, excluding samples only composed by macrophages (19). The repetition of FNAC guided by ultrasound is recommended for this category.

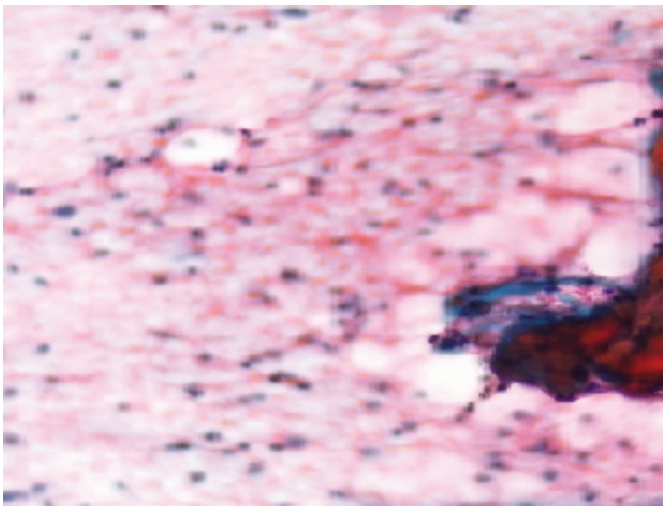

Figure 1. Nondiagnostic - paucicellular sample aspirates (*Courtesy of Dr. Victor Luiz Correia Nunes*)

3.2. Category II - Benign

Sixty to 70% of thyroid FNAC are Bethesda II. In this category the sample has varying proportions of colloid and follicular cells typically arranged in microfollicular and macrofollicular fragments (Figure 2). The majority of benign nodules are multinodular goiters or follicular adenomas.

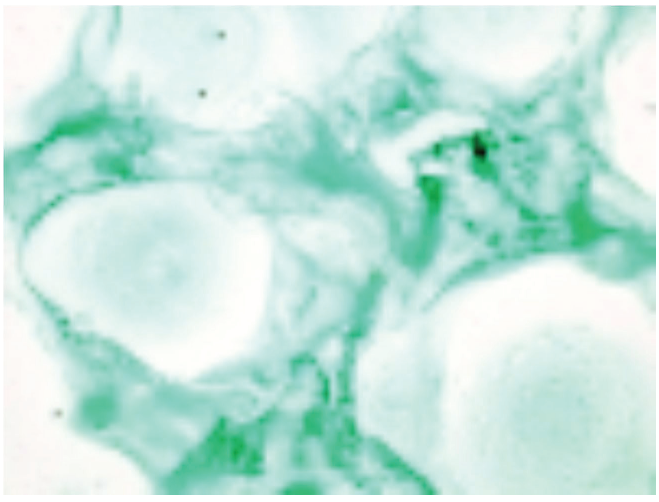

Figure 2. Follicular cells and colloid (*Courtesy of Dr. Victor Luiz Correia Nunes*)

The frequency of false-negative ranges from 0% to 3% (20), and the clinical and ultrasonographic revaluation should be performed on average after one year (21). Thyroiditis is include in category II (Figure 3), as Graves' disease (Figure 4), cysts, textural changes secondary to thyroid irradiation and reactive changes.

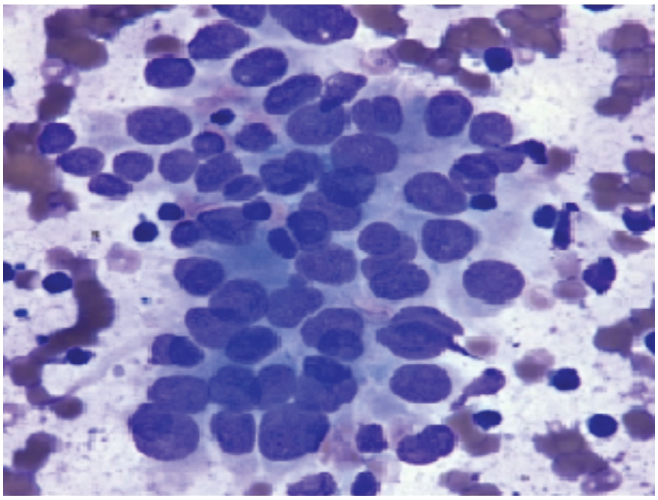

Figure 3. Lymphocytic (Hashimoto's) thyroiditis
(*Courtesy of Dr. Victor Luiz Correia Nunes*)

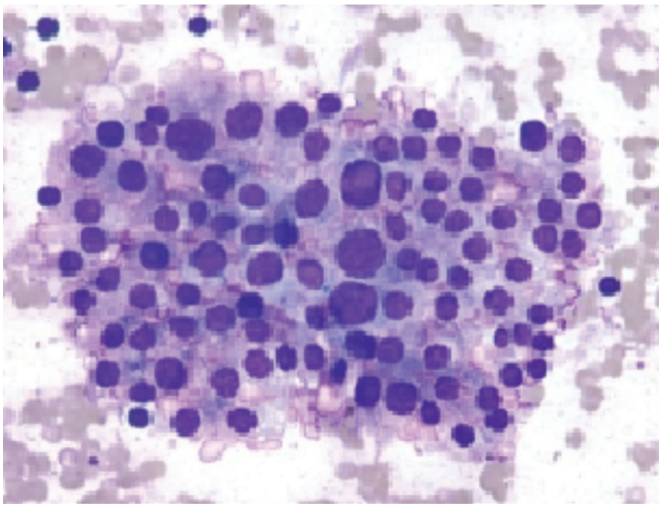

Figure 4. Graves' disease
(*Courtesy of Dr. Victor Luiz Correia Nunes*)

3.3. Category III - Atypia of Undetermined Significance / Follicular Lesion of Undetermined Significance

Some FNAC are difficult to classify by Bethesda System, due to intrinsic cytopathology limitation being classified as Bethesda III. However, this category represents a minority of FNAC. The cytological sample comprises follicular cells, lymphoid or other cells with atypia or cell array that do not meet the criteria to classify it in other categories (Figure 5). The most common scenarios in this category are described in the following situations: presence of microfollicles that do not meet the criteria of suspected follicular neoplasm; Hürtle cells predominance in an aspirated material with low cellularity and little colloid; cytological atypia impaired by pre-analytical artifacts; sample composed almost exclusively by Hürtle cells, but clinically suggestive of Hashimoto's thyroiditis and multinodular goiter; predominance of follicular cells of benign aspect, but containing focal areas suggestive of papillary carcinoma; predominance of follicular cells with benign aspect but containing coating cystic that resemble atypical cells due to the presence of cracks, enlarged nuclei and nucleoli; few atypical follicular cells found in patients who were treated with radioactive iodine or other drugs and found in patients associated with reparative changes due to cystic degeneration and hemorrhage; and finally, atypical lymphoid infiltrate in which the atypia degree is insufficient to categorize it as suspicious for malignancy.

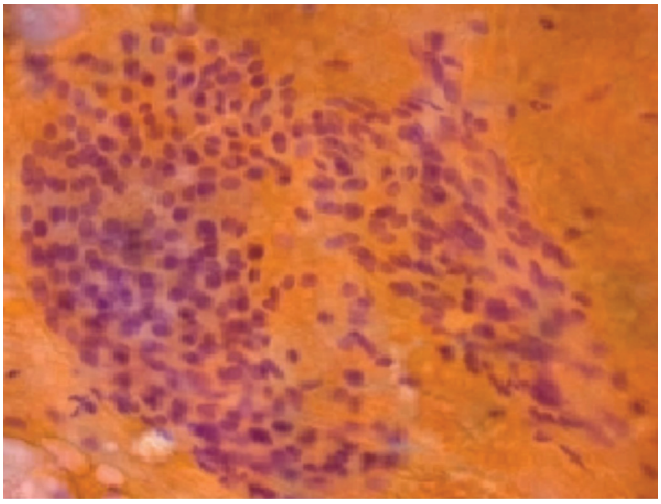

Figure 5. Follicular Lesion of Undetermined Significance
(*Courtesy of Dr. Victor Luiz Correia Nunes*)

It is noteworthy that only samples with atypia of undetermined significance should be placed in this category. 5% The risk of malignancy ranges from to 15%, and its use can be reduced by an experienced thyroid cytologist (22).

3.4. Category IV - Follicular Neoplasm / Suspicious for a Follicular Neoplasm

The purpose of this category is the identification of a suspicious nodule of follicular carcinoma and its screening for surgery. Current cytological resources are not sufficient to differentiate between follicular adenoma and follicular carcinoma, and can be cytologically reported as follicular neoplasm or suspicious for a follicular neoplasm, in which definitive diagnosis is just made with histological analysis of the specimen (21).

The cytological sample usually has high cellularity with scarcity or absence of colloid. It also presents changes in cytoarchitecture where follicular cells are arranged predominantly in microfollicular arrangements and syncytial plaques (Figure 6) (23). About 16% to 25% of the cases in this category are hyperplastic proliferations of Hürthle cell in nodular goiter or in a lymphocytic thyroiditis, while 15% to 45% of tumors are malignant (24).

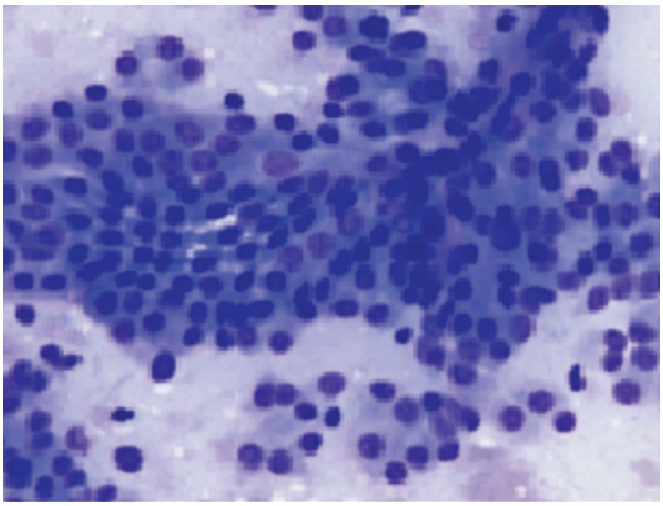

Figure 6. Follicular neoplasm/Suspicious for a follicular neoplasm
(*Courtesy of Dr. Victor Luiz Correia Nunes*)

3.5. Category V - Suspicious for Malignancy

This category is considered when the sample contains malignant characteristics, but without sufficient findings to a conclusive diagnosis (Figure 7). Such cases occur with some regularity, and they are best classified as suspicious for malignancy. The most (60% to 75%) are papillary carcinoma and

remainder follicular adenoma (25). Other malignant lesions are also included in this category such as medullary thyroid carcinoma and lymphoma; these diagnoses need immunohistochemistry and flow cytometry analysis to have a conclusive diagnosis.

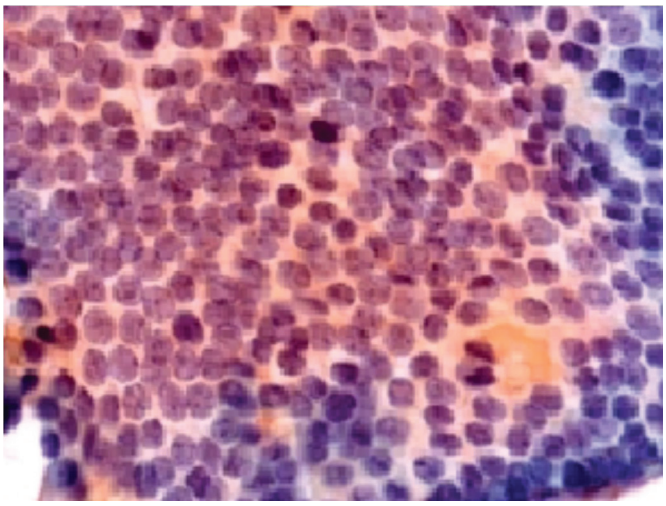

Figure 7. Suspicious for malignancy
(*Courtesy of Dr. Victor Luiz Correia Nunes*)

3.6. Category VI - Malignant

This category is used when the cytomorphological characteristics are conclusive for malignancy. Three to 7% of FANC are Bethesda VI and papillary carcinoma is the most prevalent diagnosis, with a positive predictive value in FANC of 97% to 99% (Figure 8) (19).

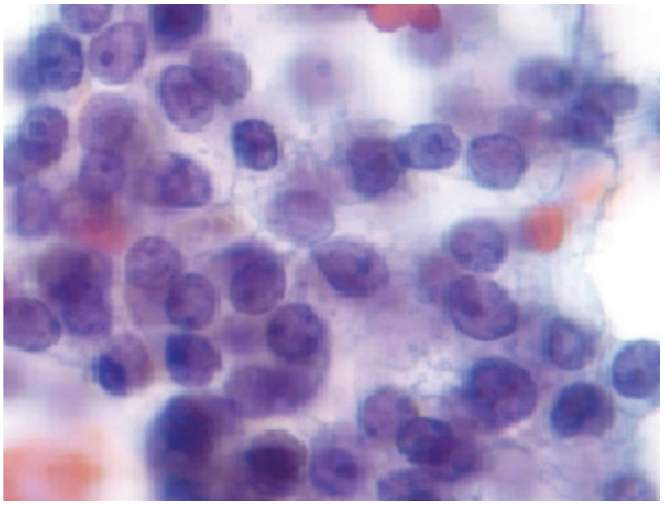

Figure 8. Papillary thyroid carcinoma
(*Courtesy of Dr. Victor Luiz Correia Nunes*)

4. CYTOLOGICAL CHARACTERISTICS OF THYROID GLAND NODULAR LESIONS

In accordance with the cytologic features encountered, the nodular lesions of the thyroid gland are classified into groups, that are heterogeneous, and can be similar or with specific characteristics (9).

4.1. Colloid Nodule Benign (Bethesda I)

It is cytologically characterized by thick and shiny abundant colloid materials or bullous standard and a layer of benign follicular epithelial cells in a "honeycomb" arrangement. Slightly hyperplastic Hürthle cells can be observed (11,26).

4.2. Microfollicular nodule (Bethesda IV)

They are characterized by a set of abundant follicular cells, acinus and small monolayers. Individual cells are scarce with ill-defined cytoplasm and oval nucleus with regular nuclear contour and invisible or protruding nucleolus. In this group are included the microfollicular hyperplastic nodules in a microfollicular nodular goiter or Hashimoto's thyroiditis, the microfollicular adenoma and well-differentiated follicular carcinoma. It has been published that 14% of microfollicular lesions are malignant. This type of lesion can be included in indeterminate or suspicious lesions category, which usually leads to surgery recommendation (11,15,27).

4.3. Nodule of Hürthle cells (Bethesda III)

It is represented by a set of polygonal epithelial cells with abundant granular eosinophilic or basophilic cytoplasm, regular oval contour nuclei and a nucleoli that can be visible or not (15,26). The presence in cytologic examination of an aggregate of syncytial cells of Hürthle cells with or without abundant prominent nucleoli without tumor cells was described as a cytological feature of Hürthle cell carcinoma (26,28). The prevalence of malignancy in Hürthle cells lesions is 13% (27).

4.4. Malignant lesions (Bethesda V and Bethesda VI)

The cytological aspects of thyroid malignant lesions are characteristic, thus allowing the identification of this lesion in the majority of cases (6,26).

Papillary carcinoma is characterized in FNAC by presence of thin or thick papillary tissue fragments with fibrovascular core, tumor cells aggregation with focal overlapping, regular nuclear contours, intranuclear cytoplasmic inclusions and grooved cores. In this lesion psamomatosos bodies and metaplastic squamous cells are also found (6,15,16). The diagnosis is made preferably with the Papanicolaou technique, due to its nuclear changes that can be easily recognized (6,10).

Microfollicular variant of papillary carcinoma is characterized in FNAC by the presence of follicular cells in acinar configuration and can be easily confused with macrofollicular adenoma or a benign colloid nodule due to nuclear changes that can be similar to both benign and malignant lesions (29).

The hyaline trabecular adenoma is an indistinguishable injury of papillary carcinoma in the cytological point of view, since it has the same nuclear features (30). Immunohistochemistry suggests that this type of lesion would be encapsulated trabecular variant of papillary carcinoma (31).

Other subtypes of papillary carcinoma include papillary carcinoma of tall-cells characterized by presence of tall-cells tumor with granular cytoplasm and a well defined and grooved core with one or more cytoplasmatic inclusions present in at least 30% of the analyzed sample (32). The columnar cells variant, shows no classical cytological feature of papillary carcinoma however, the presence of columnar-cells grouped with palisaded core and absence of classic changes of papillary carcinoma are the cytologic features of this variant (33). Finally, the diffuse sclerosing variant of papillary carcinoma is characterized by cytological squamous cells adhered to lymphocytes, follicular epithelial cells with nuclear features of papillary carcinoma and psamomatousos bodies (32).

The high-grade follicular carcinoma and the insular carcinoma are characterized by a set of pleomorphic acinar cells with prominent nucleoli (35).

The medullary thyroid carcinoma is characterized in FNAC as a mixture of single cells with polygonal cells agglomeration and an elongated tumor that can exhibit cytoplasmic inclusions (15,26).

The anaplastic thyroid carcinoma has two histological subtypes. The giant cell subtype is characterized in FNAC by presence of bizarre cells, prominent pleomorphic nucleoli, while the fusiform cell subtype present neoplastic cells adhered to a variable amount of necrotic debris (36).

The non-Hodgkin´s thyroid lymphoma is characterized in FNAC by the presence of cells similar to a lymphonode invol-

ved by a neoplastic process and it is usually of large cell type. Hodgkin's thyroid lymphoma is characterized by the presence of Reed-Sternberg cells, adhered lymphoid cells and eosinophils (6,26,34).

4.5. Thyroid cystic lesions (Bethesda II)

The thyroid cyst occurs due to hemorrhagic degeneration of a benign colloid nodule. It is characterized in FNAC by colloid material adhered to benign follicular epithelial cells and macrophages impregnated with hemosiderin.

The thyroid neoplasms can present with cystic degeneration (6,26). Papillary carcinoma is the cancer that tends to have hemorrhagic degeneration, with many blood cells and rarely tumor cells at FNAC (37).

4.6. Thyroiditis (Bethesda II)

Hashimoto's thyroiditis is characterized in FNAC by presence of benign lymphoid cells adhered to benign follicular cells and Hürthle cells (36), which are similar to follicular neoplasia or Hürthle cell neoplasia (28).

Subacute thyroiditis is characterized in FNAC by the presence of agglomerates of ephitelioid cells, scattered lymphocytes and some giant cells (37).

4.7. Other thyroid lesions (Bethesda II, Bethesda VI)

Graves' disease rarely presents as a nodular lesion of thyroid and does not have specific features at cytology (38).

A nodular metastatic lesion to the thyroid gland is not frequent. The most common metastatic neoplasia to thyroid gland is from renal cell carcinoma. Clinically occult renal cancer can initially presents as a thyroid tumor. The metastatic cancer presents different characteristics from a primary carcinoma of the thyroid gland at FNAC (26)

4.8. Nondiagnostic lesions and sequential biopsies (Bethesda I)

It is included in this category undiagnosed cellular material or inappropriate material at FNAC. The lesions can be diverse or can have the same pathological changes already previously described.

Some authors have shown that thyroid cystic lesions can be classified as Bethesda I at FNAC in approximately 50% of cases (35). Another study showed that the diagnosis was obtained in 30 to 80% of cases after sequential puncture, when initial diagnosis was not obtained (27).

Some authors have shown the limited value of sequential biopsies (38). Brito and coworkers showed that sequential biopsies in a benign TN did not present significant changes in the initial cytological diagnoses (35).

5. CONCLUSION

The FNAC currently is constituted in the best available method to differentiate benign from malignant thyroid lesions with 95% of accuracy, thus, should be the first method to evaluate the real need for surgical removal of a certain TN.

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ORIGINAL CONTRIBUTION
BEYOND HEPATITIS C VIRUS INFECTION: INSULIN RESISTANCE AND TYPE 2 DIABETES

ALÉM DA INFECÇÃO PELO VIRUS DA HEPATITE C: INSULINO RESISTÊNCIA E DIABETES TIPO2

MARCELA FERRO CAMPIOLO*

Key words: Hepatitis C virus; Type 2 diabetes; Insulin resistance; Hepatic fibrosis
Descritores: Hepatite C; Diabetes Tipo; Insulino resistência; Fibrose hepática

Abstract

This review focuses on the relationship between hepatitis C virus infection and glucose metabolism derangements. Type 2 Diabetes Mellitus has been implicated as a potential extra-hepatic manifestation of hepatitis C virus infection, due to either direct viral involvement or secondary to HCV-induced liver damage. It also impacts on the disease activity, disease course, clinical outcomes and on the antiviral treatment efficacy. **Endocrinol diabetes clin exp 2015 1775 -1777.**

INTRODUCTION

Hepatitis C virus (HCV) is an RNA virus belonging to the flaviviridae family that is transmitted parenterally (1). According to recent estimates, more than 185 million people around the world have been infected with HCV, of whom 350 000 die each year. HCV causes both acute and chronic infection. Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and hepatocellular carcinoma (2).

HCV infection has also been convincingly linked to several extra-hepatic manifestations including essential mixed cryoglobulinemia, glomeronephritis, and porphyria cutanea tarda. Type 2 diabetes (T2DM) was suggested to be another potential extra-hepatic manifestation of HCV infection, with excess risk postulated to be due to either direct viral involvement or secondary to HCV-induced liver damage (3).

Some experimental and clinical studies have shown the implication of HCV infection in the development of insulin resistance (IR) by determining a normal cutoff of the homeostasis model of assessment insulin resistance index (HOMA-IR), below 2 (1,3). Patients with chronic C hepatitis have higher HOMA-IR compared to healthy controls and on the follow up, IR was associated with fibrosis progression and also steatosis development.(4,5,6,7,8,9,10,11)

IR and T2DM have been recognized to modify the course of hepatitis C, mainly when associated to genotype type1, visceral obesity and high body mass index (IMC) by favoring the HCV multiplication. Whether IR is a good predictor of the ultimate response to HCV treatment (Interferon alpha or Ribavirin) is unclear (11). Although susceptible individuals may develop IR independently of HCV, considerable amounts of clinical and experimental data suggest that HCV is directly involved in its pathogenesis (4,11).

HCV infection and T2DM are two major rising epidemics, which represent a challenge both to clinicians and to healthcare systems in terms of diagnostic, therapeutic and economic implications (5). Thus, this review will discuss the association between HCV and T2DM, its clinical impact, and some directions for management.

HCV AND TYPE 2 DIABETES ASSOCIATION

T2DM is a common multisystem disorder, sometimes referred as a syndrome, in which hyperglycemia seems to play an important role in the outcomes and chronic complications. Many pathogenic mechanisms are implicated. A resistance to the insulin action, with increased hepatic glucose production and defect in insulin secretion, contribute to the development of overt hyperglycemia (5,6,7).

As well as skeletal muscle and adipose tissue, liver is the major target for the metabolic actions of insulin. Insulin regulates glucose homeostasis by reducing hepatic glucose output and by increasing the rate of glucose uptake by skeletal muscle and adipose tissue. Therefore IR is a common feature of liver diseases from various insults (7) independently of the etiology. However, clinical and experimental data suggest a direct role of HCV on glucose metabolism impairment (4). Interestingly, anti-HCV serum-positivity in the T2DM population ranges from 1.8% to 12.1%, whereas T2DM prevalence is 14.5 to 33.0% among HCV patients (7).

The association between T2DM and chronic hepatitis C was first reported in 1994 by Allison et al., who observed that the prevalence of T2DM was significantly higher in those with HCV related cirrhosis than those in which cirrhosis was the result of other liver diseases (8).

In a meta-analysis, White and collaborators also showed that HCV infection is associated with an increased risk of T2DM in comparison to both uninfected and Hepatitis B infected controls (9).

DOES HCV INFECTION ITSELF HAVE A DIABETOGENIC ROLE?

PATHOPHYSIOLOGICAL VIEW

HCV has a RNA genome that encodes approximately 3010 amino acids and is translated into structural (core, E1, and E2) and nonstructural (NS3-NS5B) proteins. The HCV core-induced suppressor of cytokine signaling 3 (SOCS3) increases phosphorylation of insulin receptor substrate-1 (IRS-1), which is the basis for IR. Phosphorylated IRS-1 activates phosphatidylinositol 3-kinase (PI3K), and the activation of PI3K and one of its downstream targets, AKT (or protein kinase B), are essential for most of the metabolic effects of insulin. Therefore, defects at the level of the association of PI3K with IRS-1 and a lack of PI3K activation may contribute to IR and to the increased prevalence of diabetes in HCV-infected patients. Indeed, this mechanism ultimately promotes glucose transporter-4 translocation to the plasma membrane to enhance glucose uptake (5).

The central target of HCV appears to be the AKT path, yielding impaired phosphorylation upon insulin stimulation (10).

Beyond the direct effects of HCV on IRS-1/PI3K, the HCV core protein may induce IR indirectly via stimulation of the secretion of pro-inflammatory cytokines. Post-mortem studies have

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showed that HCV replicates in the pancreas and studies with animal models have revealed a direct effect of HCV on IR in the liver (5). HCV may induce a Th1 lymphocyte immune-mediated response, which leads to the activation of tumor necrosis factor (TNF)-alpha system and elevation of interleukin-6 levels. A high TNF-alpha level was considered to be one of the bases of IR, which act by disturbing tyrosine phosphorylation of IRS-1, a central molecule of the insulin-signaling cascade. Meanwhile, HCV directly causes liver steatosis. All the above events may precipitate the development of liver fibrosis (7).

The main characteristic of T2DM is IR, which plays a significant role in fibrosis progression and has a negative impact on treatment responses to antiviral therapy viral response, disease severity in patients with HCV (8,9). Meanwhile, HCV--induced inflammatory changes may subsequently lead to increased oxidative stress and peroxidation, which evoke systemic inflammatory responses (SIR) more often than other liver diseases. SIR triggered by HCV and/or its subsequent immune cascades and cytokine storms may play a major role in the related pathogenic mechanisms in terms of liver injury and the unique extra-hepatic manifestations (Fig. 1). Cytokines (TNF alpha and IL6) triggering which interacts with innate and/or adaptive immune responses, are among the major concealed players of the scenario (7).

The detailed molecular events leading to IR in HCV infected patients are, however, unclear (5).

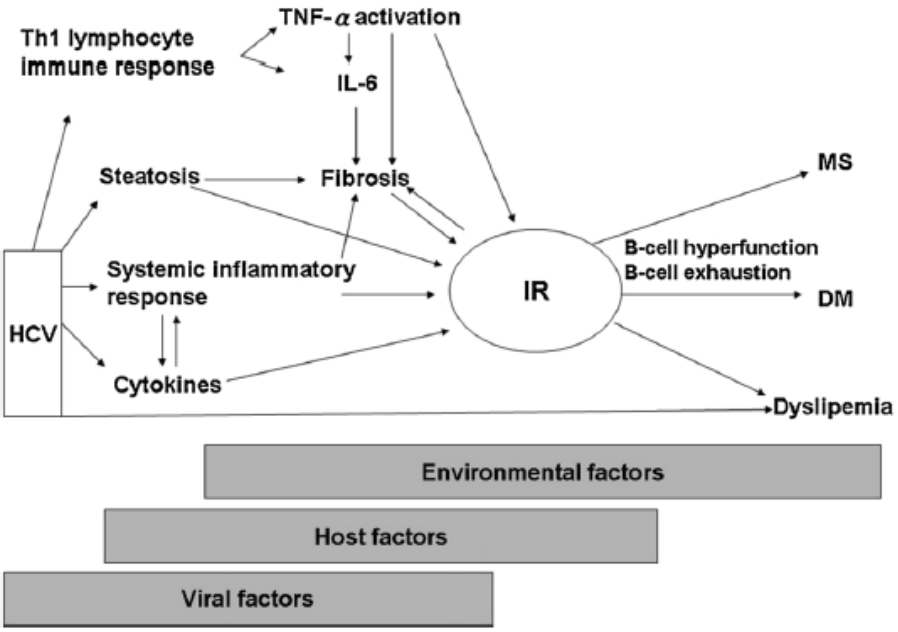

Figure 1. Possible pathogenic mechanisms leading to the development of insulin resistance and subsequent metabolic disorders. DM diabetes mellitus; HCV hepatitis C virus; IL-6 interleukin-6; IR insulin resistance; MS metabolic syndrome; TNF-a tumor necrosis factor-a.
Adapted from Huang JF, Yu ML, Dai CY, Chuang WL. Glucose abnormalities in hepatitis C virus infection. Kaohsiung J Med Sci 2013; 29:61-68.

CLINICAL CONSEQUENCES OF IR/T2D IN CHRONIC HEPATITIS C

Steatosis is a common finding in HCV chronic infection maybe related to some specific virus genotypes. A mechanism favoring hepatocyte HCV entrance with its subsequent replication provides the ideal substrate for a "first hit" HCV-related oxidative stress and cytokine release. The so called "second hit" mechanism induces necroinflammation apoptosis and fibrosis (10,11,12).

Hyperglycemia and hyperinsulinemia, when settled, stimulate the release of fibrogenic growth factors , the connective tissue growth factor from hepatic stellate cells boosting Leptin, an adipose tissue hormone with fibrogenic action. (12)

Hepatic fibrosis is a more frequent HCV-related steatosis complication compared to the Nonalcoholic fatty liver disease, suggesting that second hits" events, like the innate antiviral inflammatory response, are involved in HCV-related disease.(13).

Since the kidney is one of the highest energy expenditure tissue, it is of noteworthy to list HCV -related chronic nephropathy complications, sharing the same mechanisms (5).The presence of proteinuria, microscopic hematuria, cryoglobulinemic systemic vasculitis, acute renal failure and even nephrotic syndrome are connected to the renal deposition of circulating immune complexes. The most common renal pathology associated with hepatitis C virus infection is type I membranoproliferative glomerulonephritis with or without cryoglobulinemia (11). Combination therapy with interferon alfa (IFN-α) and ribavirin are not effective in significant renal impairment (14).

Hepatocellular carcinoma is known to be related to HCV infection and alcoholism. An attractive pathophysiology mechanism places the insulin insensitivity and its compensatory hyperinsulinemia enhancing insulin-like growth factor 1 (IGF-1) secretion, favoring cell proliferation and inhibiting apoptosis. (5) Hyperinsulinemia may also triger the development of cancer by down-regulating IGF-binding protein 1 levels, which increases the level and bioavailability of total circulating IGF-1.

RI and steatosis are associated with reduced rates of initial virological response as well as sustained virological response in chronic hepatitis C patients treated with a combination of pegylated IFN-α and ribavirin. This negative association has been reported not only in patients infected with the HCV genotype 1, but also in those with the so-called "easy-to-treat" genotypes 2 and 3 (4).

THE EFFECT OF HEPATITIS C VIRUS INFECTION ON INSULIN RESISTANCE VARIES AMONG GENOTYPES

The effect of HCV infection on IR depends on viral genotype. Genotype 3 (HCV3) subjects have lower IR compared with other genotypes. Obesity is a main feature in HCV1 patients for the development of steatosis and not so important in HCV 2a/c, but plays no role in patients infected with genotype 3a (10). This would confer a lower risk for developing T2DM compared with other HCV genotypes. It is of interest that, despite lower IR levels, HCV 3a patients are more prone to develop extensive hepatic steatosis damage. It is suspected that steatosis in HCV3 is mediated predominately by viral factors with little or no influence by the IR status(1).

HCV 1 steatosis, though, is directly influenced by the me-

tabolic syndrome factors, the activation of pro-inflammatory mechanisms as well as the underlying obesity and IR. The degree of steatosis in this genotype is independent of the HCV1 viral load, and antiviral therapy does not improve steatosis in these patients (10). Similar data have been obtained for HCV4, whereas few data are available for HCV2(5).

PERSPECTIVES FOR CLINICAL MANAGEMENT

The potential relationship between HCV infection and the development of DM increases the need for the implementation of prevention measures. Prevention must be directed toward lifestyle changes that can reduce the risk of HCV infection and/or diabetes development. Regular diabetes screening for anti-HCV-positive people and the analysis of other risk factors that can accelerate the progression of both chronic hepatitis C and T2DM, such as obesity, dyslipidaemia, and alcohol consumption. In these high-risk patients, comprehensive treatment, including lifestyle modifications, abolition of alcohol consumption and metformin or peroxisome proliferator activated receptor alpha-agonists treatment are recommended (5).

Anti-diabetic drugs may reduce some liver-related outcomes. This beneficial effect has been reported for metformin, which has been shown to reduce significantly the risk of developing HCV (15). An optimal control of glycaemia is pivotal in reducing this risk, since the incidence of HCV was significantly higher in patients with HA1C >7% than in those with levels <7% (10). The treatment of IR and T2DM in chronic hepatitis C patients has two goals, as far as the underlying liver disease is concerned: to reduce fibrogenesis (hence liver disease progression) and to increase the response to IFN-based therapy (4).

There are some possible mechanisms to explain the diabetogenic effects of treatment with alpha-IFN on pancreatic dysfunction in HCV infection:

• Viral RNA could induce apoptosis in beta cells and it should be directly cytotoxic to pancreatic beta cells;

• Alpha-IFN should activate apoptosis

• INF should increase diabetogenic hormones secretion (growth hormone, glucagon) resulting in glucose intolerance or hyperglycemia (16,17)

Meanwhile some studies have showed improvement in glucose tolerance during antiviral therapy confirming the association of HCV infection and diabetes (18)

Vitamin E (tocopherol) has shown liver biochemistry improvement in children with NASH and on histology analysis in adults patients. Betaine, an antioxidant agent, in one study , lowered serum aminotransferase levels and improved histology markers in adults with NASH (13)

A special care is needed when treating patients diagnosed also with hemocromatosis. Ascorbic acid (vitamin C) treatment stimulates hydroxyl radical production in the presence of free iron, making this option unlikely to yield better outcomes, since pro-oxidants , instead of anti-oxidants will be delivered to the liver tissue. (19).

Some reports showed that HCV eradication improves insulin sensitivity and reduces the incidence of T2DM. Future research is needed in order to show if T2DM can be prevented or reversed with HCV eradication (17).

CONCLUSION

Many epidemiological studies have shown an association between T2DM and chronic hepatitis C. The development of IR in patients with HCV infection is related to the disease activity, disease course, clinical outcomes, and treatment efficacy. It is important to disclose the HCV features and common association with IR, since many undiagnosed T2DM with poor glycemic control may be granted by the adequate infection treatment. Further studies are needed to improve prevention policies and to foster adequate and cost-effective programs for the surveillance and treatment of diabetic HCV patients.

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ORIGINAL ARTICLE
TOPICS IN MEDICAL CLINIC
SYSTEMIC LUPUS ERYTHEMATOSUS WITH AND WITHOUT SEROSITIS

LÚPUS ERITEMATOSO SISTÊMICO COM E SEM SEROSITE

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Key words: Lupus erythematosus systemic, serositis, pleuritis, pericarditis.
Descritores: Lupus eritematoso sistêmico, serosite, pleurite, pericardite.

Abstract

Background: Serositis is a common feature among the wide range of manifestations in patients with SLE. About 16% of individuals with SLE present pleuritis and pericarditis, but they rarely cause ventilatory or circulatory repercussions. The inflammation of the serous membranes, including the pericardium, pleura, and peritoneum can lead to pain, fluid accumulation, adherences and even fibrosis. **Objective:** To know the prevalence of serositis in SLE patients of the local population and to relate them to other clinical manifestations and serological profile of SLE. **Methods:** This is a retrospective study of the last 10 years (2003-2013), with analysis of 412 records of com Lupus erythematosus patients identified with serositis, from the outpatient Rheumatology from HUEC. The comparison was performed between clinical data and autoantibody profile in patients with and without serositis. All patients of both genders and of any age that have at least four qualifiers for the disease of the American College of Rheumatology and sufficient to judge the appearance of serositis data criteria were included. **Results:** Serositis was found in 20.6% (85/412 patients) and 43.5% (37/85 patients) presenting only pleuritis, 20% (17/85 patients) presenting pericarditis and only 36.5% (31/85 patients) presented both: pericarditis and pleuritis. In univariate analysis, no differences were found in the prevalence of discoid lesions, aphthous ulcers, Raynaud, psychosis, glomerulonephritis, malar rash, photosensitivity, arthritis, oral ulcers, leucopenia, lymphopenia, and hemolytic anemia (p = ns). The serositis population showed a higher prevalence of seizures (p = 0.03), antids-DNA (p = 0.01) and anti-Sm (p = 0.04). **Conclusion:** SLE patients who present antids-DNA and anti-Sm has higher chance for serositis than others, and more chance of showing convulsions. **Endocrinol diabetes clin exp 2015 1778 -1781.**

Resumo

Justificativa: A serosite é uma característica comum dentre a ampla gama de manifestações em pacientes com LES. Cerca de 16% dos indivíduos com LES apresenta pleurite e/ou pericardite, mas raramente o derrame causa repercussões ventilatórias ou circulatórias. A inflamação das membranas serosas, que incluem pericárdio, pleura e peritônio, pode levar a dor, acúmulo de fluidos, aderência e até mesmo fibrose. **Objetivo:** Conhecer a prevalência das serosites nos pacientes com LES da população local e relacionar a presença de serosite com as demais manifestações clínicas e com o perfil sorológico do LES. **Metodologia:** Trata-se de estudo retrospectivo, dos últimos 10 anos (2003-2013), com análise de 412 prontuários de pacientes com Lupus eritematoso sistêmico, identificados com serosite, do ambulatório de Reumatologia do HUEC. Foi realizada a comparação de dados clínicos e de perfil de autoanticorpos entre os pacientes com e sem serosite. Foram incluídos todos os pacientes de ambos os sexos e de qualquer idade que possuíam pelo menos quatro dos critérios classificatórios para a doença do Colégio Americano de Reumatologia e dados suficientes para julgar o aparecimento de serosites. **Resultados:** Serosite foi encontrada em 20,6% (85/412 pacientes), sendo 43,5% (37/85 pacientes) apresentando só pleurite, 20% (17/85 pacientes) apresentando só pericardite e 36,5% (31/85 pacientes) apresentando pericardite e pleurite. Na análise univariada não se encontraram diferenças quanto à prevalência de lesão discóide, aftas, *Raynaud*, psicose, glomerulonefrite, rash malar, fotossensibilidade, artrite, úlceras orais, leucopenia, linfopenia e anemia hemolítica (p=ns). A população com serosite apresentou maior prevalência de convulsões (p=0,03), antids-DNA (p=0,01) e anti-Sm (p=0,04). **Conclusão:** Pacientes com LES, que apresentem antids-DNA e anti-Sm tem maior chance de apresentar serosite do que os demais, e também pacientes com serosite, tem mais chance de apresentarem convulsões com a evolução da doença. **Endocrinol diabetes clin exp 2015 1778 -1781.**

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease of unknown origin in which cells and tissue are damaged by autoantibodies and immune complexes (1). This is a chronic disease whose the most striking feature, from clinical and pathological points of view, is the development of inflammatory reactions in various tissues and organs (2). Although both genders may be affected by SLE it is observed a ratio of 9 females (mainly in the reproductive age) to 1 male. Children and elderly people may be affected more rarely. The disease tends to be more common and more severe in black people; Chineses and some Asians also show a higher incidence (1). Genetic, environmental and hormonal factors are involved in the immune system imbalance, which produces autoantibodies against nuclear proteins, some of which participate in tissue injury (3). Familial history is present in 10-12% of cases; HLA-DR2 and HLA-DR3 increase the relative risk of acquiring SLE (1,3). Also several viruses have been implicated as possible etiologic agents, but nothing has yet been proved (1). The disease progresses in bursts of activity interspersed with periods of remission and can present quite pleomorphic clinical and laboratory manifestations (1).

Autoantibodies are an important feature of SLE and may provide clues to the clinical variants found. Although a very large

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number of autoantibodies have been described in SLE, only anti-double-stranded DNA (dsDNA), Smith (Sm) and phospholipids (PL) autoantibodies are part of the classification criteria defined by the American College of Rheumatology, although it should be noted that the anti-PL (aPL) are auto-antibodies not specific for SLE. Similarly, other nuclear and cytoplasmic major antigenic targets, including various ribonuclear proteins (RNP), proteins binding to ribonucleic acids ,while prevalent in SLE, are not specific to the disease (4,5).

The involvement of diverse organs may occur simultaneously or sequentially. The frequency of these affections varies. Skin, joints, kidneys, central nervous system, lungs, heart and serosa are some of the most frequently involved systems. Serositis is recognized as one of the 11 criteria of the American College of Rheumatology (ACR) criteria for classification of SLE. Serositis refers to inflammation of the serous membranes including the pericardium, pleura, and peritoneum, leading to pain, fluid accumulation, tissue adhesion and even fibrosis (4). It is a common feature in patients with SLE but rarely brings ventilatory or circulatory repercussions. Pleuritis appears in about 16% of individuals; peritoneal serositis presenting with ascites (called lupus peritonitis) is an especially rare manifestation (3)

In this study, the objective was to determine the prevalence of serositis in SLE patients from the local population and to relate them to the presence of other clinical manifestations and serological findings of SLE.

METHODS

This study was approved by the Ethics Committee of *Sociedade Evangélica de Curitiba* under number 235 535. This is a retrospective study including patients from the last 10 years (2003-2013) from the outpatient rheumatologic Unit of *Hospital Evangélico de Curitiba* and analyzed 412 records of patients with SLE. We included patients of both genders and of any age that completed at least four classification criteria of the American College of Rheumatology for this illness (6) and had data to judge the appearance of serositis.

The records were submitted to a protocol for information extraction that included demographic data (patient age, gender, duration of disease, race, and smoking addiction); data on clinical profile (discoid lesion, oral ulcers, malar rash, Raynaud's pleuritis, pericarditis, peritonitis, seizures, psychosis, arthritis, hemolytic anemia, leukopenia, thrombocytopenia and glomerulonephritis); and data on the presence of autoantibodies (anti-DNA, anti-Ro, anti-La, anti-Sm, anti-RNP, aCl-IgG or anticardiolipin, aCl-IgM, LAC or lupus anticoagulant and rheumatoid factor).

For the analysis and the study charts were divided into 2 groups: (1) with lupus serositis and (2) with and without lupus serositis and comparison of clinical and autoantibodies profile in patients with and without serositis was performed.

Data were analyzed in frequency and contingency tables. Fisher's and chi-square tests were used for association of nominal data and Mann-Whitney and unpaired Student t tests for numerical data. The significance adopted was 5%.

RESULTS

DESCRIPTION OF STUDIED PATIENTS SAMPLE

In the 412 patients, 29 were men and 383 women. The age of patients ranged from 16 to 79 years, with a median value of 38 and IQR (interquartile range) from 26.0 to 79.0. The duration of the disease varied from 0.5 to 36 years with a median of 5.0 and the IQR from 1.0 to 11.0. Regarding ethnicity, 44.5% were Brazilian Africans and 55.5% were Caucasian. With respect to smoking, 32% of patients reported being smokers or have made use of cigarettes at some point in life.

The study of clinical profile showed that 16.5% had discoid lesions. Oral ulcers were present in 76%; 55.7% have had malar rash. Raynaud was present in 9.4%, hemolytic anemia in 6.4%, leukopenia in 28.4%, thrombocytopenia in 23.3%, glomerulonephritis in 40.2%.

Serositis was found in 20.6% (85/412 patients) and 43.5% (37/85 patients) presenting only pleuritis, 20% (17/85 patients) presenting pericarditis and only 36.5% (31/85 patients) presenting pericarditis and pleuritis. figure 1.

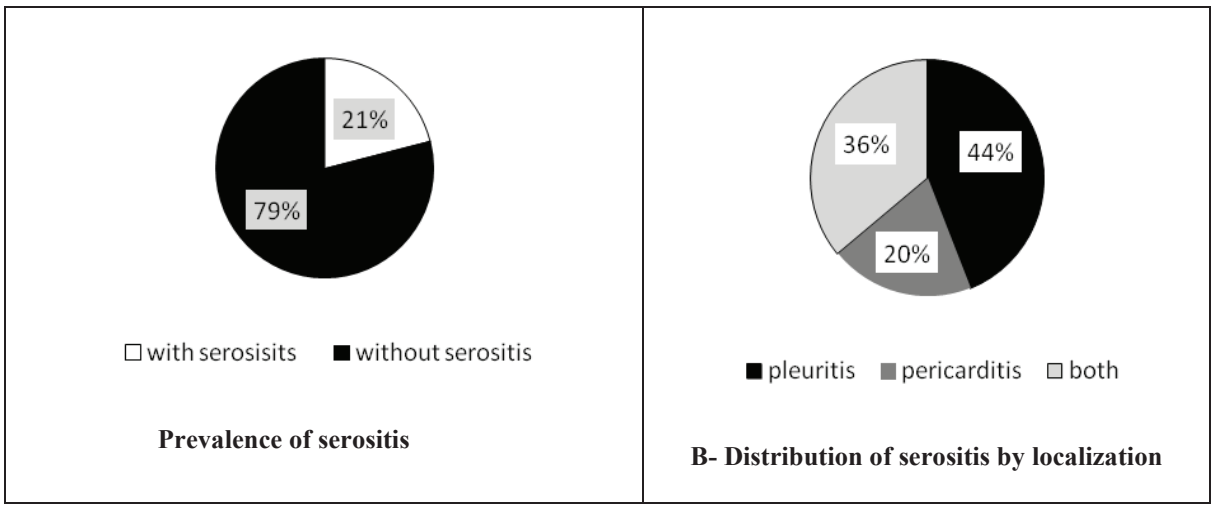

Figure 1 - Serositis prevalence and distribution in the studied population.

Serological profile can be seen in figure 2.

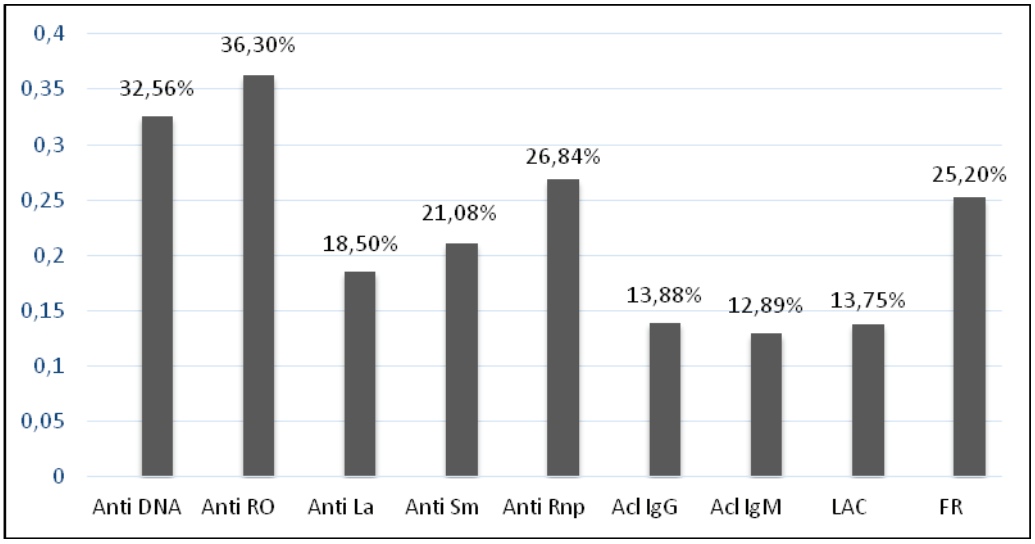

Figure 2: Serological profile in the studied systemic lupus erythematosus population.

Comparative analysis among patients with and patients without serositis

In the table 1 there is a parallel of the population with and without serositis. It is possible to note that those with serositis had a higher prevalence of seizures, anti ds-DNA and anti-Sm.

Table 1- Comparison of clinical data, and demographic and serological data of systemic lupus erythematous patients with and without serositis

	WITH serositis N=85	Without serositis N=327	P
Age (years)	16- 73,0 Median 38,0 IQR= 26,0-46,0	16-79,0 Median 38; IQR= 27,0-47,0	0,83*
Disease duration (years)	0,5-36 Median 5,0 IQR = 2,0-11,5	0,5- 32,0 Median 6,0 IQR= 1,0-11,0	0,98-*
Gender	8 males/77 females	19 males/308 females	0,23 – **
Etnia	Caucasians- 29 Afrodescendants – 16	Caucasians -101 Afrodescendants-56	0,98- **
Tobacco exposure	22/80 – 27,5	102/310 -32,9%	0,35- **
Discoid lesion	8/75 – 10,6%	51/350 – 16,7%	0,19- **
Oral ulcers	36/80 – 45%	142/308 – 46,1%	1,00- **
Photosensitivity	56/79 – 70,8%	244/319 – 76,4%	0,30- **
Rash malar	43/75 – 57,3%	166/308 – 53,8%	0,85 – **
Raynaud	38/75 – 50,6%	153/312 – 49,03%	0,80 – **
Convulsions	14/83 – 16,8%	29/322 – 9,0%	0,03- **
Psychosis	6/83 – 7,2%	12/319 – 3,7%	0,17 – **
Arthritis	54/84 – 64,2%	188/322 – 58,6%	0,35 – **
Hemolitic anemia	5/83 – 6,02%	21/316 – 6,6%	1,00 – §
Leukopenia	21/82 – 25,6%	94/318 – 29,5%	0,48 – **
Thrombocytopenia	20/83 – 24,09%	73/313 – 23,3%	0,88 – **
Glomerulonefritis	42/85 – 49,4%	131/327 – 40,4%	0,11 –**
Anti- dna	35/79 -44,3%	90/299 – 30,1%	0,01 – **
Anti- ro	30/77 – 38,9%	106/294 – 36,0%	0,63 – **
Anti- la	13/76 – 17,1%	56/291 – 19,2%	0,67 –**
Anti- sm	22/73 – 30,1%	55/286 -19,2%	0,04 – **
Anti – rnp	16/71 – 22,5%	73/261 – 27,9%	0,35 – **
Anticardiolipin igg	10/78 – 12,8%	43/299 -14,3%	0,72 – **
Anticardiolipin ig m	9/68 – 11,6%	40/299 – 13,3%	0,69 – **
Lupus anticoagulant	8/65 – 12,3%	39/274 – 14,2%	0,68 –**
Rheumatoid factor	21/74 – 28,3%	70/283 -24,7%	0,52 – **

**= Man Whitney test ; **=chi square test ; §= Fisher test*

DISCUSSION

The first aim of our study was to know the prevalence of serositis (pleuritis and pericarditis) in SLE patients from the local population. This is important since the Brazilian population is highly mixed from the ethnic point of view and does not follow the standard demarcated classification from other countries. As SLE manifestations have genetic influence, to know local data becomes essential to the knowledge of this disease in our country. It was found that 21% of patients had serositis; of these, 43.5% had only pleuritis, 20% had only pericarditis and 36.5% had pericarditis and pleuritis. A study in Hong Kong, by Man et al (4), with 310 patients, found a prevalence of 12% (37/310 patients) of serositis among those studied. In this study occurred 69 episodes of serositis and 26% had only pericarditis; only pleuritis in 44%; and 30% had peritonitis. In 35% of patients, two or three manifestations of serositis were present. Man et al data (4) is similar to those obtained in our study, especially in the case of isolated pleurisy.

In a case report followed by literature review done by Junior Pott et al (7), it is described that serositis occurs in approximately 16% of patients with SLE: pleuritis and pericarditis are more common, and more rarely, appearing peritoneal involvement. In our work we have not identified cases of peritoneal involvement.

The second aim of our study was to correlate the presence of serositis with other clinical manifestations of SLE. To recognize associations between manifestations of lupus or their connection with autoantibodies allows the clinician who attends this type of patients to predict future events and to act preventively. In the present paper, statistical significance was found only in the relation of serositis with seizures (p=0.03), with a prevalence of 16.8% of seizures in patients with serositis and 9% in patients without serositis. The same study cited above, carried out by Man et al (4) had a similar finding, wherein the neurological involvement was individually associated with serositis with an OR= 2.82 (95% CI 1.88, 4.23). Yet in the same study there was statistical significance between serositis and discoid rash [OR= 0.93 (95% CI 0:57, 1:53)], hematological involvement [OR= 2:05 (95% CI 1:38, 3.04)], anda negative relationship with photosensitivity [OR 0.73 (95% CI 0:51, 1:03)], which was not demonstrated in our research. Other authors such as Li et al (8) found serositis in association with hemolytic anemia (p=0.02) and lymphadenopathy (p=0.04), which also was not seen at present. Still others have found that malar rash was less frequent in patients with serositis (p = 0.03) (5).

The third aim of our study was to correlate the presence of serositis with serological profiles of SLE. Statistical significance between serositis and anti-DNA (p=0.01) and anti-Sm (p=0.04) was found. Among patients with serositis, 44.3% showed presence of anti-dsDNA and 30.1% of anti-Sm against 30.1% and 19.2%, respectively, in the group without serositis. The association between anti-Sm and serositis was also evidenced both by the study of Li et al (8) as in the study by Wang et al (9).

Some authors believe that there are three groups of SLE patients serologically distinct: group 1 - with anti-dsDNA; group 2 - with anti-Sm/anti-RNP/antiphospholipid and group 3 - with anti-Ro/anti-La. These authors noted that patients in group 1 (anti-dsDNA) have more kidney disorders but lower prevalence of other clinical manifestations. On the other hand, groups 2 and 3, have less renal disorders but higher prevalence of other manifestations. Exceptions are hematological involvement and serositis that overlaps between these two extremes (8). In another study, comparing the frequency of six manifestations, including nephritis, serositis, musculoskeletal, hematologic and CNS symptoms was observed that the presence of serositis correlated with the group Sm/RNP (p = 0.0022) (5). Previously the relationship between anti-Sm antibodies and serositis had only been observed in children (10). The findings of this study confirm the association with anti-Sm.

CONCLUSIONS

In the present study we conclude that:

- Patients with SLE in our population who have serositis (pleuritis and pericarditis) have more chances of having seizures;

- Serositis is more common in patients with positive anti-dsDNA and anti-Sm.

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ORIGINAL ARTICLE
ANTI-THYROID AUTOANTIBODIES IN SPONDYLOARTHRITIS PATIENTS

AUTOANTICORPOS DE TIREOIDE EM PACIENTES COM ESPONDILAORTRITES

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Key words: Spondyloarthritis, Hashimottothyroiditis, anti thyroglobulin antibodies, anti-peroxidase antibodies
Descritores: Espondiloartrites, tireoidite de Hashimotto, anticorpos anti-tiroglobulina, anticorpos anti-peroxidase

Abstract

Background: Hashimoto thyroiditis seems to be more common in rheumatic patients than in normal population. Very few studies address this issue in Spondyloarthritis (SpA) patients. **Objective:** To study the prevalence of thyroid autoantibodies (anti peroxidase and anti-thyroglobulin) in a sample of Brazilians SpA patients. **Methods:** Seventy one SpA patients were studied for anti-thyroid antibodies, epidemiologic, clinical and treatment profile. Disease activity was accesses by BASDAI, functional impairment by BASFI, and BASMI and quality of life by ASQoL. Sample with and without thyroid antibodies were compared. **Results:** The prevalence of anti-thyroglobulin antibodies was of 8.3% and anti-peroxidase, of 14.08%. Female patients and those with skin lesion were more common in the autoantibodies positive group with p=0.01 and 0.03 respectively. All other studied parameters were equally distributed. **Conclusions:**The prevalence of thyroid autoantibodies in SpA patients is the same as in normal population. These autoantibodies are more common in SpA female patients and in those with skin lesions. **Endocrinol diabetes clin exp 2015 1782 -1784.**

Resumo

Justificativa: A tireoidite de Hashimoto parece ser mais comum em pacientes reumáticos do que na população normal. Raros estudos abordam esta questão nos pacientes com espondiloartrite (SpA). **Objetivo:** Estudar a prevalência de auto-anticorpos tireoidianos (antiperoxidase e anti-tireoglobulina) em uma amostra de pacientes brasileiros SpA. **Métodos:** Setenta e um pacientes com SpA foram estudados para detecção de anticorpos anti-tireoideanos do ponto de vista epidemiológico, clínico e de tratamento. A atividade da doença foi acessada pelo BASDAI, o comprometimento funcional pelo BASFI e pelo BASMI e a qualidade de vida por ASQoL. Amostras com e sem anticorpos de tireoide foram comparadas entre si. **Resultados:** A prevalência de anticorpos anti-tiroglobulina foi de 8,3% e anti--peroxidase, de 14,08%. Pacientes do sexo feminino e aqueles com lesão de pele foram mais comuns no grupo positivo para auto-anticorpos com p = 0,01 e 0,03, respectivamente. Todos os outros parâmetros estudados foram igualmente distribuídos nos dois grupos. **Conclusões:** A prevalência da presença de anticorpos em pacientes SpA é o mesmo do que na população normal. Esses auto-anticorpos são mais comuns em pacientes de SpA do sexo feminino e naqueles com lesões de pele. **Endocrinol diabetes clin exp 2015 1782 -1784.**

INTRODUCTION

Hashimoto thyroiditis is one of the most common organ specific autoimmune diseases (1) and it is known to have a higher prevalence in systemic autoimmune rheumatic patients than in the general population (2). Among these diseases are rheumatoid arthritis, systemic lupus erythematosus and scleroderma. It is believed that the association of autoimmune conditions in the same patient may be due to a common genetic background or to an exposition to ashared trigger agent (3,4). This association seems to be controversial when the rheumatic diseases are spondyloarthritis.

Spondyloarthritis (SpA) are systemic rheumatic diseases with a different profile than the collagen diseases; they have a male gender preference and are considered seronegative as no autoantibodies can be implied in its pathophysiology (5). There are very few studies addressing this association of SpA with thyroiditis. Peluso et al (6) found that indices of thyroid autoimmunity were higher in a patients with SpA than controls (24.09% vs 10.69%) and that they were more common in patients with longer disease duration and with active disease. Antonelli et al (7) studying patients with psoriatic arthritis found a significantly higher prevalence of thyroid autoimmunity and of subclinical hypothyroidism in Psoriatic Arthritis (PsoA) than in the general population.

To look further into this issue we studied patients with SpA for the presence of anti-thyroglobulin and anti-peroxidase autoantibodies and if its presence modified the clinical SpA profile in a Brazilian population.

METHODS

The sample had 71 patients with SpA diagnosed according to ESSG classification criteria (8). After approval of the Committee of Ethics in Research and signed consent these patients were submitted to interview and physical examination for BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) (9), BASFI (Bath Ankylosing Spondylitis Disease Functional Index)(10), ASQoL (Ankylosing Spondylitis Quality of Life Index)(11) and BASMI (Bath Ankylosing Spondylitis Disease Metric index) (8) determination. BASDAI, BASMI and BASFI are indexes that are measured from 0-10 and reflect disease activity, degree of disease repercussion in the skeletal system and patient's functional index respectively. Zero means no repercussion while 10 is the worst scenario. BASDAI and BASFI are evaluated through a set of pre stablished questions while BASMI is determined through a set of measurements of degree of cervical rotation, lumbar spine flexion, lateral spine flexion, etc. ASQoL is formed by 18 questions about physical and emotional health. Each item "yes" receives a score one, reaching a total of 18 points. Higher

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scores mean worse quality of life.

Charts were review for epidemiologic and cumulative clinical profile (patient age and gender, disease duration, race, smoking addiction, type of spondyloarthritis, articular and extra-articular manifestations, presence of HLA B27, sacroiliitis etc. Autoantibodies for thyroid were measured by chemiluminescence method. Normal values considered are: anti-peroxidase below 5.61 IU / ml and anti-thyroglobulin of less than 4.11 IU / ml.

Data were analyzed by frequency and contingency tables using the Kolmogorov-Smirnov test to analyze the data distribution. Measures of central tendency were expressed as mean and standard deviation (SD) for data with Gaussian distribution and median intervals and inter quartiles rates (IQR) when the data samples were not Gaussian. Association studies were made using chi-square and Fisher tests (nominal data) and Mann Whitney or Student t unpaired (for numeric data).The adopted significance was of 5%. The calculations were made with the help of Graph Pad Prism® software, version 4.0.

RESULTS

In the sample of 71 studied SpA patients, 56.3% were males, 43.6% females. Their mean age was 49.5±11.4 years and 54.9% had ankylosing spondylitis, 21.1% had psoriatic arthritis, 12.6% had undifferentiated spondyloarthritis, 5.6% had reactive arthritis; 4.2% had disease associated with inflammatory bowel disease and 1.4% had the juvenile form. The median disease duration was 9.0 years (range 1-40 years) and 47.8% auto declared Caucasian and 52.1% auto declared Afrodescendants. Methotrexate was used in 13/71 (18.3%); sulphasalazine in 17/71(23.9%); anti TNFα on 20/71(28.1%) and nonsteroidal anti-inflammatory drugs in 21/71(29.5%).

In this sample 28/71 (39.4%) had peripheral arthritis ; 7/71 had entesitis (9.8%), Dactilitis was found in 11.2%, cutaneous lesions in 18.3%, uveitis in 23.9% and positive HLA B27 in 76.08%. The mean BASDAI was 3.8 ±2.39; the mean BASFI was 4.23±2.74; the mean ASQoL was 7.49±4.74; the median BASMI was 4.0(IQR=2.0-6.0).

Anti-thyroglobulin and anti-peroxidase autoantibodies were found in 13/71 (18.3%) of SpA patients; 10/71 (14.08%) had anti peroxidase and 6/71 (8.4%) had anti thyroglobulin autoantibodies. Hypothyroidism was present in 4/71 (5.6%). When patients with and without autoantibodies were compared, the results on Table 1 were found.

Table 1- Comparison of patients with spondyloarthritis with and without thyroid autoantibodies (anti-peroxidase and anti-thyroglobulin).

	With autoantibodies N=13	Without autoantibodies N= 58	P
Age in years	31-74	26 - 74	0.94 (*)
(median and IQR)	(48.0; 45.0-60.5)	(50.0; 43.2-57.0)	
Ethnic background	9 C/4 A	43 C/15 A	0.73 (§)
Disease duration in years	2 - 30	1 a 40	0.19(*)
(median and IQR)	(10.0; 5.5-22.0)	(8.00: 3.7-12.2)	
Gender (female/male)	10/3	21/37	0.01(§)
Exposure to tobacco	7/13 (53.8%)	30 /58 (51.7%)	1.00(§)
Axial disease	9/13 (53.8%)	46/58 (%)	0.47(§)
Peripheral disease	6/13 (46.1%)	22/58 (37.9%)	0.58(§§)
Enthesitis	2/13 (15.3%)	5/58 (8.6%)	0.60(§)
Dactilitis	0/13	8/58 (13.7%)	0.33(§)
Skinlesions	5/13 (38.4%)	8/58 (8.6%)	0.03 (§§)
Uveitis	3/13 (23.0%)	14/58 (13.7%)	1.00 (§)
HLA B27 positive	5/6 – 83.3%	30/40- 75%	0.08(§)
BASDAI (mean± SD)	0-8.55 (4.39±3.29)	0-9.15 (3.69±2.16)	0.41(**)
BASFI(mean± SD)	0-8.2 (4.37±3.02)	0-9.8 (4.20±2.7)	0.83 (**)
AsQOL (mean± SD)	0-16 (7.84±5.36)	0-15(7.41±4.65)	0.76 (**)
BASMI(medianand IQR)	1.0-8.0(3.0; 2.0-6.0)	0-10(4.0; 2.0-6.0)	0.89(*)
Methotrexate use	3/13 (23.07%)	10/58 (17.2%)	0.69 (§)
Sulphasalazine use	3/13 (23.07%)	14/58 (24.1%)	1.00(§)
Anti TNF-α use	4/13 (30.07%)	16/58 (27.5%)	1.00 (§)
NSAID use	5/13 (38.4%)	16/58 (27.5%)	0.50 (§)

(§)- Fisher test
(§§) chi squared test
(*)- Mann Whitney test
(**) Teste t nãopareado test
IQR= interquartile range
SD= standard deviation
TNF-α= tumor necrosisfactor-α
C= Caucasian
A= Afrodescendant
BASDAI= Bath Ankylosing Spondylitis Disease Activity Index
BASFI= Bath Ankylosing Spondylitis Functional Index
BASMI= Bath Ankylosing Spondylitis Metrology Index
AsQOL= Ankylosing Spondylitis Quality of Life
NSAID= no steroidal anti- inflammatory drugs

DISCUSSION

The estimated prevalence of anti-thyroglobulin antibodies in the normal population is of 5-20% and of anti-peroxidase is 8-27% (1) so our results (14.1% and 8.4% respectively) did not differ from the normal population.

When comparing SpA with and without anti thyroid autoantibodies, we found that they were more common in patients of female gender. As Hashimoto's thyroiditis is a disease more common in women this finding is not unexpected (1). Most of autoimmune disease are more common in women although the reasons for it are not completely stablished. Sex hormones are implicated in the immune response, with estrogens as enhancers of the humoral immunity (12). It has been documented that higher circulating estradiol is related to thyroid autoimmunity even in males (13).

We also found that patients with skin lesions had more autoantibodies than those without it. In this sample we can consider skin lesion as a surrogated marker for Psoriatic SpA as none of reactive arthritis patients had skin lesion. Similarly, Antonelli et al (7) found high prevalence of thyroid autoimmunity in patients with psoriatic arthritis although they also studied peripheral forms of psoriatic arthritis that we did not. In their study of 36 patients they found higher prevalence of anti-peroxidase but not anti-thyroglobulin autoantibodies in psoriatic arthritis patients than controls. An imbalance of Th17 cytokines profile has been found both in thyroiditis (14) as well as in psoriatic arthritis (15).

Comparing patients with and without thyroid auto antibodies no differences could be found in the prevalence of musculoskeletal complaints as well as in Spa activity and repercussion on daily living.

Finally no differences in treatment profile in anti-thyroid antibodies positive and negative population was found. This observation is interesting since some authors (16) have described the appearance of anti-thyroid autoantibodies in patients using anti TNFα

CONCLUSIONS

We concluded that, in our sample, the prevalence of thyroid autoantibodies in Spa patients is the same as in normal population. These autoantibodies are more common in SpA female patients and in those with skin lesions.

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TOPIC IN MEDICAL CLINIC
CUMULATIVE DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND ITS ASSOCIATION WITH CLINICAL, SEROLOGICAL AND THERAPEUTIC VARIABLES. A STUDY IN 131 SLE BRAZILIAN PATIENTS.

DANO CUMULATIVO EM LUPUS ERITEMATOSO SISTÊMICO E SUA ASSOCIAÇÃO COM PERFIL CLINICO, SOROLÓGICO E TERAPÊUTICO: UM ESTUDO EM 131 PACIENTES LÚPICOS BRASILEIROS

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Key words: Systemic lupus erythematosus, Cumulative damage, Glomerulonephritis, Convulsion, Glucocorticoids
Descritores: Lúpus Eritematosos Sistêmico, Dano cumulativo, Glomerulonefrite, Convulsões, Glicocorticoides

Abstract

Background: Survival in systemic lupus erythematosus (SLE) has increased but the quality of life of these patients may be affected by residual damage of the disease. This may be caused by the SLE itself or medications used to treat it. ***Objective:*** To study cumulative damage in SLE and its association with clinical, serological and therapeutic variables ***Methods:*** We studied 131 SLE patients for cumulative damage through SLICC/ACR questionnaire (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus). Their charts were reviewed for clinical and serological profile and for treatment used. ***Results:*** SLICC/ACR ranged from 0.0 to 7.0 (median 2.0). In univariated analysis SLICC was found associated with age (p=0.02), glomerulonephritis (p<0.0001), seizures (p<0.0001), psychosis (p=0.03), oral ulcers (p=0.005); hemolysis(p=0.01), presence of anti-Ro (0.02), cyclophosphamide use (p=0.01), mycophenolate mofetil use (p=0.01), glucocorticoid use (dose with p<0.0001; duration with p= 0.04) and with patient's age (p=0.02). In multiple logistic regression analysis patient's age (p<0.0001); renal involvement (p<0.0001); seizures (p<0,0001) and higher used dose of glucocorticoid (p=0.04) remained significant. ***Conclusion:*** In the studied population patient's age, renal involvement, seizures and glucocorticoid use were associated with damage accrual. **Endocrinol diabetes clin exp 2015 1785 -1789.**

Resumo

Justificativa: A sobrevida em lúpus eritematoso sistêmico (LES) tem aumentado, mas a qualidade de vida nestes pacientes permanece afetada pelo dano residual associado. Este dado residual pode ser causado pela doença em si ou pelos medicamentos utilizados em seu tratamento. **Objetivo:** Estudar o dano cumulativo de pacientes com Lupus Eritematoso Sistêmico (LES) fazendo associação com perfil de autoanticorpos, clínica e tratamentos utilizados. **Métodos:** Estudo epidemiológico transversal com 131 pacientes com LES os quais foram submetidos à medida de dano cumulativo por meio do questionário SLICC/ACR ((Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus)) e coleta de dados quanto ao perfil demográfico, clínico, sorológico e terapêutico por revisão de prontuário. **Resultados:** Em análise univariada encontrou-se maior SLICC nos pacientes com glomerulonefrites (p<0,0001), úlceras orais (p=0,05); convulsões (p<0,0001) e psicoses(p=0,03), anemia hemolítica (p=0,01), presença de anti-Ro (p=0,02), uso de ciclofosfamida (p=0,01), uso de mofetil micofenolato (p=0,01); exposição ao fumo (p=0,009), idade (p=0,02), tempo de uso e maior dose já usada de corticóide (p=0,04 e 0,001 respectivamente). Em análise multivariada, só a ocorrência de glomerulonefrites, maior dose de corticoide já usada, idade e convulsões mantiveram-se como variáveis independentes associadas ao SLICC/ACR. **Conclusão:** Observou-se associação de danos cumulativo em pacientes com envolvimento renal e do sistema nervoso central (convulsão), maior dose de corticóide usada e idade do paciente. **Endocrinol diabetes clin exp 2015 1785 -1789.**

INTRODUCTION

Systemic lupus erythematosus (SLE) is a disease with changing pattern. As new therapeutic and laboratory armamentarium allows early diagnosis, better control of disease activity and co-morbidities, mortality has decreased. Prognosis has improved from less than 50% survival in 1955 (1) to more than 90% ten-year survival more recently (2,3,4). Increased survival in these patients has enabled a clearer view of the residual damage caused not only by disease but also by drugs used to control it. Renal and central nervous system involvement have been associated with accrual damage (5); accelerated atherosclerosis, infections and cancer may be related to aggressive treatment approach mainly cyclophosphamide and corticosteroid (6). Thus, nowadays, choosing SLE patient's treatment must take into account not only the pattern of organ involvement by the disease but also the long term disease prognosis. It is important not only to preserve life but also its quality.

Organ pattern involvement and disease severity has been associated with gender (7), ethnic background (8), autoantibody profile (9) and socio economic conditions (8). Renal disease is more aggressive in black and hispanic patients and more prevalent in those with anti ds-DNA. Antiphospholipid antibodies have been linked to central nervous system involvement and with

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increased mortality (7). Lower socio economic status precludes access to health care and raises mortality and work disability (10). Such variables differ according to the studied population. In Brazil we have a highly mixed population with peculiar racial patterns and few studies addressing SLE cumulative damage.

In this context, the present analysis aimed to verify the association of SLE cumulative damage with clinical, autoantibody and treatment profile in a Southern Brazilian population.

MATERIAL AND METHODS

This study was approved by the local Committee of Ethics in Research and all participants signed consent. One hundred thirty one patients with at least 4 of 1987 American College of Rheumatology (ACR) classification criteria for SLE (11) from a Rheumatologic Unit were consecutively included in the study in the period from August 2012 to August 2013, according to appointment order and willingness to participate in the study.

Charts were reviewed for demographic, clinical and serological profile. Collected clinical data was cumulative and considered as defined by 1997 revised Classification Criteria of ACR for SLE (11). Auto antibodies considered for analysis were: anti Ro/SS-A, anti La/SS-B, anti RNP, anti Sm, anti dsDNA, anticardiolipin (aCl) IgG, aClIgM, LA (lupus anticoagulant) and direct Coombs. At our institution anti Ro/SS-A, anti La/SS-B, anti RNP, anti Sm, aCl (anticardiolipin) IgG, aCl IgM were done by ELISA (Alka and Orgentec Kits®), anti dsDNA is done by immunofluorescence technique (IFT) using *Crithidia luciliae* as a substrate. Lupus anticoagulant (LA) is searched through a screening test, the dRVVT (dilute Russell viper venom test) and confirmed by RVVT. Cumulative damage was measured by SLICC/ACR (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus)(12).

Data was collected in contingency and frequency tables. Sample distribution was studies by Kolmogorov-Smirnov test. Studies of SLICC values comparison according to clinical, serological and demographic variables were done through Mann Whitney test. Correlation of SLICC values and glucocorticoid dose, glucocorticoid treatment duration, patient's age and disease duration were done by Spearman test. Variables with $p<0.1$ on univariated analysis were further studied through multiple regression. Calculation was done with help of the software Medcalc version 12.1.3.0 and the adopted significance was 5%.

RESULTS

Analysis of the studied population

In the 131 studied patients, 4.2% (6/131) were male and 125/131 (95.4%) female with mean age of 38.9±11.2 years (range from 16-72 years) and median disease duration of 8.0 years (IQR =5.0-11.0; range from 1-24 years). In this population 29/131(22.1%) had less than 8 years of formal education; 33/131(25.1%) had between 8-12 years; 61/131 (46.5%) had between 12- 16 years and 8/131 (6.1%) had a university degree. Also 71/131 (54.1%) self-declared Caucasians and 60/131 (45.8%) self-declared Afrodescendants.

The clinical, serological and treatment profile of studied population is on Table 1.

Table 1 – Clinical, serological and treatment profile of 131 patients with systemic lupus erythematosus.

	Nº	%
Arthritis	109/131	83.20%
Discoid Rash	16/131	12.21%
Malar Rash	87/131	66.41%
Photosensitivity	105/181	80.15%
Serositis	22/131	16.79%
Oral ulcers	68/131	51.9%
Glomerulonephritis	63/131	48.09%
Seizures	20/131	15.26%
Psychosis	24/131	18.32%
Hemolyticanemia	15/131	11.45%
Leukopenia	20/131	15.26%
Thrombocytopenia	30/131	22.905
Anti-Ro	55/131	41.98%
Anti-La	24/131	18.32%
Anti-RNP	37/131	28.24%
Anti-dsDNA	47/131	35.87%
Anti-Sm	29/131	22.13%
Anticardiolipin IgG	21/131	16.03%
Amticardiolipin IgM	20/131	15.26%
Lupusanticoagulant	25/131	19.08%
At least one antiphospholipid	42/131	32.06%
Antimalarial use	103/131	78.62%
Cyclophosphamide (cumulative use)	40/130	30.76%
Methotrexate use	55/131	41.98%
Cyclosporine use	2/131	1.6%
Azathioprine use	63/131	48.09%
Thalidomide use	9/131	6.87%
Mycophenolate mofetil use	19/ 131	14.50%
Glucocorticoid use (at least once)	130/131	99.23%
Glucocorticoid (*) (higher used dose- mg/day)	10-120	Median 40.0 (IQR=20-60)
Glucocorticoid (treatment duration-years)	1 - 19	Median 6.0(IQR=3.0-8.0)
Present dose of glucocorticoid(*) (mg/day)	0 - 60	Median 5.0 (IQR 0-10)

(*)- prednisone or equivalent; IQR= interquartile rate.

In this population the SLICC/ACR ranged from 0.0 to 7.0 (median 2.0; IQR 1.0-3.0). The most commonly affect domains were: musculoskeletal (61.8%); renal (31.2%); eyes (25.2%); neuropsychiatric and peripheral vascular (18.3% each) and cardiovascular (16.03%).

Study of association between clinical, serological, treatment variables and SLICC/ACR

The results of association analysis between clinical, serological, treatment variables and SLICC/ACR in univariated analysis are seen in Table 2. One can note that nephritis, central nervous system involvement, hemolytic anemia, presence of anti Ro, cyclophosphamide and mycophenolate mofetil use influenced the SLICC result.

Table 2 - Comparison of SLICC/ACR values according to clinical, serological and treatment variables in 131 systemic lupus erythematosus patients.

	Positive (*)	Negative (**)	P
Arthritis	1-7.0 Median 2.5 (IQR=2.0-3.0)	0-7.0 Median 2.0 (IQR=1.0 a 3.0)	0.94
Discoid Rash	0.0- 5.0 Median 3.0 (IQR=1.2-3.7)	0-7.0 Median 2.0 (IQR=1.0-3.0)	0.35
Malar Rash	0.0 -7.0 Median 2.0 (IQR= 1.0-3.0)	0.0 -7.0 Median 2.0 (IQR= 2.0- 3.0)	0.84
Photosensitivity	0.0-7.0 Median 2.0 (IQR= 1.0-3.0)	0.0- 4.0 Median 2.0 (IQR=1.0-3.0)	0.32
Serositis	0.0- 7.0 Median 2.0 (IQR=1.0-3.0)	0.0- 6.0 Median 2.0 (IQR= 1.0-3.0)	0.82
Oral ulcers	0.0- 7.0 Median 3.0 (IQR =2.0-3.0)	0.0- 6.0 Median 2.0 (IQR =1.0-3.0)	0.05
Glomerulonephritis	0.0-7.0 Median 3.0 (IQR =2.0-4.0)	0.0-5.0 Median 2.0 (IQR= 1.0- 3.0)	<0.0001
Seizures	0.0- 7.0 Median 4.0(IQR 3.0-4.0)	0.0- 7.0 Median 2.0 (IQR=1.0-3.0)	<0.0001
Psychosis	0.0-7.0 Median 3.0 (IQR=2.0-4.0)	0.0 a 6.0 Median 2 (IQR=1.0-3.0)	0.03
Haemolytic Anemia	0.0-4.0 Median 2.0 (IQR= 1.0-2.0)	0.0- 7.0 Median 2.0 (IQR=2.0-3.0)	0.01
Leukopenia	0.0- 7.0 Median 2.0 (IQR= 1.0-3.2)	0.0- 5.00 Median 2.0 (IQR =2.0-3.0)	0.81
Thrombocytopenia	0.0- 5.0 Median 2.0 (IQR =1.0- 3.0)	0.0- 7.00 Median 2.0 (IQR =1.0-3.0)	0.81
Anti-dsDNA	0.0- 6.0 Median 3.0 (IQR=2.0- 3.0)	0.0- 7.0 Median 2.0 (IQR= 1.0-3.0)	0.24
Anti-Sm	0.0- 5.0 Median 2.0 (IQR=2.0-3.0)	0.0 – 7.0 Median 2.0 (IQR =1.0-3.0)	0.77
Anti-RNP	0.0 – 5.0 Median 2.0 (IQR=1.0-3.0)	0.0- 7.0 Median 2.0 (IQR =1.0-3.0)	0.92
Anti-Ro	0.0- 6.0 Median 3.0 (IQR =2.0- 4.0)	0.0- 7.0 Median 2.0 (IQR =1.0-3.0)	0.02
Anti-La	1.0 -5.0 Median 3.0 (IQR =2.0-3.7)	0.0- 7.0 Median 2.0 (IQR =1.0-3.0)	0.26

	Positive (*)	Negative (**)	P
Anticardiolipin IgG	0.0-7.0 Median 3.0 (IQR =2.0-4.0)	0.0- 7.0 Median 2.0 (IQR=1.0-3.0)	0.18
Anticardiolipin IgM	0.0- 6.0 Median 3.0 (IQR=2.0- 4.0)	0.0- 7.0 Median 2.0 (IQR= 1.0-3.0)	0.26
Lupus anticoagulant	0.0- 7.0 Median 3.0 (IQR=2.0-3.5)	0.0- 7.0 Median 2.0 (IQR=1.0-3.0)	0.33
Cyclophosphamide use	0.0- 7.0 Median 3.0 (IQR =2.0-4.0)	0.0-6.0 Median 2.0 (IQR=1.0-3.0)	0.01
Methotrexate use	0-7.0 Median 3.0 (IQR =1.0-3.0)	0.0-7.0 Median 2.0 (IQR =1.2 – 3.0)	0.34
Azathioprine use	0-7 Median 3.0 (IQR=2.0-3.0)	0.0-7.0 Median 2.0 (IQR= 1.0-3.0)	0.10
Thalidomide use	0.0-7.0 Median 2.0 (IQR=1.0-3.0)	0.0-5.0 Median 3.0 (IQR= 1.0-4.0)	0.68
Mycophenolate mofetil use	0.0- 5.0 Median 3.0 (IQR= 2.0- 4.0)	0.0- 7.0 Median 2.0 (IQR=1.0-3.0)	0.01
Antimalarial use	0,0- 7,0 Median 2,0 (IQR =1,0- 3,0)	0,0 a 1,0 Median 3,0 (IQR= 2,0-4,0)	0.09

(*)- refers to SLICC values when the variable is present; (**) refers to SLICC values when the variable is absent.

Studying demographic data in relation to SLICC we found that gender, ethnic background (Caucasians vs Afrodescendants) and years of formal study did not hold significant associations with p=0.85; 0.18 and 0.86 respectively. Tobacco exposure was associated with higher SLICC (median values of 3.0 vs 2.0; p=0.009).

Correlation studies of age, disease duration, glucocorticoid use (higher dose ever used, present dose and treatment duration) with SLICC showed results on table 3.

	Spearman R	**95% confidence interval**	**P**
Age (years)	0.19	0.01 to 0.35	0.02
Disease duration (years)	0.05	-0.11 to 0.23	0.50
Glucocorticoid (higher used dose)	0.14	-0.02 to 0.31	0.09
Glucocorticoid (treatment duration)	0.17	-0.001 to 0.34	0.04
Glucocorticoid (present used dose)	0.27	0.09 to 0.42	0.001

Re-studying clinical and serological data (glomerulonephritis, seizures, aphtae, psychosis, hemolysis and presence of anti-Ro), treatment data (cyclophosphamide, mycophenolate mofetil, antimalarial, glucocorticoid use), patient's age and tobacco exposure that are variables with p≤0.1 in univariated analysis through linear multiple regression, we found that patient's age (t=4.3; p<0.0001); renal involvement (t=4.8; p<0.0001); seizures (t=4.3; p<0,0001) and higher used dose of glucocorticoid (t=1.9; p=0.04) remained significant.

DISCUSSION

It is estimated that organ damage occurs in 50% of all patients within 5 years of the diagnosis of SLE (13). Cumulative damage includes non-reversible changes in organs and system affected by the disease or inter-current diseases and their therapy (12). Accrual damage has been associated with mortality (8). The present data analysis suggests that the renal and central nervous system manifestations, higher dose of glucocorticoid and age impact the cumulative damage in SLE Brazilian patients.

Renal and central nervous system are among the most feared lupus complications. Glomerulonephritis occurs in up to 60 percent of patients with this disease and is a major source of morbidity (14). Approximately 10 to 30 percent of patients with proliferative lupus nephritis progress to end-stage renal disease (7) and association of renal disease with higher cumulative damage has already been described by others (3,5,6,8). Interestingly we have found association of SLICC with renal disease but not with the presence of anti-ds DNA. Although this autoantibody is considered a marker of renal involvement, it is possible that not all circulating anti-dsDNA antibodies in SLE are necessarily nephritogenic (9). A study that compared 14 patients with both anti-dsDNA antibodies and active nephritis with 14 patients who had anti-dsDNA antibodies but no nephritis, found that the plasma anti-dsDNA antibodies in these two groups were indistinguishable based upon isotope, charge, or cross-reactivity

with histones although clinically they behaved differently (9). Furthermore, dissociation of anti-dsDNA presence and renal disease in Brazilian population has already been noted (15).

Early damage has been linked to neurological involvement in a study in 82 patients by Bezerra et al (5) and neurological disease is also associated with patient's unemployment (10,16). Seizure in SLE usually represents single isolated events while recurrent seizures (epilepsy) are less common but have a significant impact on morbidity and mortality (17). According to Kovaks et al (18) convulsion, vascular accident, transverse myelitis and other focal neurological manifestations are related to a worse prognosis with higher mortality than diffuse neuropsychiatric manifestations such as psychosis. Accordingly, in the present study, convulsions but not psychosis remained associated with SLICC after multivariated adjustment.

At present we found that exposure to glucocorticoid was associated with higher cumulative damage. Glucocorticoid use in lupus is a double edge sword. While this drug is lifesaving in severe flares, its use is associated with a wide spectrum of side effects. Impaired cellular and humoral immune functions seen in patients with SLE favor infection which risk is increased by glucocorticoid use (19). Infections are a leading cause of death in SLE patients (19). Cataracts, osteonecrosis, osteoporosis, glucose intolerance, dyslipidemia are some other side effects that are responsible for a great deal of damage seen in these patients (20). A study in 525 patients (21) suggests that while low dosage of prednisone does not result in a substantially increased risk of irreversible organ damage, the chances increase with prednisone dose. Zonana-Nacach et al (22) found that cumulative prednisone dose was significantly associated with the development of osteoporosis fractures (RR=2.5, 95%CI 1.7-3.7), symptomatic coronary artery disease (RR=1.7, 95% CI 1.1-2.5) and cataracts (RR=1.9, 95% CI 1.4-2.5). Each additional 2-month exposure to high-dose prednisone was associated with a 1.2 fold increase in the risk of both avascular necrosis (95%CI 1.1- 1.4) and stroke (95%CI 1.0- 1.5).

Although we could not study cumulative dose of glucocorticoid due to difficulty to calculate it, we found that the higher daily doses ever used were associated with higher cumulative damage.

In the current study we could not demonstrate the influence of the ethnic background in the cumulative damage. The role of ethnicity in morbidity and mortality by SLE has been demonstrated by several authors (13,23,24) that found that African-American, African-Caribbean and Hispanic patients have worse prognosis when compared to Caucasians. It is necessary to note that the Brazilian population is highly mixed and the ethnic background does not always correspond to external appearance.

CONCLUSION

Summarizing, renal involvement, seizures, older age and higher glucocorticoid use are associated with higher cumulative damage in Brazilian lupus population.

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