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SECTIONS

ORIGINAL ARTICLES

REVIEW ARTICLES

Cheers!!!

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Cheers!!!
Here's to the numerous achievements of this innovative health system!!!

Let us honor and reward those responsible for these victories!!!

Let us sit at the same table, walk alongside them, and become one of them...

It is humanly impossible to understand how it is possible to produce so much, with so little resources, so little power, so little time and so little policy. There is so much evidence of the benefits that the words written here would be insufficient to describe it, especially in relation to the important results obtained in one's personal healthcare.

So, struggling not to hold back on the truth, without minimizing the recognition of such evidence, I will limit myself to ten (10) minor aspects, in which the results are not very visible and palpable, but can clearly illustrate these actions and their effects.

Action nº 1: standardizing conducts for various clinical situations, through evidence-based guidelines. **Effect nº 1:** homogeneity and equity in healthcare for all patients, to the point of not identifying differences in the quality of the public and private systems.

Action nº 2: releasing (all based on scientific evidence) the register of medications, but at the same time not clearing its use in the public system. **Effect nº 2:** conflict and chaos in decision making, putting physicians, patients and service providers against each other.

Action nº 3: valuing physicians and healthcare professionals, providing them with optimal working conditions. **Effect nº 3:** irresistible attraction among physicians and professionals to work mainly in the public system, including "international physicians" who voluntarily cooperate with the program.

Action nº 4: involving the judiciary in decision-making in health, as evidence of scientific credibility and multidisciplinary vision. **Effect nº 4:** judges take on a role that does not belong to them, and for which they are not prepared, although despite this they have to defend the rights denied to patients.

Action nº 5: minimal and improper investment in public health policies, maintaining the epidemic incidence of old and new diseases in the territory. **Effect nº 5:** standing out on the world scenario as an exporter of diseases, but always with a certain degree of internal exclusivity.

Action nº 6: regulating the release of diagnostic procedures, based on evidence and with fair distribution in the territory. **Effect nº 6:** encouragement and consolidation of the culture of "overdiagnosis" in society, where doing more, no matter what it entails, is better than doing nothing or doing less.

Action nº 7: regulating the indications for therapeutic procedures, and encouraging shared decision-making between physician and patient. **Effect nº 7:** world record holder in unnecessary and inadvisable procedures (such as cesarean section), with physician and/or patients attributed with co-authoring this record.

Action nº 8: using evidence in the fight against futility and waste, the applicability to the individual, and the implementation according to a loco-regional distribution of the main problems. **Effect nº 8:** achievement of economic sustainability in health and the strengthening of primary care.

Action nº 9: providing health services properly throughout the entire territory, guaranteeing the necessary minimum, attending to differences in local priorities, measuring the results, and modulating strategies. **Effect nº 9:** improvement of health indexes and achievement of patient satisfaction.

Action nº 10: educating based on scientific evidence, with masters of strange languages, who teach what they do not do, do not understand what we write or speak, but who cares? What matters is that everyone wins. **Effect nº 10:** Effects nº 1 to nº 10.

Numerous other actions could be described here, but these would redundantly lead to the same conclusions: the scientific evidence created in this country (or these countries), the values and preferences of its patients, and the experience of its physicians were, until recently, the mainstay support in decision-making for these innovative systems of private and public health.

RAMB, the *Journal of the Brazilian Medical Association*, has been a vehicle for selfless and competent minds who strive every day to produce scientific evidence to be used in the best care for our patients. Each edition serves as a

living memory that records the results of that effort, allowing it to be measured, used, and never forgotten.

This editorial was also written to register a few of the results measured in an innovative health system, lest we forget those (the "system" is not a person) who have innovated the healthcare of their patients and, lastly, so we could reflect on the usefulness and adoption of these "parents", because in their world there is no threat of change or variation, although there is and always will be the appropriate toast to their health!!!

Nutritional therapy assessment – Outpatient mobility monitoring (MAM)

Avaliação nutrológica – Monitorização ambulatorial da mobilidade (MAM)

Authorship: Associação Brasileira de Nutrologia (Abran)
Participants: Ribas DF[1], Simões RS[2], Buzzini RF[2], Kelman G[2], Bernardo WM[2]
Final draft: March 11, 2016

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Evidence collection method

This policy followed the pattern of a systematic review with retrieval of evidence based on the principles of evidence-based medicine (EBM), according to which clinical experience is integrated with the ability to critically analyze and rationally apply scientific information, thus improving the quality of medical care. EBM uses existing scientific evidence available at the time, with good internal and external validity, applying its results to the clinical practice.[1,2] (**D**)

Systematic reviews are considered today as level I evidence for any clinical question as systematically summarize information on a particular topic based on primary studies (clinical trials, cohort studies, case-control or cross-sectional studies). The method used for this is reproducible, and integrates information on effectiveness, efficiency, efficacy and safety.[1,2] (**D**)

We use a structured way to ask the question, summarized by the acronym PICO, where P is the patient or population, I intervention or indicator, C comparison or control, and O is the outcome. Based on structured question, the keywords or descriptors that will form the basis of the search for evidence in the various available databases are identified (Annex I).[1,2] (**D**)

Clinical question

What is the role of outpatient mobility monitoring (MAM) in the monitoring of physical activity and energy expenditure in children, adolescents or adults?

Grade of recommendation and strength of evidence

A: Experimental or observational studies of higher consistency.
B: Experimental or observational studies of lower consistency.
C: Case reports/non-controlled studies.
D: Opinions without critical evaluation, based on consensus, physiological studies, or animal models.

Objective

To determine the role of outpatient nutritional therapy assessment in the monitoring of physical activity and energy expenditure of children, adolescents and adults.

Conflict of interest

No conflict of interest was declared by the participants in the development of this guideline.

Introduction

Physical activity is an important health indicator and regular practice provides a broad spectrum of benefits, impacting on the prevention of cardiovascular risk factors and the development of chronic diseases such as obesity, type 2 *diabetes mellitus*, dyslipidemia and hypertension.[3] (**D**) Epidemiological studies have unequivocally demonstrated that mortality from any cause is lower among physically active individuals in contrast to that observed in inactive individuals, respecting the parameters of age, gender, and co-morbidities.[4,5] (**B**) Furthermore, it has been noted that the adequacy of the lifestyle, including the practice of physical activity, is related to a reduction of all causes of mortality, showing unique importance in maintaining functional independence and good quality of life in the elderly population.[6] (**B**) Physical activity as a form of therapeutic exercise is also important in rehabilitation programs for cardiovascular, neuromuscular, motor control and cortical plasticity aspects.[7] (**B**) Thus, with the measurement of physical activity becoming more common in clinical practice, it is imperative to search for simple, practical and non-invasive tools that are suitable for assessing the level of physical activity and energy expenditure.

What are the assessment methods for physical activity and energy expenditure?

Although individuals are able to describe their daily physical activity habits in general terms, detailed and accurate measurement is an extremely difficult task because it is

a complex and multidimensional health-related behavior. The literature has described a variety of measurement methods and techniques, which are classified as direct and indirect. Examples of direct techniques include the use of double labeled water, calorimetry, and portable monitoring through the use of heart rate monitors, pedometers and accelerometers. As for indirect methods, we can highlight questionnaires, and self-reports involving the use of instruments in the form of self-administered questionnaires, interviews and activity diaries.[8-10] (**D**) The combination of the calorimetry and doubly labeled water measurements provides a method for accurate measurement of energy expenditure due to physical activity. However, they require specific knowledge for application and interpretation of the results, in addition to being expensive and inconvenient when used in large populations. Direct calorimetry is based on measuring the amount of total heat produced by the body in a given period of time. In turn, indirect calorimetry is based on the total amount of energy produced from the oxygen consumed in the use of energy substrates and the production of carbon dioxide eliminated by breathing.[11] (**D**)

The method of double labeled water is considered the gold standard for determining energy expenditure. It is based on the ingestion of water labeled with radioactive isotopes of oxygen and hydrogen (the oxygen isotope is eliminated from the body incorporated into carbon dioxide molecules and water; the hydrogen isotope is eliminated only as water). As such, the difference between these two isotopes can predict the measurement of carbon dioxide production and thereby the energy expenditure, indirectly.[12] (**C**) This technique is accurate in assessing the energy expenditure. However, it does not enable an analysis of the type of physical activity, which is the main limitation of this method.

Traditionally, subjective methods such as self-administered questionnaires, notes in diaries and interviews (surveys) are the techniques used the most for estimating the total amount of daily or weekly physical activity, remaining as low-cost tools, and the option used the most in epidemiological studies.[7] (**B**) Nevertheless, there are limitations inherent in these instruments, given that they ate dependent on individual observation and subjective interpretation and therefore prone to inconsistent evaluations. The use of motion sensors such as accelerometers and pedometers has been consolidated as the most frequently used objective methods for measuring physical activity.[8] (**D**)

A study analyzing the Physical Activity Scale for the Elderly (PASE) questionnaire aimed at quantifying the level of physical activity in patients undergoing total knee arthroplasty demonstrated deficiencies in the validity and reproducibility of the results when compared to the accelerometer.[13] (**B**) However, in view of the low cost and simplicity, in epidemiological research, especially large-scale observational studies, questionnaires are generally used in the assessment of physical activity, with measurement of varying complexity from the self-administered form to interviews.

Questionnaires generally provide descriptions of the patterns of physical activity and can estimate how much energy individuals spend on a given activity. However, despite their large scale applicability, the reliability and validity of the measurement are low.[14,15] (**B**) A systematic review conducted in order to evaluate questionnaires aimed at the young population (under 18 years of age) found that none of the 61 questionnaires identified were reliable and valid. The same findings were identified when the focus of the analysis was the adult population.[16,17] (**A**) To compare the subjective methods (via questionnaires) with the objective methods (using accelerometers), for the assessment of physical activity in the population of children and adolescents (from 3.7 to 19 years), it has been shown that subjective methods overestimated physical activity by more than 70% to the detriment of the objective methods.[18] (**A**)

Another method for the objective assessment of physical activity is heart rate monitoring based on the linear relationship between heart rate and energy expenditure. Relatively inexpensive and with the capacity for minute by minute heart rate storage, continuous recording by means of monitors is a method considered feasible and attractive for the assessment of physical activity. However, factors such as age, proportion of muscle mass, emotional and cardiorespiratory stress, state of hydration and fatigue can influence the heart rate/oxygen consumption ratio. Another limitation is due to the fact that monitoring can mask the patterns of activity given that even after the cessation of motion the heart rate tends to remain high, and that in sedentary individuals the heart rate measured over 24 hours barely surpasses the rest limits, making it difficult to distinguish between light and moderate activities.[19] (**D**)

On the other hand, mechanical and electronic motion detectors such as pedometers and accelerometers eliminate many problems of subjectivity by providing an objective measurement of physical activity. However, as with all assessment methods, they possess measurement limitations, such as the ability to discriminate the different activity types and the seasonal bias inherent at the moment when the mechanical device is applied.[20] (**C**)

Pedometers are the simplest portable sensors used for monitoring human movement and record movements in response to vertical acceleration. Using a mechanism that detects the impacts produced by steps during locomotion, it is possible to calculate the distance covered and therefore the energy expenditure. The main disadvantages are the inability to evaluate static activities, isometric exercises and activities involving the arms, thereby resulting in inaccurate energy expenditure estimates. To analyze the effectiveness of physical activity based on the use of pedometers among adults in an outpatient setting, a study identified that pedometer users significantly increased their physical activity by around 2,500 steps per day compared to participants in the control group (who did not use the pedometer), as well as being associated with a reduction in body mass index and systolic blood pressure.[21] (**A**) Another systematic review analyzing the use of the pedometer identified that this intervention provided a modest, yet significant reduction in body weight, while the magnitude of the weight loss was associated with the time using the device.[22] (**A**) The use of pedometers by overweight or normal weight children was identified as an imprecise method at slower speeds, and was shown to be more accurate at higher speeds. For the control group, a smaller error was identified at all speeds, and it was concluded that for overweight or obese children the use of the pedometer is related to a lack of precision.[23] (**B**)

Accelerometers are electronic devices that measure the acceleration of body's movement in the vertical and horizontal direction by means of a microprocessor that scans and filters the acceleration signal and converts it into a numerical sign, presenting this value as movement counts over a time interval. As such, they provide an objective way of quantifying the frequency, duration and intensity of physical activity given that they are able to assess the magnitude and the total volume of movement as a function of time. They are classified into uniaxial, unidirectional or triaxial, based on their ability to measure the acceleration of movement on one or more planes (vertical, mid-lateral and anteroposterior).[24] (**D**) The combination of heart rate monitoring and accelerometer as a way of measuring energy expenditure compensates for the limitations of both techniques, especially with regard to discriminating between different types of physical activity. A study with the aim of estimating energy expenditure used the combination of accelerometry and heart rate as a measurement method, identifying a good level of agreement with the adopted gold standard (double labeled water).[25] (**B**)

Recommendation

Technological development has enabled the establishment of techniques for the assessment of physical activity and the quantification of energy expenditure. Each method has advantages and disadvantages that depend heavily on the type of activity, age group and body composition. As such, until an instrument that fulfills all of the desired features is identified, a combination of methods could provide more reliable and accurate data. It is important to apply an objective questionnaire that helps monitor the increase or reduction in physical activity, as well as to identify the style of activity practiced, which may be associated with heart rate monitoring and accelerometry.

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Annex I

Clinical question

What is the role of outpatient mobility monitoring (MAM) in the monitoring of physical activity and energy expenditure in children, adolescents or adults?

Structured question

P: Children, adolescents or adults
I: Outpatient ambulatory monitoring
C: ----------
O: Monitoring of physical activity and energy expenditure

Strategy for search of evidence

PubMed-Medline

Strategy 1: (Weight reduction OR Weight Loss OR Diet, Reduction OR Nutrition Disorder OR Nutritional Disorders OR Nutritional Disorder OR Nutritional Status OR Nutrition Status OR Nutrition Assessment OR Nutrition Disorders OR Malnutrition OR Deficiency Diseases OR Overnutrition OR Obesity OR Avitaminosis OR Ascorbic Acid Deficiency OR Vitamin A Deficiency OR Vitamin B Deficiency OR Vitamin D Deficiency OR Vitamin E Deficiency OR Vitamin K Deficiency OR Magnesium Deficiency OR Potassium Deficiency OR Protein Deficiency OR Protein-Energy Malnutrition OR Swayback OR Scurvy OR Choline Deficiency OR Folic Acid Deficiency OR Hyperhomocysteinemia OR Pellagra OR Riboflavin Deficiency OR Thiamine Deficiency OR Beriberi OR Wernicke Encephalopathy OR Vitamin B 12 Deficiency OR Anemia, Pernicious OR Subacute Combined OR Degeneration OR Vitamin B 6 Deficiency OR Rickets OR Osteomalacia OR Renal Osteodystrophy OR Steatitis OR Kwashiorkor OR Overweight OR Obesity, Abdominal OR Obesity, Morbid OR Wasting Syndrome) = 623,855.

Strategy 2: (Activities of Daily Living OR Mobility OR Wireless Technology OR Motor Activity OR Physical Activity OR Daily Ambulatory Activity OR Walking OR Exercise Test OR Energy OR Monitoring, Ambulatory OR Ambulatory Monitoring of Mobility) = 1,029,052.

Strategy 3: (Strategy 1 AND Strategy 2) = 77,330.

Methodological search filter: (Strategy 4) = ((specificity[Title/Abstract]) OR random* OR ((prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract]))) = 1,813,617.

Total 1[a] Retrieval: (Strategy 3 AND Strategy 4) = 12,535.

Studies retrieved

Database	Number of studies
Primary	
PubMed-Medline	12,535

Number of studies retrieved using search strategies. Final search: 12/20/2014.

Exclusion criteria

Selection of studies, assessment of titles and abstracts obtained from the search strategy in the consulted databases was conducted by two researchers with skills in the preparation of systematic reviews, both independent and blinded, who separated the studies with potential relevance. Whenever the title and the summary were not enlightening, researchers sought the full article.

Articles that did not meet the specificities of PICO, that were not available for access in full, and those written in languages other than English, Portuguese or Spanish were excluded.

Primary cutaneous histoplasmosis in an immunocompromised patient with long-standing rheumatoid arthritis

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Introduction

Histoplasmosis is the most common endemic fungal infection in Latin America and North America, and an important cause of endemic mycoses worldwide. The fungus is often present in soil contaminated by feces of birds and bats.[1]

Cutaneous manifestations of histoplasmosis can be divided into primary and secondary lesions.[2] Once the fungus undergoes early hematogenous spread, exclusive cutaneous presentation is rare even in immunosuppressed patients, and thus these patients usually present severe systemic disease.[3]

Primary cutaneous histoplasmosis is a rare form of presentation initially described in 1947,[4] with only 23 cases reported in the literature to date.[5]

We report the case of an immunocompromised patient with rheumatoid arthritis (RA) who developed, unexpectedly, primary cutaneous histoplasmosis (PCH).

Case report

The patient, a 52-year-old man, presented clinical, laboratory and radiological findings compatible with RA since childhood. As the disease progressed, regardless of a variety of therapies employed, he developed major deformities of the hands, wrists, elbows, hips, knees and ankles. Recently, using low-dose prednisone and methotrexate, he suddenly presented nodular ulcerated lesions on the face as seen in Figures 1 and 2. The diagnostic hypotheses were cutaneous lymphoma, leishmaniasis, sporotrichosis, cryptococcosis, cutaneous tuberculosis, histoplasmosis and tertiary syphilis. Histological examination showed diffuse granulomatous infiltrate with the presence of intracytoplasmic yeast structures (Figure 3). Curettage was performed for culture of material from the necrotic-suppurative areas of ulcerated lesions. *Histoplasma capsulatum* was the fungus detected by direct mycological examination (Grocott staining). The chest radiograph was normal. Blood cell count was unremarkable. After 6 months of therapy using itraconazole 300 mg daily, the nodules on the skin of the face disappeared. The patient continued to be monitored after completion of treatment without any disease recurrence signals.

Discussion

Histoplasmosis is a disease caused by the dimorphic fungus *Histoplasma capsulatum*, which is common in tropical and temperate countries. The usual form of presentation is the respiratory one, second to inhalation of airborne conidia.[6]

In our immunosuppressed RA patient, a disseminated form of histoplasmosis would be the expected presentation, but atypical PCH turned out to be the final diagnosis. Primary cutaneous histoplasmosis has been described in immunocompetent individuals, but reports of this form of presentation in immunocompromised are rare. Today, it is clear that the infection is the result of a complex interaction between pathogen and host.[7]

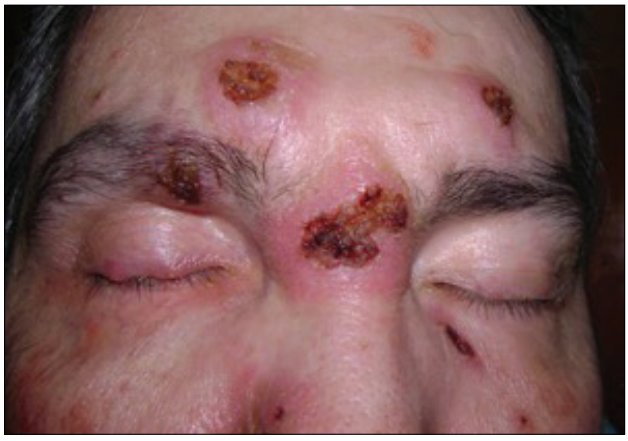

FIGURE 1 Ulcerated nodular lesions in the frontal region.

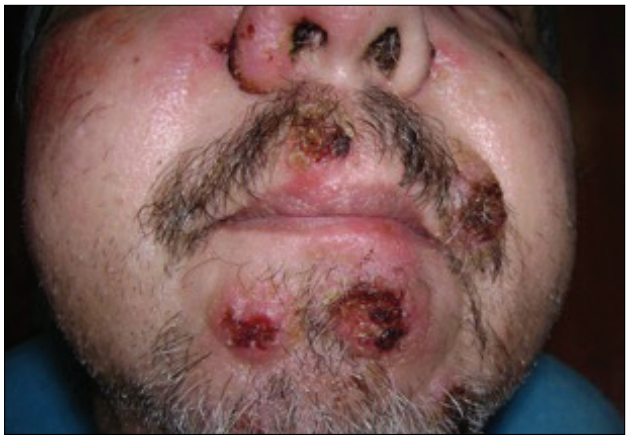

FIGURE 2 Detail of ulcerated nodular lesions in the chin region.

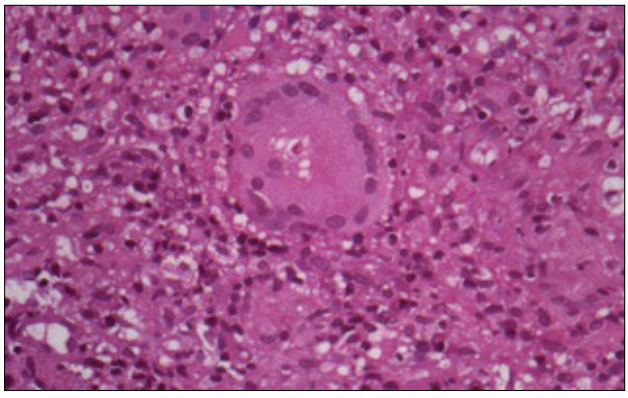

FIGURE 3 Histopathological examination, HE 400x.

The patient presented lesions with no regional lymphadenopathy and no evidence of systemic involvement. Also, *Histoplasma capsulatum* was isolated and identified. There were only a few descriptions of PCH in patients with autoimmune rheumatic diseases such as the current case.[5] As previously reported,[3] the use of itraconazole as therapy of choice yielded complete response.

In summary, we describe an unusual case of PCH in a patient with long-standing RA treated with steroids and methotrexate. We stress the need for histological and mycological examination of skin lesions suspected in such patients.

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Endoscopic ultrasound in the diagnosis of foreign bodies of the colon and rectum

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Summary

Although the ingestion of foreign bodies is a common clinical problem, severe complications such as perforation are rare and occur in less than 1% of cases. Different types of foreign bodies and the various affected regions within the gastrointestinal tract make foreign body ingestion a complex entity, with a wide range of presentation requiring different diagnostic modalities. We report two cases of patients who underwent endoscopic ultrasound for evaluation of subepithelial lesions consisting of foreign body granulomas in the colon and rectum. Colorectal foreign body granuloma is a rare complication after accidental ingestion. Endoscopic ultrasound can be a useful diagnostic tool and can avoid the need for more invasive procedures.

Keywords: foreign bodies, colon, rectum, granuloma, endoscopic ultrasound.

Introduction

Although the ingestion of foreign bodies is a common clinical problem, severe complications like perforation are rare and occur in less than 1% of cases.[1,2] Different types of foreign bodies and the various affected regions within the gastrointestinal tract make foreign body ingestion a complex entity, with a wide range of presentation requiring different diagnostic modalities.

In the last three decades, endoscopic ultrasound has gained importance both as a diagnostic and as a therapeutic tool for gastrointestinal tract disorders. Ten years ago, 60% of gastroenterologists were already using endoscopic ultrasound in the United States.[3-10] However, in other parts of the world such as Brazil, this method is still not widespread, especially within the public health system and in rural regions.

We report two cases of patients who each underwent endoscopic ultrasound for evaluation of colorectal subepithelial lesions consisting of foreign body granulomas.

Case 1

A 62-year-old healthy white male was referred for endoscopic ultrasound after a screening colonoscopy that showed two elevated lesions adjacent to each other in the ascending colon. The lesions measured approximately 10 mm and 7 mm in their greater diameter, had normal appearing covering mucosa, which was firm to compression with closed biopsy forceps (no pillow-sign); biopsies were not performed (Figure 1).

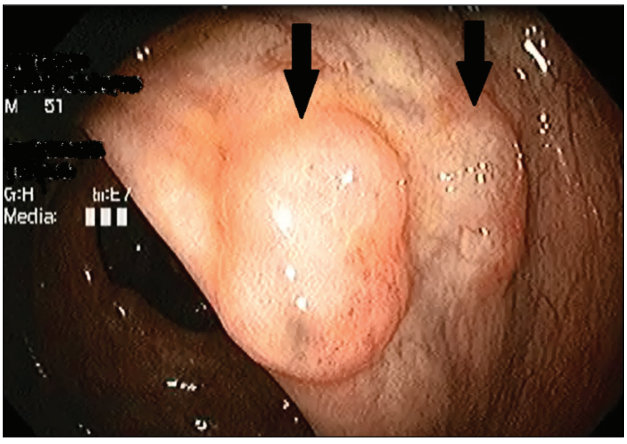

FIGURE 1 Colonoscopic view of subepithelial lesions in the ascendant colon (black arrows).

Laboratory examinations were normal. Endoscopic ultrasound showed hypoechoic oval lesions arising from the submucosal layer, with a linear hyperechoic image within the lesions. These were suggestive of granulomas secondary to a foreign body reaction, probably due to a fishbone (Figure 2). The patient was informed of the findings and expectant management was indicated. CT scan was performed to exclude other abnormalities and future follow-up by colonoscopy was indicated.

Case 2

A 51-year-old healthy white male was referred for endoscopic ultrasound after the finding of a subepithelial rectal lesion, measuring approximately 10 mm in its greater diameter, with discrete mucosal enanthema and central umbilication on screening colonoscopy (Figure 3). Biopsy has shown mild unspecific inflammatory changes in the mucosa. A concomitant lesion was seen in the ascending colon with a pale yellow color and soft consistency to the touch (pillow sign present), considered to be a lipoma.

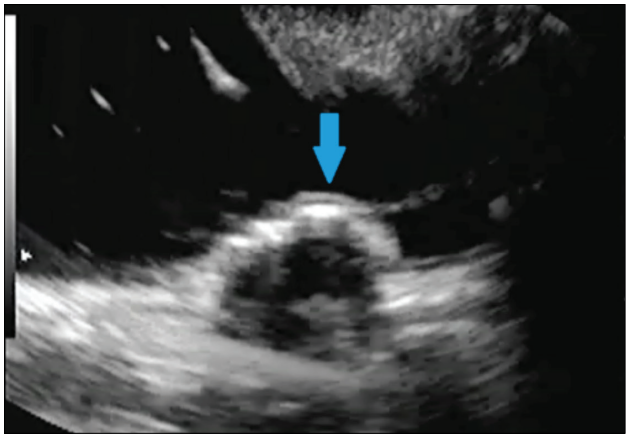

FIGURE 2 Endoscopic ultrasound image – hypoechoic nodule with a linear hiperechoic image in its interior (blue arrow).

Endoscopic ultrasound showed a lesion with mixed echogenicity (predominantly hypoechoic) and a hyperechoic linear structure in its interior (Figure 4). The lesion was considered a granuloma due to foreign body reaction (the patient reported ingestion of a fishbone a few months prior). The patient underwent expectant management and will be followed up with subsequent proctologic screening.

Discussion

Perforation secondary to ingested foreign bodies has been reported in all segments of the gastrointestinal tract. Acute perforation with extraluminal contamination and sepsis can require emergent surgical treatment. Sharp pointed objects such as toothpicks, needles, dental plates, and fish and chicken bones are usually associated with perforation or penetration in the gastrointestinal organ walls. Foreign body complications can also arise after sutures and in some unusual situations such as formation of a barium granuloma after radiologic examination.[11-13] Most recently, with the advent of endoscopic therapeutic modalities, foreign body reactions are becoming more frequent after positioning of stents (gastrointestinal and biliary) and after injection of materials such as cyanoacrylates for the treatment of varices.[14] Furthermore, the impaction of foreign bodies in the rectum can cause anorectal abscesses and fistulas.

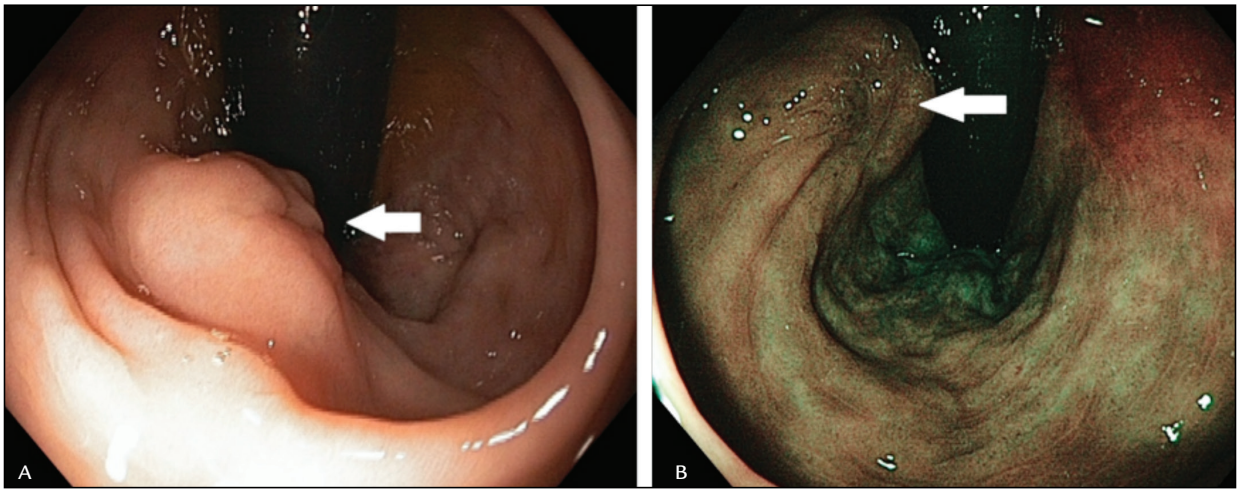

FIGURE 3 A. Colonoscopic view of the rectal subepithelial lesion with central umbilication and mild hyperemia (white arrow). B. Same lesion – NBI view (white arrow).

Diagnosis of foreign body complications can be difficult due to the varied presentation, different types of foreign bodies, unsuspected or a long interim after ingestion, and a wide range of differential diagnosis in the gastrointestinal tract. Foreign body granulomas have been confused with inflammatory bowel disease and tumors throughout the gastrointestinal tract.[11,12,15] Plain radiograph is the most commonly used modality to detect ingested foreign bodies; radiographs can reveal radiopaque objects and also assess the presence of pneumoperitoneum in cases of perforation.[16] In cases of radiolucent objects, computed tomography appears to be the modality of choice and can show the presence of abscess, free air, and any involvement of the surrounding structures.[17] Endoscopic ultrasound images can vary according to the type of foreign body. Wood and plastic materials tend to produce acoustic shadow, metals are typically hyperechoic and cause reverberation, and glass is hyperechoic but does not cause reverberation. The inflammatory reaction can lead to a hypoechoic ring around the foreign body. Parasites produce hyperechoic images with a hypoechoic band in its interior and transverse images show a targeted lesion.

Gastrointestinal lesions such as gastrointestinal stromal tumors (GIST) and neuroendocrine tumors usually present as hypoechoic lesions. Some gastrointestinal tumors can show a hyaline deposition under the mucosa and increased refringence; this is an important differential diagnosis. A definitive diagnosis of a small foreign body granuloma is typically made by the pathologist after its removal, but sometimes an invasive procedure can be avoided.

The follow-up regimen of patients with foreign body granulomas is unclear. Since most published studies are case reports, there are no algorithms to monitor these patients. A long chronic course has been reported such as in a patient who required colonic resection secondary to foreign body ingestion 10 years prior.[18] The patient had an inflammatory tumor after perforation of the transverse colon. He underwent examinations for abdominal pain and a palpable mass was found on physical examination. Conversely, resolution without any long-term consequences has also been reported. Kikuchi et al. reported the case of a patient with an esophageal foreign body causing a granuloma. The authors repeated esophagogastroduedonoscopy, esophagography and CT after one year and reported a progressively smaller lesion and no identifiable foreign body.[19]

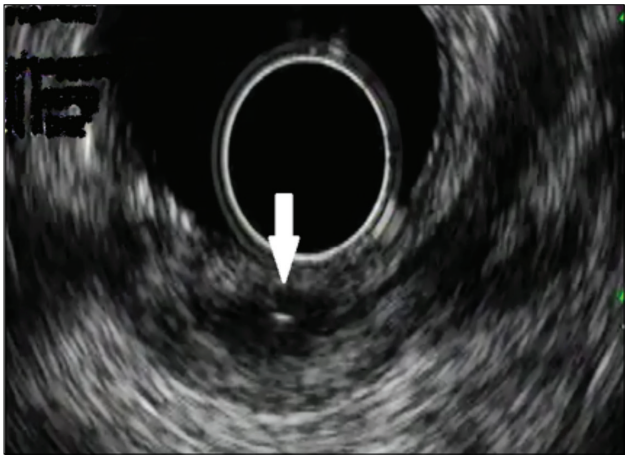

FIGURE 4 Endoscopic ultrasound images of the rectal lesion showing a predominantly hypoechoic lesion with a linear hyperechoic image in its interior (white arrow).

Conclusion

Colorectal foreign body granuloma is a rare complication after accidental foreign body ingestion. Endoscopic ultrasound can be a useful diagnostic tool and can avoid the need for more invasive procedures.

Resumo

Ultrassonografia endoscópica no diagnóstico de corpos estranhos no cólon e no reto

Embora a ingestão de corpos estranhos seja uma condição clínica frequente, complicações graves como perfuração são raras e ocorrem em menos de 1% dos casos. Tipos diferentes de corpos estranhos e as diversas regiões afetadas do trato gastrointestinal fazem da ingestão de corpos estranhos uma entidade complexa, com uma variada gama de apresentações, demandando várias modalidades diagnósticas. Nós reportamos dois casos de pacientes que foram submetidos à ultrassonografia endoscópica para avaliação de lesões subepiteliais, consistindo em granulomas de corpo estranho no cólon e no reto. Granulomas de corpo estranho colorretais são uma complicação rara após ingestão acidental. Ultrassonografia endoscópica pode ser uma ferramenta diagnóstica útil e pode evitar procedimentos mais invasivos.

Palavras-chave: corpos estranhos, colo, reto, granuloma, ultrassonografia endoscópica.

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Black coated tongue in integrative medicine: An alarm signal

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Introduction

In integrative medicine (IM), western medicine (WM) is associated with other non-conventional medicines, provided these are based on scientific evidence.[1] All events are considered as part of the individual's health/disease process, which includes physical, mental, emotional and environmental factors. Traditional chinese medicine (TCM) includes the inspection of the tongue as an important means for diagnosis and prognosis of disease.[2]

In WM, black coated tongue is associated with smoking, the use of medication such as antibiotics or corticosteroids, radiotherapy, or poor oral hygiene. It is considered a benign change resulting from decreased apoptosis of the epithelium on the dorsum of the tongue, with consequent elongation of the papillae and modification of the local flora, with an increase of fungi and chromogenic bacteria.[3-5] Resolution is spontaneous, or involves removal while brushing the teeth and tongue.[4] In TCM, however, it has another meaning. It demonstrates a state of internal heat[2] with extreme decompensation of the internal equilibrium, with a tendency towards the emergence of diseases.[2,6]

Case report

A 72-year-old female patient had a photo of her tongue recorded during a tongue inspection course. Darkened, blackish-looking coating was seen in the posterior region of the tongue, and she was sent for monitoring. There was also a severe deviation of the tongue to the left. This procedure was adopted in the service after a case monitored in the outpatient clinic, reported in an article published in 2014.[7] She had no current complaints, except a burning sensation on the tongue for a year, which she considered normal.

She reported initial insomnia with interruptions due to nocturia, *diabetes mellitus* type 2 currently controlled with a hypocaloric diet, and metrorrhagia, with a diagnosis of uterine fibroids, submitted to partial hysterectomy at 46 years of age. Also at age 46, she presented suppurative appendicitis and underwent appendectomy. At the age of 62 years, she began to present right-sided flank pain with increased flatulence and alternation between diarrhea and intestinal constipation not related to food. The patient was diagnosed with idiopathic ulcerative rectocolitis. She used oral cortisone for 3 years. She is currently under medical monitoring, with annual control, without the use of medication. At the age of 70 years, she had two non-malignant polyps removed from her stomach. She currently uses vitamin D weekly for replenishment, omega 3, 6 and 9 and coenzyme Q10.

On physical examination, she presented a distended abdomen, tympanic to percussion, with diffuse light pain on deep palpation. The tongue was diverted with a black coating in the posterior region (root) (Figure 1).

Discussion

Inspection of the tongue has been carried out for a long time in WM. Several studies have described the atypical features of the tongue.[3-5] Some are observed in diseases, such as pale color of the tongue or lack of taste in anemia, and macroglossia in Down's syndrome and hypothyroidism.[8] However, many conditions, such as geographic tongue, fissures and abnormal coatings have been con-

sidered as benign and without clinical significance up to now.[3-5] Black coated tongue is reported as a nonspecific change in some pathological conditions, but its etiopathogenesis is still unclear. In TCM these characteristics (and many other) inform the state of the internal functioning, guiding the diagnosis, prognosis and treatment of diseases.[2,6,9]

It is possible to assess risk situations with a systematic assessment of the tongue's characteristics.[10] Although the patient did not have a current complaint, her personal and family history indicate the need for periodic medical monitoring, with investigations for tumor markers, which was already undertaken some years ago (Chart 1).

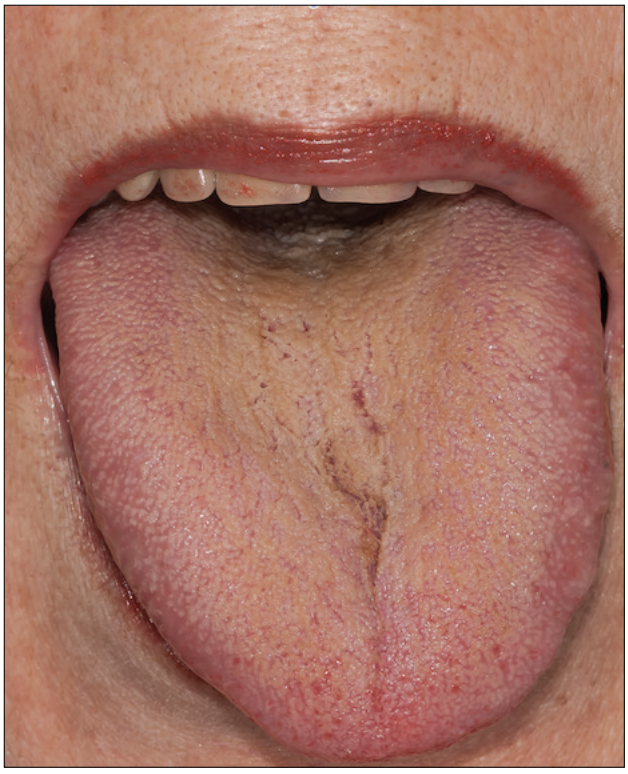

FIGURE 1 Tongue with black coating in the posterior region, and deviation to the left.

Clinical monitoring was undertaken without intervention. After 3 months, there was worsening of abdominal pain, and a digestive endoscopy showed nonerosive distal esophagitis, hiatal hernia with minor sliding, and mild antral erosive gastritis. Eight months after the first assessment, the doctor undertaking routine monitoring requested control tests that revealed high tumor markers CEA, CA 19-9 and CA 125 (Chart 1). This motivated the request for imaging examinations to investigate tumors in the abdomen and central nervous system (ultrasound and tomography of abdomen and skull), which were normal. Clinically, she presented worse abdominal and lower back pain.

Given the overall clinical assessment, no medication was prescribed. In the TCM assessment there was need for intervention based on the history and evolution of the signs and symptoms, as the bizarre changes to the tongue in this patient indicated possible reactivation of ulcerative rectocolitis or even the appearance of tumoral processes.[11,12] The patient underwent abdominal massage (Qi Nei Zang) and systemic acupuncture. After 2 months of treatment, there was less abdominal pain and the examinations normalized (Chart 1). The coating of the tongue became yellow (Figure 2), which shows disease regression, albeit without normalization of the internal heat. According to the clinical parameters and appearance of the tongue,[11] we believe the patient is no longer in a condition of instability and risk of harm, but should still continue the treatment. The "spontaneous" resolution of black coated tongue stated by several authors indicates that the process changes over time, with clinical improvement or worsening, depending on the interventions carried out.

CHART 1 Medical monitoring of tumor markers between 2013 and 2015.

Tests (normal values)	Dates				
	1/16/2013	5/13/2013	7/20/2013	1/24/2015*	4/17/2015**
CEA (up to 3 ng/mL)	-	4.4	5.5	6.2	4.6
CA 19-9 (up to 3.5 U/mL)	54.5	31.8	31.9	51.8	24.6
CA 125 (up to 35 U/mL)	5.7	5.4	-	6.8	5.7

*Tumor markers previously to intervention; **tumor markers 2 months after treatment with acupuncture and abdominal massage (Qi Nei Zang).

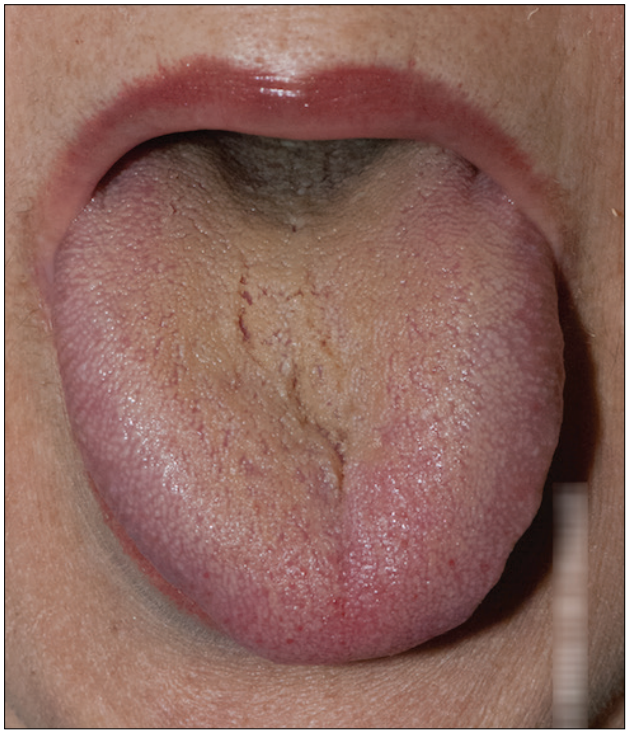

FIGURE 2 Tongue with diffuse yellow coating, with a slight deviation to the left.

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Imaging aspects of Camurati-Engelmann disease

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Case report

A 35-year-old female patient undergoing outpatient monitoring at the Specialist Medical Outpatient Clinic (AME, in portuguese acronym) in Mogi Guaçu, São Paulo, Brazil.

Since childhood the patient has presented generalized pain in the body, mainly in the lower limbs, which has been more intense for the last 2 years, with no relation to physical effort, and which gets worse with changes in ambient temperature. Generalized weakness, reduced muscle strength and discreetly staggering gait have also been reported, as well the use of hearing aids. Faced with these symptoms, the patient sought successive health services, where she only received symptomatic treatment. Due to the persistence of the complaint, she underwent an X-ray of the lower limbs. Based on the radiographic changes found, bone scintigraphy and magnetic resonance imaging (MRI) examinations were requested. There are no known cases in the family.

Results

The MRI revealed exuberant diffuse cortical thickening in the bone diaphyses, increased diameter of both femurs, intramedullary and peripheral femoral hyperintensity focal areas in the T2 weighted sequences, with enhancement after infusion of the intravenous contrast medium, which may correspond to areas of edema or inflammatory activity. The contracting mass of the muscle and subcutaneous plane had a preserved signal (Figure 1).

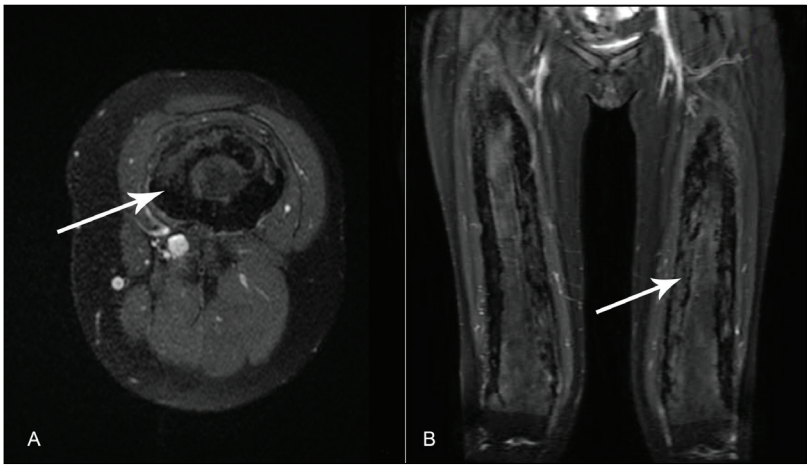

FIGURE 1 A. T1-weighted fat-suppressed cross-section of the left thigh after the intravenous injection of paramagnetic contrast agent. Note the thickening and heterogeneity of the femoral cortex (arrow). The adjacent muscles and subcutaneous tissue are preserved. B. T2-weighted fat-suppressed coronal section of the thighs showing increased diameter of both femurs with irregular thickening of the cortical bone, diffuse central and medullary edema (arrow).

The X-ray of upper limbs, lower limbs and skull also showed diffuse cortical thickening, notably in the bone diaphyses and flat bones, while the bone scintigraphy revealed diffuse increase in osteogenic activity at these sites.

Discussion

It is noteworthy that the involvement of the femurs occurs mainly in the cortical region, restricting diagnostic hypotheses to basically hereditary sclerosing bone dysplasias, particularly those resulting from defects in intramembranous ossification.[2,3] Intramembranous ossification occurs in the cortex of tubular bones (such as femurs) and the flat bones of the skullcap, the upper facial bones, tympanic temporal bones, vomer and medial pterygoid plate.[4] The hereditary disorders related to this type of ossification are: generalized cortical hyperostosis (van Buchem's disease and variants), hereditary multiple diaphyseal sclerosis (Ribbing disease) and progressive diaphyseal dysplasia (Camurati-Engelmann's disease).[4] Although Erdheim-Chester disease is considered part of an acquired (and not inherited) syndrome that simulates sclerosing bone dysplasia,[4] it is also part of the differential diagnosis.[3] Eventually, the possibility of osteopetrosis could be suggested; however, this disorder derives from an endochondral ossification defect (which gives rise to bone marrow)[4] and is therefore an ossification condition of the medullary and not the cortical region.

According to the phenotypic presentation, some of these pathologies can be excluded. In generalized cortical hyperostosis (van Buchem's disease and variants),[4] facial abnormalities occur, such as flattened forehead, elongated jaw and syndactyly of the second and third fingers. Meanwhile, in hereditary multiple diaphyseal sclerosis (Ribbing disease)[4] there is unilateral or bilateral asymmetric/asynchronous involvement of the long bones, typically the tibia and femur,[4] as well as non-involvement of skullcap.[4] Since the patient in this study has atypical fascicles, bilateral and symmetrical bone involvement and cortical thickening in the skull radiography, other diagnostic possibilities would be more likely. These characteristics[4] are seen both in Erdheim-Chester disease (non-Langerhans cell histiocytosis), and in progressive diaphyseal dysplasia (Camurati-Engelmann disease). However, the extra-osseous manifestations of Erdheim-Chester disease (diabetes insipidus, painless bilateral exophthalmos, chronic renal failure, hydronephrosis, pulmonary fibrosis, and heart failure) and associated bone infarcts[4] were not found, as the only comorbidity presented by the patient was dysacusis.

Dysacusis, in turn, is described as one of the symptoms of progressive diaphyseal dysplasia (Camurati-Engelmann disease). Bone involvement in this disease begins in the tibial and femoral diaphyses,[3,5] in a bilateral and symmetrical manner[1,6] progressing to the other long bones with progressive bone deformity. In descending order of frequency, it affects the tibia, femur, fibula, humerus, ulna and radius[3,5] and, more rarely, the middle segment of the clavicles.[4,7] In severe cases, isolated sclerosis in the posterior region of the vertebral body can also be observed.[3,4]

The metaphysis and epiphysis are typically not involved, as these regions are formed by endochondral ossification[4] (Figure 2), although during disease progression they may become involved secondarily.[5]

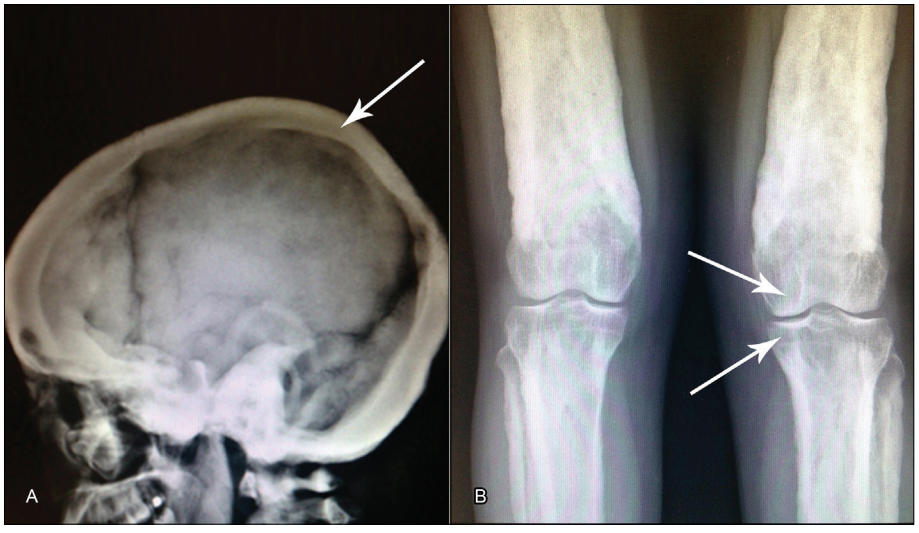

FIGURE 2 A. Radiography of skull in profile. Note the diffuse cortical thickening of the skull cap (arrow). B. Radiography of the knees in anteroposterior view. Preservation of the cortical thickness of the epiphyses of the femurs, tibias and fibulae (arrows) is observed.

In rare cases, sclerosis can be found at the base of the cranium[4] due to an endochondral ossification defect, suggesting the possibility of two forms of progressive diaphyseal dysplasia: a pure one, with exclusive disturbance in intramembranous ossification, and a mixed one, in which there is also the endochondral component.[3] Cranial nerve palsy may develop in such cases. Hearing loss occurs in 18% of cases and may be conductive, through fixation of the staples in the oval window, mixed or sensorineural, due to stenosis of the internal auditory meatus.[7]

Unlike other bone metabolism disorders, in Camurati-Engelman disease low-impact fractures are rare, and there is controversy about neuromuscular impairment[1,5] probably due to the wide variety of phenotypic expressions described.[8]

MRI is as effective as computerized tomography for demonstrating the hyperostotic bone, and the compressive effect on specific cranial nerves (mainly II, VII and VIII) can be characterized well.[2] Perhaps in the near future techniques such as high resolution peripheral quantitative computed tomography (HR-pQCT)[9] could provide additional information.

Increased osteoblast activity can be detected early through skeletal scintigraphy[5] even before the radiographic changes[7] or be normal in some cases.[5] In bone scintigraphy with 99m Tc-MDP, heterogeneous abnormal uptake can be seen in the affected bones[3] in a bilateral and symmetrical manner[1,6] similarly to the findings of our study[3] (Figure 3).

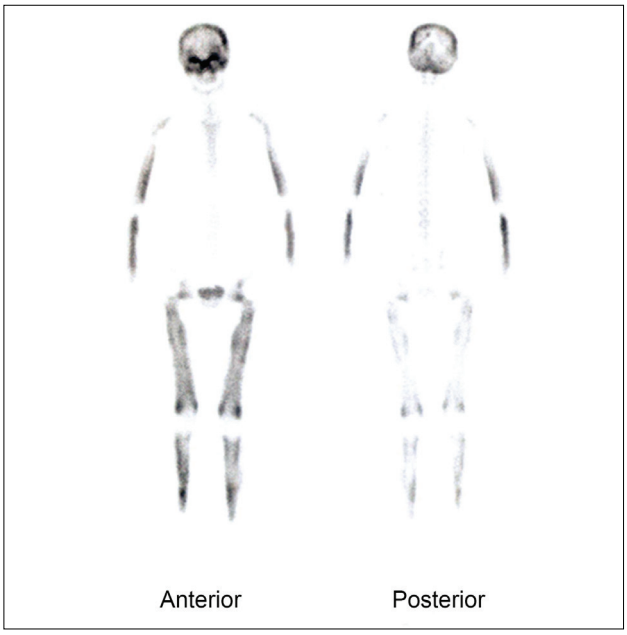

FIGURE 3 Bone scintigraphy after intravenous administration of 99mTc- MDP. Diffuse increase of osteogenic activity in the skull cap and long bones of the upper and lower limbs is observed, suggesting hereditary disease of the bone metabolism.

Conclusion

We were able to guide the diagnostic reasoning based on the image findings and clinical data. Knowledge of the different types of ossification was also fundamental to narrow down the range of differential diagnoses. MRI helps to improve the evaluation of the neuromuscular component in these cases and complements the radiographic images in the analysis of bone changes, in relation to their inflammatory activity and cortical thickening. Despite this being a rare disease whose treatment has been palliative through use of corticosteroids,[2] bisphosphonates (with controversial usage),[5] decompressive surgeries[2] and physiotherapy,[5] doctors must be aware of this possibility in order to avoid late diagnoses and to offer early multidisciplinary support to improve the quality of life of these patients.

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Giant scalp arteriovenous malformation

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Summary

Arteriovenous malformations (AVMs) of the scalp are rare lesions. The clinical picture presents with complaints of increased scalp, scalp disfigurement, pain and neurological symptoms. Its origin can be congenital or traumatic. We present a case of giant scalp AVMs and its management, followed by a brief literature review on the subject. The diagnosis of scalp AVMs is based on physical examination and confirmed by internal and external carotid angiography or computed tomographic angiography (CTA). Surgical excision is especially effective in scalp AVMs, and is the most frequently used treatment modality.

Keywords: scalp, arteriovenous malformations, vascular diseases.

Introduction

Extracranial scalp arteriovenous malformations (AVMs) are relatively rare, accounting for only 8.1% of cases of AVMs.[1] They are vascular aberrations that develop during the fetal period and result from failure of embryonic vasculature to differentiate into arteries and veins.[2] Although controversy exists regarding the cause of these lesions, it is generally accepted that they may be either congenital or traumatic in origin.[3]

The clinical picture is characterized by increased scalp, scalp deformation, pulsatile mass, headache, tinnitus, convulsion, bleeding and dizziness, but it can often be asymptomatic. Diagnosis of AVMs is based on physical examination and confirmed by internal and external carotid angiography, or computed tomographic angiography (CTA).[4] Treatment options include endovascular occlusion, direct percutaneous injection of sclerosing agents and, in selected cases, surgical resection.[5]

We present a case of scalp AVM and its management at our institution. We provide below a brief literature review and some commentaries regarding the clinical and radiological features of this rare entity.

Case report

We present the case of a 33-year-old male with a complaint of a pulsatile and increasingly bigger mass within the left temporo-occipital region of scalp for 3 years. There was no previous trauma. We identified an area of focal thickening of the scalp, above the lateral and occipital skull surfaces, soft and pulsatile on palpation. There was no audible bruit or any abnormalities on neurologic examination. The CTA demonstrated a lesion of vascular nature, presumably an arteriovenous malformation beneath the scalp. There was a nidus fed by branches from ipsilateral superficial temporal and occipital arteries (Figure 1). There was no communication with the intracranial circulation. The treatment of choice was surgical, with ligation of the feeder branches without scarifying parent vessels, with total excision of the malformation. Scalp irrigation was preserved (Figure 2). Postoperative period was uneventful, and postoperative CTA showed no significant and/or pathologic vessels left (Figure 3).

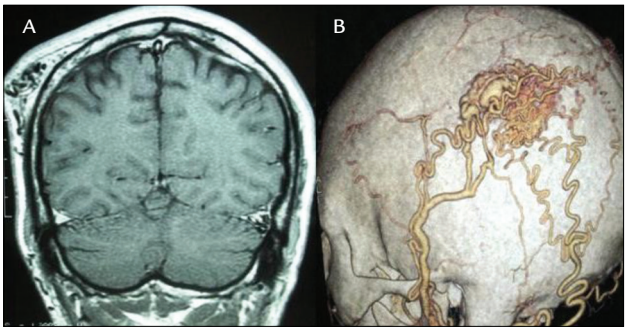

FIGURE 1 A. Coronal T1-W MRI showing the scalp AVM on the left parieto-occipital region. B. Markedly dilated superficial temporal and occipital arteries supplied the nidus; a draining vein can also be seen.

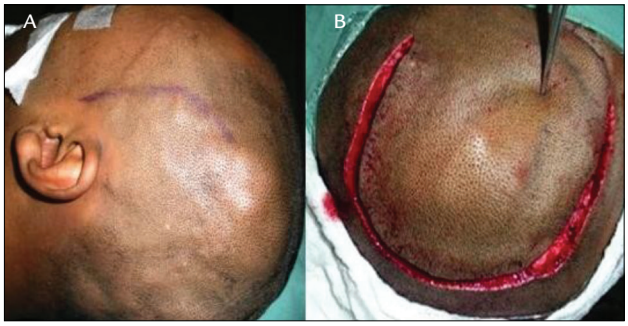

FIGURE 2 A. Soft thickened scalp can be seen above the left temporal and occipital skull surfaces, corresponding to the scalp AVM. B. A horseshoe incision was made with a view to preserving scalp irrigation, critical to the success of the surgery.

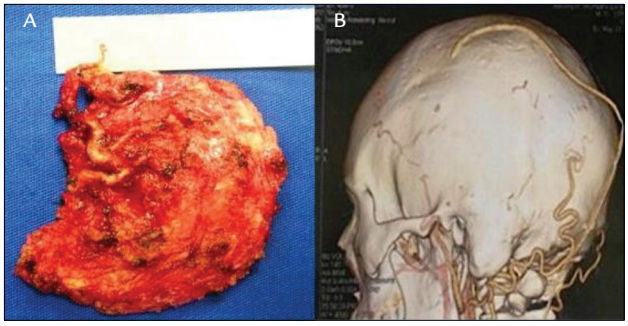

FIGURE 3 A. The scalp AVM shown after *en bloc* resection. B. Postoperative CT showing no significant and/or pathologic vessels relative to the AVM.

Discussion

AVMs of the scalp are abnormal fistulous connection between the feeding arteries and draining veins, without an intervening capillary bed within the subcutaneous layer. Their rarity and unpredictable behavior render systematic studies, assessment of prognosis, and treatment controversies.[6] Different names have been used to describe these lesions, and the most common are cirsoid aneurysm, plexiform angioma, scalp arteriovenous fistula, arteriovenous aneurysm and arteriovenous malformation.[7]

Almost all patients present with a scalp swelling that has gradually increased in size from birth or after head trauma. Rapid increases in size have been reported to occur at puberty, during menstruation and during pregnancy. Their clinical signs are associated with the size of AVMs. Associated symptoms and signs include pain, throbbing headaches and bruit,[3,8,9] hemorrhage,[8,10] seizures and psychomotor retardation.[11] Large lesions have also been associated with scalp necrosis.[8] AVMs cause direct shunting of high-volume arterial blood through low-resistance arteriovenous fistulae, often resulting in venous hypertension, hypoperfusion of vessels and tissue downstream, and reduced cerebral perfusion, known as the steal phenomenon.[12] About 10 to 20% of scalp AVMs develop following penetrating or non-penetrating trauma to the scalp.[3,13]

Total excision of a scalp AVM requires comprehensive knowledge of the feeding arteries, draining veins and nidus. Catheter angiography has been the gold standard for diagnosis[14] but CTA can also provide a very high imaging resolution and the observation of related bony structures, which may be important for surgical planning, as in the case of our patient.[4]

Treatment of scalp AVMs allows many possibilities and individualization is key. Surgical excision is especially effective in selective cases, when endovascular treatment is difficult or not feasible.[3,5,15] Moreover, successful endovascular treatment of scalp AVMs has been reported, but has often been found to be insufficient for those with more extensive fistulae or with other complicating components.[16]

In relation to surgical treatment, common complications consist of hemorrhage, necrosis of the scalp, and sepsis caused by wound infection.[3,17] Hemorrhage may be prevented with preoperative embolization, clamping, and suturing of feeding vessels. Several authors recommend preoperative endovascular treatment to reduce blood supply of large lesions, as to facilitate surgery.[18,19]

Resumo

Malformação arteriovenosa gigante de escalpo

Malformações arteriovenosas (MAV) do couro cabeludo são lesões raras. O quadro clínico apresenta-se com queixas de aumento do couro cabeludo, desfiguração do couro cabeludo, dor e sintomas neurológicos. A origem pode ser congênita ou traumática. Apresentamos um caso de MAV gigante de couro cabeludo e o tratamento adotado, seguindo-se uma breve revisão da literatura. O diagnóstico das MAV de couro cabeludo baseia-se no exame físico e é confirmado pela angiografia carótida interna e externa ou angiografia por tomografia computadorizada. A excisão cirúrgica é especialmente eficaz em MAV de couro cabeludo e é a modalidade de tratamento mais frequentemente utilizada.

Palavras-chave: couro cabeludo, malformações arteriovenosas, doenças vasculares.

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Body composition in adults with neurofibromatosis type 1

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Summary

Objective: To evaluate the body composition and nutritional status of neurofibromatosis type 1 (NF1) adult patients.
Method: A cross-sectional study of 60 NF1 patients (29 men, 31 women) aged ≥ 18 years who were evaluated from September 2012 to September 2013 in a Neurofibromatosis Outpatient Reference Center. Patients underwent nutritional assessment including measurements of weight, stature, waist circumference (WC), upper-arm circumference (UAC), and skinfolds (biceps, triceps, subscapular, suprailiac). Body mass index (BMI), upper-arm total area (UATA), upper-arm muscle area (UAMA), upper-arm fat area (UAFA), body fat percentage (BFP), fat mass, fat-free mass, fat mass index, and fat-free mass index were also calculated.
Results: The mean age of the study population was 34.48±10.33 years. The prevalence of short stature was 28.3%. Low weight was present in 10% of the sample and 31.7% of patients had a BMI ≥ 25 kg/m^2. Reduced UAMA (<5th percentile) was present in 43.3% and no difference was found in UAFA between the sexes. The BFP was considered high in 30% and 17 (28.3%) patients had a WC above the World Health Organization cutoffs.
Conclusion: In this study, NF1 patients had a high prevalence of underweight, short stature, and reduced UAMA, with no difference between the sexes. Reduced UAMA was more prevalent in underweight patients; however, this was also observed in the normal and overweight patients. Further studies should investigate the distribution of body tissues in NF1 patients, including differences between men and women, and the influence of diet and nutrition on clinical features in NF1.

Keywords: neurofibromatosis type 1, nutritional status, anthropometry, body composition, adult.

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Introduction

Neurofibromatosis type 1 (NF1) is the most prevalent form in a group of three genetic diseases called neurofibromatoses, and is caused by inherited or *de novo* mutations on chromosome 17, resulting in reduced neurofibromin synthesis, which subsequently reduces tumor suppression.[1] The diagnostic criteria for NF1 are almost exclusively clinical, and were established by the National Institutes of Health (NIH) Consensus.[2] The most common clinical features of NF1 are *café au lait* spots, dermal neurofibromas, plexiform neurofibromas, axillary and/or inguinal freckling, Lisch nodules, and bone dysplasia. However, NF1 can also exhibit multisystemic involvement including musculoskeletal, cardiovascular, endocrine, ophthalmic, central and peripheral neural system, learning deficits and speech disorders.[3-5]

Recently, the first study of nutrient intake in NF1 patients was published,[6] and, although the clinical manifestations of NF1 are well established, data on body composition are scarce[4,7-10] and not well known. Low weight, short stature, and reduced body mass index (BMI) were found previously in NF1 patients and can be used as nutritional status indicators. However, these characteristics had different prevalence rates in the small number of studies available.[4,7-10] Most of these studies were conducted in children only, or included children and adults in the same sample.

Body composition is related to health.[11] Altered body composition, or excess fat, can greatly increase the risk of cardiovascular disease, diabetes, hypertension, and cancer.[11] In other hand, muscle plays a central role in whole-body protein metabolism and altered muscle metabolism plays a key role in the genesis and prevention of many common pathologic conditions and chronic diseases.[12] Epidemiological and clinical studies use the anthropometry by measuring circumferences and skinfolds. The upper-arm composition is also used as an indicator of fat and muscle distribution. Several studies have shown the direct association of disease, biochemical changes, and nutritional status with upper-arm composition.[13,14]

The NF1 nutritional status assessment is relevant, because features of this disease as underweight or short height can influence patients' health and quality of life. Therefore, the present study aimed to assess the body composition of NF1 adult patients.

Method

Sample

The present cross-sectional study included all NF1 patients aged ≥ 18 years from a Brazilian Neurofibromatosis Outpatient Reference Center (NORC) evaluated between September 2012 and September 2013. The study was approved by the Ethics Committee of the Federal University of Minas Gerais. All patients provided their written informed consent. Patients were excluded based on musculoskeletal limitations, presence of a neurofibroma at the measurement site, or the use of medications that might compromise the nutritional assessment.

Data collection

The anthropometric measurements used in this study followed the protocol provided by the World Health Organization (WHO).[15] Weight was measured to the nearest 100 g with a mechanical scale (Welmy®), which was checked regularly before each investigation, and height was measured using a vertical stadiometer (Welmy®). Weight and height were used to calculate patients' BMI.[15] The BMI categories used in this study were normal weight (BMI 18.5-25 kg/m^2), underweight (BMI < 18.5 kg/m^2), and overweight (BMI ≥ 25.0 kg/m^2).[15] Fat mass index (FMI) and fat-free mass index (FFMI) were also calculated using the equations according to VanItallie et al.:[16]

FMI = fat mass (kg) / height (m)^2
FFMI = fat-free mass (kg) / height (m)^2

Waist circumference (WC) was measured at the midpoint between the iliac crest and the rib cage. According to the WHO,[11] the minimum normal cutoff points for WC are 94 cm and 80 cm in men and women, respectively. To calculate the body fat percentage (BFP), skinfold thickness was measured to the nearest millimeter (mm) using a caliper (Cescorf®). These readings were made at four sites on all subjects: at the biceps (BS), triceps (TS), subscapular (SS), and supra-iliac (SIS) areas. These measurements were taken on the right side of the body with the subject standing in a relaxed position. Body density was calculated using the linear regression equations for men and women according to Durnin and Womersley.[17] These equations do not use plenty of skinfold thickness, which may be of interest in NF1 patients, as the presence of a neurofibroma at the measurement site was an exclusion criterion in this study, as previously stated. The BFP was then calculated using Siri's equation,[18] and classified as normal, high, or low according to Lohman's criteria.[19]

The upper-arm circumference (UAC)[20] was measured at the midway point between the acromion and the olecranon process of the elbow of the right arm using a tape measure to the nearest 0.10 cm. The upper-arm composition was assessed based on anthropometric measurements of UAC and TS utilizing standard equations, with values in percentiles, according to the National Center for Health Statistics (NCHS) reference and classified by Frisancho.[20] The following equations[20,21] for upper-arm total area (UATA), upper-arm muscle area (UAMA), and upper-arm fat area (UAFA) were used:

a. UATA (cm^2) = (UAC)^2 / (4 x π)
b. UAMA (cm^2) = {(UAC – TS x π)^2 / (4 x π)} – 10 → Male
c. UAMA (cm^2) = {(UAC – TS x π)^2 / (4 x π)} – 6.5 → Female
d. UAFA (cm^2) = UATA – UAMA

Statistical analyses

All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS®) version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate normality and determine the appropriate statistical test. Qualitative variables were described using absolute and relative (percentage) frequencies. Grouped comparisons of qualitative variables were performed using chi-square tests. Quantitative variables with normal distribution were expressed as mean and standard deviation, and compared using the two-tailed

Student's t-test for independent samples. Quantitative variables that were not normally distributed were presented as median and interquartile range (IQR), or minimum and maximum, and compared using the non-parametric Mann-Whitney U test. P-values < 0.05 were considered statistically significant.

Results

Sixty patients aged 18 to 64 years were included in this study. Twenty-nine patients (48.3%) were men. The mean age was 34.48±10.33 years, and there was no difference between men and women (p=0.980). No patients were excluded based on the exclusion criteria. Anthropometric and body composition data are shown in Table 1.

The distribution of anthropometric data classified in categories of height, BMI, WC, and BFP are also presented in Table 1. Using the BMI categories, 6 of the 60 patients (10%) were classified as underweight, 35 (58.3%) were normal weight, and 19 (31.7%) were overweight. After analyzing the WC categories, 17 of the 60 (28.3%) patients had measurements above the WHO minimum normal cutoff points.[11] After analyzing the BFP categories, 18 of the 60 (30%) patients were classified as having a high BFP. There were no significant differences in the categorization of BMI, WC, and BFP between the sexes.

Table 2 shows the classification of body composition variables using upper-arm parameters. Regarding the UAFA, there was no difference between sexes, and only 6.6% of patients had increased UAFA (> 95th percentile). However, in terms of UAMA, 43.3% of patients had values below the 5th percentile, representing 51.7% of men and 35.5% of women with NF1 in this study. When this data was stratified by sex, men showed greater UAMA than women, which was to be expected (p<0.001).

TABLE 1 Anthropometric and body composition data of NF1 patients and its distribution in categories.

Parameters	All patients (N=60)	Men (n=29)	Women (n=31)	p-value
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Weight (kg)	63.47 (16.98)	70.38 (18.00)	57.00 (13.25)	**0.002**
Height (m)	1.62 (0.10)	1.68 (0.09)	1.57 (0.08)	**<0.001**
BMI (kg/m^2)	23.86 (4.73)	24.79 (5.06)	22.98 (4.30)	0.139
WC (cm)	79.87 (12.18)	85.40 (12.49)	74.70 (9.44)	**<0.001**
Body fat percentage (%)	24.53 (7.75)	19.51 (6.30)	29.23 (5.84)	**<0.001**
Fat mass (kg)	15.86 (7.37)	14.50 (7.91)	17.14 (6.71)	0.168
Fat free mass (kg)	47.60 (12.35)	55.88 (11.12)	39.87 (7.54)	**<0.001**
Fat mass index (kg/m^2)	6.03 (2.71)	5.11 (2.61)	6.90 (2.53)	**0.009**
Fat-free mass index (kg/m^2)	17.82 (2.99)	19.69 (2.67)	16.08 (2.10)	**<0.001**
	n (%)	**n (%)**	**n (%)**	
Short stature*[a]	17 (28.3)	9 (31.0)	8 (25.8)	0.653
BMI categories*				0.101
BMI < 18.5 kg/m^2	6 (10.0)	2 (6.9)	4 (12.9)	
BMI ≥ 18.5 and < 25 kg/m^2	35 (58.3)	14 (48.3)	21 (67.7)	
BMI ≥ 25 kg/m^2	19 (31.7)	13 (44.8)	6 (19.4)	
WC categories*				0.351
M: < 94 cm and F: < 80cm	43 (71.7)	21 (72.4)	22 (71.0)	
M: ≥ 94 cm and F: ≥ 80cm	17 (28.3)	8 (27.6)	9 (29.0)	
Body fat percentage categories*				0.128
Normal	42 (70.0)	23 (79.3)	19 (61.3)	
High	18 (30.0)	6 (20.7)	12 (38.7)	
Low	0	0	0	

SD: standard deviation; BMI: body mass index; WC: waist circumference; M: male; F: female; [a]short stature was considered when percentile < 5; *categorical variables were compared using Pearson Chi-square. Means were compared using Student's t-test.

TABLE 2 Classification of body composition variables in percentiles according to the NCHS Standard.[20]

Parameters	All patients (N=60)	Men (n=29)	Women (n=31)	p-value*
UATA (cm^2) – Mean ± SD	65.52±20.92	72.78±22.31	58.72±17.24	**0.008**
UATA categories – n (%)				0.505
< p5 (Low)	9 (15.0)	5 (17.2)	4 (12.9)	
p5 – p95 (Normal)	50 (83.3)	23 (79.3)	27 (87.1)	
> p95 (High)	1 (1.7)	1 (3.5)	0	
UAMA (cm^2) – Mean ± SD	39.59±14.69	48.01±14.87	31.71±9.24	**<0.001**
UAMA categories – n (%)				0.205
< p5 (Low)	26 (43.3)	15 (51.7)	11 (35.5)	
p5 – p95 (Normal)	34 (56.7)	14 (48.3)	20 (64.5)	
> p95 (High)	0	0	0	
UAFA (cm^2) – Mean ± SD	25.93±8.93	24.77±9.08	27.01±8.79	0.337
UAFA categories – n (%)				0.067
< p5 (Low)	1 (1.7)	0	1 (3.2)	
p5 – p95 (Normal)	55 (91.7)	25 (86.1)	30 (96.8)	
> p95 (High)	4 (6.6)	4 (12.9)	0	

SD: standard deviation; NCHS: National Center for Health Statistics; UATA: upper-arm total area; UAMA: upper-arm muscle area; UAFA: upper-arm fat area; < p5: percentile under 5; p5-p95: percentile between 5 and 95; > p95: percentile above 95. *Means were compared using Student's t-test and categorical variables were compared using Pearson Chi-square test.

Comparing patients with normal or reduced UAMA (< 5th percentile), there was no difference in height between groups (p=0.316), but comparing sexes, there was no difference for height between men with normal or reduced UAMA (p=0.526), and it was significantly lower in women with UAMA under 5th percentile (p=0.022). NF1 patients with reduced UAMA showed lower weight (p<0.001), BMI (p<0.001), fat mass (p<0.001) and fat-free mass (p=0.024), for both men and women, but FMI were lower only for women (0.013).

Discussion

In our study, compared to the non-NF1 population, NF1 patients were found to be underweight and present short stature, as well as reduced UAMA, with no sex differences for categories of these variables. Reduced muscle mass (as indicated by UAMA) was more prevalent in underweight patients (83.3%); however, this was also observed in normal (54.3%) and overweight (11.8%) patients. A small number of patients (1.7%) had low adipose tissue.

With regard to anthropometric characteristics, the prevalence of underweight adults in the Brazilian population is 2.7% (1.8% in men and 3.6% in women).[22] In this study, the prevalence of underweight is above the 5% mark that the WHO uses to identify malnutrition in a population.[22] In addition, 13 of the 29 men (44.8%) and 6 of the 31 women (19.4%) were overweight, while in the Brazilian adult population, this prevalence is 49% (50.1% in men and 48% in women).[22]

Short stature was present in 28.3% of the sample, which was higher than seen in a study by Petramala et al.,[7] and lower than seen in the studies of Souza et al.[4] and Trovo-Marques et al.[8] These studies were conducted in different age groups, and also included children in the analyses. In the Brazilian population survey,[22] the average height (in centimeters) of adults living at the same region in Brazil was high compared to patients with NF1 of this study.

The body composition analysis showed that women had a higher BFP compared to men with NF1, although in absolute values of fat (in kilograms), there was no difference between the sexes. This may be due to the lower weight and lower fat-free mass shown by women with NF1.

Men with NF1 had a larger UATA, UAC, and UAMA compared with women, while UAFA was similar between the sexes. This difference may be caused primarily by muscle mass, as there was no difference in UAFA and the bone gap difference between the sexes was already considered in the equations used.[21] The UAMA was considered low in 43.3% of patients in this study, representing 51.7% of men and 35.5% of women. The average values of UAMA have been shown to be higher in men than in women in other studies; however, the absolute values of this research were lower than the values found in other national and international studies.[23-26]

Stevenson et al.[10] used quantitative peripheral computed tomography to compare the bones and skeletal

muscle of NF1 patients and volunteers not affected by the disease. This study demonstrated that children with NF1 have lower muscle cross-sectional area than their controls, but this did not lead to major advances in the pathophysiology of this finding. Furthermore, reduced muscle strength is a feature described in NF1 patients by Souza et al.[27] also recruited from NORC. According to Pompeu et al.,[23] the UAMA has good correlation with the maximal voluntary strength.

This study found anthropometric differences between men and women with NF1. Although changes in weight and fat accumulation are expected comparing sexes, it seems that this difference is larger than the commonly found in people without NF1 and should receive attention in further studies. Probably, men and women are affected by NF1 in different ways in their body compartments, which can be related to situations like AMB greater in men and/or fat accumulation greater in women. Other studies[28,29] have also found differences between men and women for variables such as BMI, reinforcing the need to assess the impact of NF1 in each sex.

In our study, body composition was inadequate in terms of muscle mass. Low muscle mass is usually associated with low weight and malnutrition,[15] which was also found in this study. However, we also found low muscle mass in normal weight and overweight patients, suggesting that the BMI values should be interpreted with caution when assessing the nutritional status in NF1 patients, or that the BMI cutoff points must be adapted to changes in body composition. The reduced muscle mass can indicate an early sarcopenia in NF1 patients. It may have multiple causes that should be investigated in further studies, as poor blood flow to muscle, mitochondrial dysfunction, decreased caloric intake, a decline in anabolic hormones, or an increase in proinflammatory cytokines.[30] Souza et al.[6] showed a decreased caloric intake in NF1 patients, but the authors discussed a possible overestimation of the daily energy expenditure when using the predictive equations.

Nutritional status can influence patients' quality of life.[31,32] Previous studies have shown that the clinical severity and social representations of NF1 are correlated with quality of life, as reported by NF1 patients and their families.[33,34] The importance of nutritional care in NF1 patients and their clinical features must be investigated further in future studies.

This study has limitations, such as convenience sampling and selection bias, that may have been caused by selecting patients with nutritional conditions including obesity and diabetes. All patients who had previously been treated in the outpatient center were invited to participate in this study to minimize this error. Randomization and the inclusion of a control group (with unaffected patients) would be useful in improving the external validity of similar studies. Additionally, UAMA is not the gold standard method for assessing muscle mass, and further studies should use better parameters to investigate the muscle mass in NF1 patients.

Conclusion

NF1 patients in this study had a high prevalence of underweight, short stature, and reduced UAMA, with no difference between the sexes. Reduced UAMA was more prevalent in underweight patients; however, it was also observed in the normal and overweight patients. Further studies should investigate the distribution of body tissues in NF1 patients with standard methods and investigate the possible correlation and impact of the nutritional status on the clinical features of the disease.

Resumo

Composição corporal em adultos com neurofibromatose tipo 1

Objetivo: avaliar a composição corporal e o estado nutricional de adultos com neurofibromatose tipo 1 (NF1).
Método: estudo transversal com 60 pacientes com NF1 (29 homens, 31 mulheres) com idade ≥ 18 anos que foram avaliados de setembro de 2012 a setembro de 2013 em um Centro de Referência em Neurofibromatoses. Pacientes foram submetidos à avaliação nutricional, incluindo medidas de peso, estatura, circunferência da cintura (CC), circunferência do braço e dobras cutâneas (bíceps, tríceps, subescapular, suprailíaca). Índice de massa corpórea (IMC), área total do braço (ATB), área muscular do braço (AMB), área adiposa do braço (AAB), percentual de gordura, massa gorda, massa livre de gordura, índice de massa gorda e índice de massa livre de gordura foram calculados.
Resultados: a idade média da amostra foi de 34,48±10,33 anos. A prevalência de baixa estatura foi 28,3%. Baixo peso esteve presente em 10% da amostra e 31,7% apresentaram IMC ≥ 25 kg/m2. A AMB reduzida esteve presente em 43,3% e não foram encontradas diferenças na AAB entre os sexos. O percentual de gordura foi considerado alto em 30% da amostra, e 28,3% apresentaram CC acima dos pontos de corte da Organização Mundial de Saúde.
Conclusão: neste estudo, pacientes com NF1 apresentaram alta prevalência de baixo peso, baixa estatura e AMB reduzida, sem diferenças entre os sexos. AMB reduzida

foi mais prevalente em pacientes com baixo peso, no entanto também foi observada em pacientes com peso normal ou sobrepeso. Estudos futuros devem investigar a distribuição de tecidos corporais na NF1, incluindo diferenças entre sexos, e a influência da nutrição nas manifestações clínicas da doença.

Palavras-chave: neurofibromatose tipo 1, estado nutricional, antropometria, composição corporal, adulto.

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Pregnancy outcomes after chemotherapy for trophoblastic neoplasia

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Summary

Introduction: The successful development of chemotherapy enabled a fertility-sparing treatment for patients with trophoblastic neoplasia. After disease remission, the outcome of a subsequent pregnancy becomes a great concern for these women.

Objective: To analyze existing studies in the literature that describe the reproductive outcomes of patients with trophoblastic neoplasia treated with chemotherapy.

Method: Systematic review was performed searching for articles on Medline/Pubmed, Lilacs and Cochrane Library databases, using the terms "gestational trophoblastic disease" and "pregnancy outcome".

Results: A total of 18 articles were included. No evidence of decreased fertility after chemotherapy for trophoblastic neoplasia was observed. The abortion rates in patients who conceived within 6 months after chemotherapy was higher compared to those who waited longer. Some studies showed increased rates of stillbirth and repeat hydatidiform moles. Only one work showed increased congenital abnormalities.

Conclusion: The pregnancies conceived after chemotherapy for trophoblastic neoplasia should be followed with clinical surveillance due to higher rates of some pregnancy complications. However, studies in the literature provide reassuring data about reproductive outcomes of these patients.

Keywords: gestational trophoblastic disease, hydatidiform mole, choriocarcinoma, chemotherapy, pregnancy, fertility.

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Introduction

Gestational trophoblastic disease is a group of placental disorders that include hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor. Hydatidiform mole is the most common form of trophoblastic disease, and is considered a benign condition that may develop into other malignant forms, referred indistinctly as gestational trophoblastic neoplasia.[1,2]

The incidence of hydatidiform mole varies in different populations, affecting 1:1,000 pregnancies in Europe and the United States, while in Asian countries the incidence may reach up to two cases in every 1,000 pregnancies.[2] In Brazil, there is no official database for gestational trophoblastic disease. A large Brazilian epidemiological study showed the occurrence of 5,250 cases of gestational trophoblastic disease in ten reference centers over the course of 11 years, which can be translated into 477 new cases per year.[3]

The diagnosis of hydatidiform mole is based on clinical symptoms, serum level of human chorionic gonadotropin (hCG), ultrasound scans and histopathological analysis of the material obtained after uterine evacuation. Hydatidiform mole is characterized into complete and partial mole according to clinical, histological and genetic features. In general, complete moles are generated by the fertilization of an empty oocyte by a sperm that

duplicates its genetic material or by two spermatozoa, giving rise to an androgenetic diploid conception with intense trophoblastic hyperplasia and diffuse hydropic villi. In contrast, the partial mole originates from dispermy, with fertilization of an oocyte by two spermatozoa, producing a triploid pregnancy, with focal histological abnormalities.[1,2,4]

About 15% of patients with complete moles and less than 5% of those with partial moles develop gestational trophoblastic neoplasia, therefore, the monitoring of these women is fundamental to enable early detection of post-molar disease. The persistence of raised hCG levels and abnormal ultrasound imaging after uterine evacuation leads to the diagnosis of trophoblastic neoplasia, and in some cases metastasis may also be present.[1,2]

There is a choice between chemotherapy and/or surgery in the treatment of trophoblastic neoplasia, depending on staging, risk classification and reproductive desire. Patients with trophoblastic neoplasia are classified by the presence of risk factors according to the International Federation of Gynecology and Obstetrics' (FIGO) prognostic score (2002). Patients with a score from 0 to 6 are classified as having low-risk disease, receiving a single chemotherapy agent, whereas those with a score of 7 or more are considered as high-risk and benefit from receiving combination chemotherapy.[2]

More than 90% of patients with trophoblastic neoplasia undergo successful treatment with chemotherapy.[2] Thus, an additional concern is related to their reproductive future. A study by Matsui et al. (1997) showed that 46.8% of patients using etoposide in the treatment of trophoblastic neoplasia had impaired ovarian function.[5] Cytotoxic drugs are potentially mutagenic and teratogenic, so there is also a concern about the adverse effects of the subsequent pregnancy. For example, methotrexate, which is used as a chemotherapy agent, inhibits the metabolism of folic acid, an essential vitamin in fetal development.[6]

In this review, we analyzed the studies existing in the literature that describe the reproductive future of patients with trophoblastic neoplasia treated with chemotherapy.

Method

The search was carried out by two independent researchers without any language restrictions in the following databases: Medline/Pubmed, Lilacs and the Cochrane Library. The keywords in Medline used in the searches (obtained using the Medical Subject Headings – MeSH) were "gestational trophoblastic disease" and "pregnancy outcome".

The inclusion criteria used in this review were: studies that evaluated gestational rate and outcomes after chemotherapy treatment for gestational trophoblastic disease. There was no restriction on the time interval between treatment and pregnancy. All articles were written in English or Portuguese.

After reading the articles, the references of interest from the original studies were also included.

In the initial search, 163 articles were found, with 26 articles selected by reading the title and abstracts after being reviewed by two independent researchers. Eight articles were excluded because they related to case reports (two studies), articles written in Chinese, the same case series reported by another study, gestational trophoblastic neoplasia concomitant with current pregnancy, gestational prognosis after prophylactic chemotherapy during molar evacuation, pregnancy after chemotherapy associated with partial uterine resection and after uterine perforation. At last, 18 articles were included in this review. The flow diagram for the selection of the articles can be found in Figure 1. No articles were found in the search on Cochrane and Lilacs.

Results

The results of this study are summarized in Table 1, with the number of patients in each article included, as well as the number of pregnancies and their outcomes.

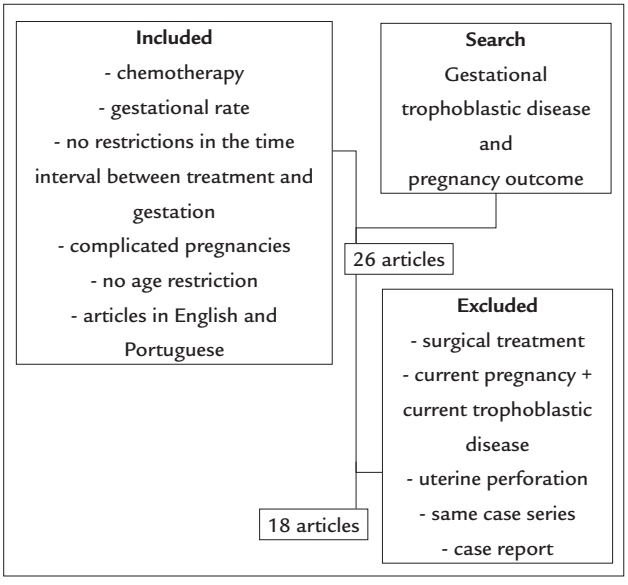

FIGURE 1 Search mechanism and algorithm for selection of articles for the review.

Fertility

The articles did not show decreased fertility rates after treatment of the trophoblastic disease with chemotherapy.[6-23]

Time to pregnancy conception after the end of chemotherapy

Studies comparing pregnancies which were conceived within 6 months of the end of chemotherapy with those occurring after this period showed a higher spontaneous miscarriage rate in those who waited for a shorter time. Matsui et al. (2004) noted that the incidence of miscarriage, stillbirth and mole was higher in those conceiving within 6 months of the completion of chemotherapy compared to those who waited 1 year.[17] Matsui et al. (2002) and Braga et al. (2009) also found that the incidence of miscarriage was higher in patients who became pregnant within 6 months.[13,20] Lan et al. (2001) noted that patients presented a higher miscarriage rate when waiting 6.5±3.75

TABLE 1 Pregnancy outcomes of women after receiving chemotherapy for gestational trophoblastic neoplasia.

Study	Patient (n)	Pregnancy (n)	Term [n (%)]	Stillbirth [n (%)]	Abortion and ectopic [n (%)]	Repeat mole [n (%)]	Preterm [n (%)]	Malformations [n (%)]
Rustin et al., 1984[7]	245	368	273 (74.1)	8 (2.1)	55 (15)	-	5 (1.3)	2 (0.5)**
Song et al., 1988[8]	205	355	279 (78.6)	5 (1.4)	28 (8)	-	20 (6.7)	3 (1)*
Kim et al., 1998[9]	517	115	89 (77.4)	1 (0.9)	17 (15)	5 (4.3)	3 (2.6)	3 (3.2)*
Woolas et al., 1998[6]	680	1,313	1,000 (76.2)	19 (1.4)	190 (14.5)	18 (1.4)	-	18 (1.7)*
Tuncer et al., 1999[10]	43	29	22 (75.9)	-	3 (10.3)	1 (3.4)	3 (10.3)	1 (4.1)*
Amr et al., 1999[11]	42	120	94 (78.3)	3 (2.5)	8 (6.8)	-	15 (12.5)	-
Lan et al., 2001[12]	22	22	9 (40.9)	1 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)	-
Blagden et al., 2002[14]	1,532	230	164 (71)	2 (1)	26 (11)	3 (1.3)	-	3 (1.3)**
Garner et al., 2002[15]	-	581	393 (67.6)	9 (1.5)	106 (18)	8 (1.4)	35 (6)	10 (2.3)*
Matsui et al., 2002[13]	129	243	169 (69.5)	2 (0.8)	27 (11.1)	5 (2.1)	5 (2.1)	-
Lok et al., 2003[16]	50	21	16 (76)	-	2 (9)	-	2 (9)	2 (11)*
Matsui et al., 2004[17]	137	258	180 (69.8)	3 (1.2)	29 (11.2)	5 (1.9)	5 (1.9)	-
Goto et al., 2004[18]	50	43	34 (79)	0	4 (9.3)	0	0	3 (8.8)*
Garrett et al., 2008[19]	-	631	422 (66.9)	9 (1.4)	7 (1.1)	9 (1.4)	42 (6.7)	10 (2.1)*
Braga et al., 2009[20]	-	252	172 (68.2)	2 (0.8)	42 (16)	7 (2.8)	6 (2.4)	6 (2.4)**
Williams et al., 2014[21]	1,204	255	174 (68.2)	2 (0.8)	34 (13.4)	3 (1.4)	14 (5.4)	-
Total		**4,836**	**3,490 (72)**	**66 (1.4)**	**579 (12)**	**65 (1.6)**	**156 (4.7)**	**89 (2.3)****

*Number of malformations / delivery; **number of malformations / pregnancy.

months to conceive, while those who had an uneventful pregnancy showed an interval of 9.78±2.22 months between chemotherapy and pregnancy.[12]

Single and multi agent chemotherapy

Blagden et al. (2002) compared the pregnancy rates among women who conceived within a year of chemotherapy treatment with single or combined agent. The conception rate was higher in the single agent group. It was also noted that the miscarriage rate in the combination chemotherapy group was higher than the group treated with single agent. There was no difference in the rate of congenital anomalies, which was similar to the general population.[14] However, Williams et al. (2014) compared the groups treated with single and combined agents and found no significant increase in the risk of miscarriage, ectopic pregnancy, repeat molar pregnancy or stillbirth, not even after comparing with the general population of the United Kingdom.[21] Woolas et al. (1998) and Braga et al. (2008) also found no difference in the groups with single and combination chemotherapy.[6,20]

Repeat molar pregnancy

Woolas et al. (1998), Kim et al. (1998) and Lan et al. (2001) observed an increase in new molar pregnancy compared to the general population while analyzing the influence of chemotherapy on the reproductive future of patients with trophoblastic neoplasia.[6,9,12] Matsui et al. (2002) showed a molar pregnancy recurrance rate that was seven times higher than the general population.[13]

Higher stillborn rate

Woolas et al. (1998), Garner et al. (2002), Garrett et al. (2008) and Vargas (2014) noted a higher stillbirth rate in patients treated with chemotherapy for gestational trophoblastic disease compared to the general population.[6,15,19,22]

Higher malformation rate

Only the study by Goto et al. (2004), which assessed choriocarcinoma patients treated with combination chemotherapy, noted a higher incidence of congenital anomalies.[18]

Discussion

The high cure rates of trophoblastic neoplasia after chemotherapy have enabled those patients to have a chance to concieve after the completion of the treatment. In the mid-1960s the mortality rate was 90%, whereas the current survival rate is 90 to 95%.[19] However, due to the potential adverse effects of chemotherapeutic agents, the reproductive success rates as well as gestational complications have become a concern for these women.

The number of studies in the literature regarding this theme is still small. In general, most of them monitor the reproductive rates up to the first year after the end of treatment and the outcome of these pregnancies. All of studies found were retrospective.

The studies point out that there is no change in fertility. Most of the patients who wish to conceive end up doing so successfully. However, not all of the studies take into account the patients's desire to conceive.

It is advisable for patients to use birth control for at least 1 year after chemotherapy with negative hCG levels in order to enable them to safely become pregnant, since this is the time period when most relapses occur. The higher rate of miscarriage in the first 6 months after the end of treatment shown in the literature stresses the importance of not become pregnant around this period.[12,13,17,20] In women who already experienced a failed pregnancy, another unsuccessful pregnancy can lead to negative psychological impact.

Four articles showed a higher prevalence of stillbirths in comparison to the general population.[6,15,19,22] However, the etiology of this phenomena is still unknown, and it is important to increase clinical surveillance in these pregnancies.

Sebire et al. (2003) have shown a 20-fold increase chance (1 in 55 pregnancies) of another molar pregnancy in patients with prior hydatidiform mole.[24] In this review, four studies showed an increased chance of a repeat hydatidiform mole in patients who underwent chemotherapy for gestational trophoblastic neoplasia.[6,9,12,13] This event does not seem to be associated with chemotherapy itself, as the risk of presenting with another hydatidiform mole is higher even in patients with spontaneous regression of molar disease.

Only one study out of the four that compared single and combined agents found a difference between the two groups; showing that the conception rate was higher in the single agent group, and the miscarriage rate was higher in the combination group.[14] The other three articles did not find any difference between the groups in relation to ectopic pregnancy, second molar pregnancy, miscarriage or stillbirth.[6,20,21]

Trophoblastic disease affects women, especially in the age group of 20 to 30 years. The data collected in the literature presents a small sample of studies. Nevertheless,

the results are homogeneous and comforting for those patients desiring motherhood. More studies with larger samples are necessary to ensure safer monitoring of patients with trophoblastic neoplasia who underwent chemotherapy.

Conclusion

The introduction of chemotherapy has changed the prognosis of patients with gestational trophoblastic neoplasia. Despite the new concern being the preservation of fertility, the studies did not show a decrease in fertility. The data is reassuring regarding pregnancies following chemotherapy. However, greater attention should be given to these patients, especially those who conceive within 6 months of treatment.

Resumo

Futuro reprodutivo após tratamento quimioterápico da neoplasia trofoblástica

Introdução: o sucesso do desenvolvimento da quimioterapia no tratamento da neoplasia trofoblástica proporcionou a possibilidade de conservação da fertilidade das pacientes, tornando o futuro reprodutivo uma nova preocupação após a remissão da doença.
Objetivo: analisar os estudos existentes na literatura que descrevem o futuro reprodutivo de pacientes com neoplasia trofoblástica tratadas com quimioterapia.
Método: revisão sistemática que buscou artigos nas bases de dados Medline/Pubmed, Lilacs e Biblioteca Cochrane, utilizando as palavras-chave "gestational trophoblastic disease" e "pregnancy outcome".
Resultados: foram selecionados 18 artigos de acordo com critérios de inclusão e exclusão. Não foi observada diminuição da fertilidade após a quimioterapia para neoplasia trofoblástica. Pacientes que engravidaram até 6 meses do término da quimioterapia apresentaram maiores taxas de abortamento quando comparadas às que esperaram mais de 6 meses. Alguns artigos encontraram maiores taxas de natimorto e nova mola hidatiforme. Apenas um estudo mostrou aumento da taxa de malformação.
Conclusão: as gestações subsequentes à neoplasia trofoblástica devem ser acompanhadas com vigilância clínica em decorrência da maior taxa de complicações na gestação, principalmente nas mulheres que engravidam até 6 meses após o término da quimioterapia. No entanto, os dados encontrados nos estudos tranquilizam quanto ao futuro reprodutivo dessas pacientes.

Palavras-chave: doença trofoblástica gestacional, mola hidatiforme, coriocarcinoma, quimioterapia, gravidez, fertilidade.

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Translation and validation of Hyperhidrosis Disease Severity Scale

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Summary

Introduction: The evaluation of patients with hyperhidrosis (HH) can be accomplished, among other ways, through questionnaires and scales. The Hyperhidrosis Disease Severity Scale (HDSS) has been used as a simple and quick tool to perform this evaluation. Although HDSS has been well established in several languages, it has not been translated into Portuguese, restricting its specific use for Brazilian patients. The aim of this study was to translate HDSS into Portuguese and validate it in a sample of Brazilian subjects.
Method: 290 Brazilian patients (69% women, with a mean age of 28.7±9.6 years and BMI 22.4±3.9 kg/m^2) diagnosed with HH were evaluated using HDSS, Quality of Life Questionnaire (QLQ) and Sweating Evolution Questionnaire (SEQ) before and after a five-week oxybutynin treatment. Regarding validation, an association between HDSS results and two other questionnaires was performed. To analyze HDSS sensitivity, evaluation of effects pre- and post-treatment with oxybutynin was conducted. Furthermore, HDSS reproducibility was analyzed in a subsample in which the scale was applied again after 7 days of the first follow-up appointment.
Results: There was statistical correlation between HDSS and QLQ and between HDSS and SEQ before treatment and after 5 weeks. Additionally, HDSS was reproducible and sensitive to clinical changes after the treatment period.
Conclusion: The Portuguese version of HDSS has been validated and shown to be reproducible in a Brazilian sample. Therefore it can be used as a tool to improve medical assistance in patients with HH.

Keywords: hyperhidrosis, scales, questionnaires, translations, validation studies.

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Introduction

Hyperhidrosis (HH) is a somatic disorder characterized by local excess sweating in specific regions of the body due to hyperfunction of eccrine sweat glands, often related to an emotional distress.[1]

There are several ways to diagnose and predict outcomes of HH. In general, objective measures such as transepidermal water loss measurement are used to estimate the amount of sweat of each suspected site affected by HH. However, this approach is expensive and limited by its daily-based measures,[2,3] resulting from measurements acquired at a particular time of the day and not allowing the analysis of sweating during longer periods.

Hence, questionnaires and scales have been developed to evaluate HH.[4] The main advantages of their use include low cost, simplicity, potential self-filling and large-scale application.[5] Recently, the Hyperhidrosis Disease Severity Scale (HDSS – International Hyperhidrosis Society®) was developed as a quick method,[6] since it presents only one question with four options of answers related to the implications to patient's daily routine and the degree of tolerance to the symptoms. The advantage of this scale is that its only question is simple and easy to respond, reducing the number of errors and optimizing medical evaluation.

Despite its global acceptance, HDSS has not been validated or translated into Portuguese, preventing its use in Brazil. Thus, the aim of this project was to translate and validate the Portuguese version of the HDSS, in order to use it as an important scale in Brazilian patients with HH.

Method

Sample

A convenience sample of 290 patients of both genders was recruited to this study. After a clear explanation of all procedures, those who agreed to participate in the research protocol signed a consent form. This study was approved by the Local Research Ethics Committee (Approval number at Plataforma Brasil: CAAE40512414.7.0000.0071). Inclusion criteria comprised individuals at the age of 18 years or older with a clinical diagnosis of palmar, axillary, or any association of these two forms of HH. All the patients included in the study had the palmar or axillary form of HH, or an association of both. Patients with compensatory sweating were excluded.

Study design

After translation and back-translation, HDSS was applied before and after 5 weeks of treatment with oxybutynin. All patients followed the same protocol. Oxybutynin was taken in progressively higher doses: starting at 2.5 mg once daily, which was increased to twice daily after one week, and 5 mg twice daily at the third week. If necessary and tolerated, for patients weighing more than 40 kg, the total dose was increased to 20 mg/day. For patients weighing less than 40 kg, the total dose was not increased after 3 weeks.

In addition, the Quality of Life Questionnaire (QLQ) and the Sweating Evolution Questionnaire (SEQ) were applied. In order to analyze the reproducibility of the Portuguese version of HDSS, a subsample was recruited and reassessed using HDSS 7 days after the first appointment.

Hyperhidrosis Disease Severity Scale translation

A native qualified Portuguese-speaking professional, specialized in technical translations and fluent in English, as well as experienced with medical literature, carried out the translation. Following the translation there was a trial phase where the understanding of the Portuguese version of HDSS scale was checked out by an additional sample of 40 patients with HH. They outlined major areas for improvement to make it more coherent and understandable. Later, experts evaluated HDSS to make sure its content included all the necessary elements for satisfactory evaluation of the disease, in the light of Brazilian culture, and included the modifications suggested by the patients. After applicable and convenient changes, the "new" HDSS scale (Portuguese version) was back translated into English by another professional with the same skills, who had no access to the original scale (in English). The "new" HDSS scale (in Portuguese) and its classical version in English were compared, and discrepancies were corrected, preserving semantic and idiomatic equivalences to compose a straightforward scale (Figure 1).

Hyperhidrosis Disease Severity Scale

HDSS consists of a simple and straightforward question with four available answers (grades 1 through 4) related to patient tolerance of HH symptoms and the negative implications of body perspiration to their everyday lives. Patients are asked to indicate a HDSS score specifically for each site of HH.

In our study, we evaluated only palmar and axillary symptoms, and patients could indicate different site-specific HDSS scores, according to the impairment of quality of life caused by excessive sweating in each area. Patients answered this scale twice: in the first appointment (before starting treatment, week 0), and in the end of the five-week treatment (week 5). Answer graded as 1 meant no perceptible sweating and lack of interference in everyday life; grade 2, tolerable sweating with seldom interference in everyday life; grade 3, little tolerable sweating with frequent interference in everyday life, and grade 4, intolerable sweating with constant interference in everyday life.

	Escala de gravidade da hiperidrose O meu suor:
1	**Não é perceptível** e **nunca** interfere com minhas atividades do dia a dia
2	**É tolerável,** mas **às vezes** interfere com minhas atividades do dia a dia
3	**É pouco tolerável** e **frequentemente** interfere com minhas atividades do dia a dia
4	**É intolerável** e **sempre** interfere com minhas atividades do dia a dia

FIGURE 1 Translation of Hyperhidrosis Disease Severity Scale (HDSS) into Portuguese.

For data purposes, the analysis yielded a delta of improvement on HDSS. For example: Pre-treatment (week 0) minus post-treatment (week 5) = delta. Thus, delta = 0 or 1 was considered no improvement; delta = 2 was considered slight improvement, and delta = 3 was considered good improvement. For example, if the patient reported at the first appointment HDSS = 4 (intolerable sweating with high interference in everyday life) and after 5 weeks reported HDSS = 1 (not noticeable sweating and lack of interference in routine activities), delta was 3 (good improvement).

Quality of Life Questionnaire

The QLQ is a 20-question form divided into five domains. Each of these domains or group of actions has five levels of answers based on tables that admit a single response. The sum of all points varies between 20 and 100. Quality of life was rated as: much better (20-35), slightly better (36-51), and no improvement (52-100).[7,8]

Sweating Evolution Questionnaire

The SEQ is based on a scale from 0 to 10, in which 0 means no sweating improvement and 10 refers to total resolution of symptoms. It was applied 5 weeks after treatment in the follow-up medical appointment. Patients chose a score from 0 to 10, according to the degree of symptomatic improvement. Results were classified as: no improvement (0-4), slight improvement (5-7) and great improvement (8-10).[9-13]

Statistical analysis

To determine an association between the HDSS responses and the other two questionnaires (QLQ and SEQ), chi-square test was used. Kappa coefficient was performed to examine the reproducibility of HDSS scale. Finally, sensitivity to treatment was calculated using the Wilcoxon test. Statistical analysis was performed using SPSS software (v. 17, SPSS Inc. Chicago, IL). P-values lesser than 0.05 were considered statistically significant.

Results

Patients' demographics are summarized in Table 1. Regarding general characteristics of the sample population, 69% were female. Patients were young, with an average age of 28.7 years [standard deviation (SD) 9.6; range 18-60]. Additionally, mean body mass index (BMI) was 22.4 kg/m^2 (SD 3.9; range 10.6-35.4).

Table 2 shows the association between responses obtained with HDSS and QLQ. There was a significant association between the responses obtained with HDSS and QLQ in the palmar group ($p<0.001$), and 94% of patients who reported good improvement in HDSS were more likely to report much better results with QLQ. There was no significant correlation between HDSS and QLQ in the axillary group.

Table 3 shows the association between responses obtained with HDSS and SEQ. There was a significant association between the responses obtained with HDSS and SEQ in both axillary ($p<0.01$) and palmar groups ($p<0.01$). As in SEQ, 92 and 96% of patients who reported good improvement with HDSS (delta = 3) in the axillary and palmar groups, respectively, showed to be more likely to report great improvement with SEQ (in both regions).

In a subsample of 34 patients, we conducted HDSS test-retest after a seven-day interval for patients with axillary HH. This resulted in a kappa index = 0.65 (0.29 to 0.97, CI 95%), showing moderate levels of agreement. In this group, 94% of patients reported the same values at the first appointment and after a seven-day follow-up. In addition, we carried out HDSS test-retest in a subsample of 58 patients with palmar HH, with a resulting kappa index of 0.84 (0.61 to 1.00, CI 95%), showing substantial degree of agreement. In this group, 96% of patients reported the same values at the first appointment and after 7 days.

Finally, to evaluate the degree of change in the HDSS scale, we analyzed the patients' responses in the pre-treatment period and after 5 weeks of oxybutynin intake. Wilcoxon values showed differences in median values of HDSS pre- and post-treatment, and turned out to be significant for both groups, palmar ($z=-11.1$ and $p<0.01$) and axillary ($z=-8.7$ and $p<0.01$), respectively.

Discussion

The aim of this study was to translate and validate the HDSS for Brazilian patients with HH. Results showed that its Portuguese version has good reliability, reproducibility, and is sensitive to changes after clinical treatment, therefore being useful for management of patients with HH.

Currently, there are several ways to evaluate and predict HH prognosis. In our institution, patient follow-up is now performed using two independent questionnaires: one assesses the degree of improvement in sweating after treatment, and another evaluates the changes in quality of life before and after treatment. These two have been used in different studies,[7,8] but we believe that the HDSS adds value to medical assistance since it is objective and simple, providing a good evaluation of degree of sweating in different body parts. Moreover, HDSS can be used by non-specialists, as a referral triage tool for patients with HH.

To assess the reliability of the Portuguese version of the HDSS, an association was made between its results and those obtained through QLQ and SEQ. By comparing data from HDSS and SEQ, we found significant association between the palmar and axillary groups.

On the other hand, comparing responses obtained with HDSS and QLQ, we verified that there was a significant association only in patients with palmar HH. One possible cause for the absence of association in patients with axillary HH is that QLQ is based on questions related to issues regarding excessive sweating in hands, which affects the evaluation of patients with primary axillary HH. Because SEQ is wider on its assessment with an extensive evaluation of other body parts, a positive association between HDSS and SEQ could be due to this fact.

More than association analyses, a comprehensive investigation to evaluate the degree of change in the HDSS scale pre- and post-oxybutynin treatment was performed. This study showed statistical evidence that both palmar and axillary HH improved in the HDSS, expressing its sensitivity to demonstrate changes in patients' symptoms over time under treatment.

Finally, we conducted in a subsample a test-retest 7 days after the first follow-up. Results showed satisfactory reproducibility rates, with 94 and 96% of axillary and palmar HH patients, respectively, reporting the same HDSS values when comparing first and second queries.

Our study has some limitations. This Portuguese version of the HDSS was only applied to patients with palmar or axillary HH and, therefore, the results cannot be generalized to patients with symptoms in other areas. Moreover, we only analyzed the association between HDSS and subjective methods to evaluate HH. Further studies regarding the correlation between HDSS and objective

TABLE 1 Demographic characteristics of patients.

		Palmar	Axillary	Total
Gender	Female	70%	68%	69%
	Male	30%	32%	31%
Age (years)	Average±SD	26.5±9.0	31.2±9.8	28.7±9.6
	Range	18-59	18-60	18-60
BMI (kg/m²)	Average±SD	22.4±3.9	23.8±3.8	22.4±3.9
	Range	10.6-35.0	13.4-35.4	10.6-35.4

SD: standard deviation; BMI: body mass index.

TABLE 2 Association between responses from Hyperhidrosis Disease Severity Scale (HDSS) and Quality of Life Questionnaire for patients with axillary (N=115) and palmar hyperhidrosis (N=175).

	Quality of Life Questionnaire			
HDSS (axillary)	**No improvement**	**Slightly better**	**Much better**	**Total**
No improvement	21%	45%	33%	100%
Slight improvement	7%	44%	49%	100%
Good improvement	0%	50%	50%	100%
HDSS (palmar)				
No improvement	22%	43%	45%	100%
Slight improvement	3%	40%	57%	100%
Good improvement	0%	6%	94%	100%

TABLE 3 Association between responses from Hyperhidrosis Disease Severity Scale (HDSS) and Sweating Evolution Questionnaire for patients with axillary (N=115) and palmar hyperhidrosis (N=175).

	Sweating Evolution Questionnaire			
HDSS (axillary)	**No improvement**	**Slight improvement**	**Great improvement**	**Total**
No improvement	28%	25%	47%	100%
Slight improvement	0%	11%	89%	100%
Good improvement	8%	0%	92%	100%
HDSS (palmar)				
No improvement	28%	25%	47%	100%
Slight improvement	0%	11%	89%	100%
Good improvement	0%	6%	94%	100%

evaluations of HH (e.g. sudorometer) are required to validate these results.

As can be seen from our results, we believe that the translation and validation process of HDSS into Portuguese was successful. It showed significant statistical correlation with other questionnaires (construct validation), good reproducibility rates and sensitivity to changes after clinical treatment. Thus, we can confidently state that the Portuguese version of the HDSS can be used in clinical practice to evaluate the degree of sweating and patient outcomes, as well as manage the treatment of patients with HH, in both palmar and axillary HH.

Conclusion

The Portuguese version of the HDSS showed reliability and reproducibility in a Brazilian sample and can be used as healthcare tool in patients with HH.

Resumo

Tradução e validação da Hyperhidrosis Disease Severity Scale

Objetivo: a avaliação de pacientes com hiperidrose (HH) pode ser realizada, entre outras maneiras, por questionários e escalas. O Hyperhidrosis Disease Severity Scale (HDSS) tem sido utilizado como uma forma simples e rápida. Embora o HDSS seja utilizado em outros idiomas, ainda não foi traduzido para o português, limitando sua utilização em pacientes brasileiros. O objetivo deste estudo foi traduzir o HDSS para o português e validá-lo em uma amostra brasileira.

Método: duzentos e noventa (290) pacientes brasileiros (69% mulheres, idade média de 28,7±9,6 anos e IMC médio de 22,4±3.9 kg/m²) com HH foram avaliados pelo HDSS, pelo Questionário de Qualidade de Vida (QQV) e pelo Questionário de Evolução da Sudorese (QES) antes e após 5 semanas de tratamento com oxibutinina. Para a validação de constructo do HDSS, foi realizada a associação entre seus resultados com os dos outros dois questionários. Para analisar a sua sensibilidade, foi realizada a análise do efeito pré e pós-tratamento com oxibutinina. Além disso, foi analisada a sua reprodutibilidade em uma subamostra, na qual a escala foi aplicada novamente após 7 dias da primeira consulta.

Resultados: observamos correlação estatística entre o HDSS e o QQV e entre o HDSS e o QES antes do tratamento e após 5 semanas. O HDSS demonstrou ser reprodutível e sensível em relação ao efeito do tratamento.

Conclusão: a versão em português da escala HDSS apresentou validade e reprodutibilidade em amostra brasileira e pode ser utilizada como instrumento na assistência à saúde de pacientes com HH.

Palavras-chave: hiperidrose, escalas, questionários, traduções, estudos de validação.

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Health-related quality of life in Brazilian community-dwelling and institutionalized elderly: Comparison between genders

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Summary

Objective: To compare the health-related quality of life (HRQL) indicators between institutionalized and community-dwelling elderly men and women.
Method: This was a cross-sectional study with a sample of 496 elderly men and women, surveyed by researchers at a private hospital that attends institutionalized and community-dwelling elderly. HRQL (World Health Organization Quality of Life), daily living activities (Katz questionnaire), and instrumental daily living activities (Lawton questionnaire), mini-mental state examination, handgrip strength test, and function capacity (timed up and go test) were obtained.
Results: Institutionalized men presented higher scores in physical and psychological domains of HRQL compared to elderly men living alone ($p<0.05$). Among women, the scores in all domains (physical, psychological, relationship, and environment) were similar between institutionalized and community-dwelling individuals.
Conclusion: Institutionalized elderly men reported better scores in physical and psychological domains of HRQL compared to their community-dwelling pairs, while both institutionalized and community-dwelling elderly women presented similar HRQL.

Keywords: aging, institutionalization, physical function, cognition.

Introduction

Improvements in life expectancy in Brazil have increased the demand for long-term care among elderly subjects (≥ 65 years).[1,2] Institutionalization has been considered an important alternative to provide adequate health care, especially for elderly who present poor functional capacity, advanced chronic diseases, and dependence.[3,4]

Although institutionalization improves elderly physical and cognitive functions and disease management, leading to an increase in life expectancy, their health-related quality of life (HRQL) is lower compared to community-dwelling elderly.[5] However, it is unknown if these differences occur in a gender-dependent way. Given that the prevalence of disability and chronic diseases is higher in women,[6] our hypothesis is that institutionalization could have greater impact on HRQL among women compared to men. Thus, the aim of this study was to compare the HRQL indicators between institutionalized and community-dwelling elderly men and women attended in a private hospital in Brazil.

Method

Sample

This was a cross-sectional study composed by 496 consecutive elderly men (n=176) and women (n=320) recruited in a Geriatric Hospital [Vila Mariana's unit of Hospital Israelita Albert Einstein (HIAE), São Paulo – Brazil]. Vila Mariana's unit of the HIAE is specialized in the care of elderly over 65 years. The patients attended included institutionalized and community-dwelling elderly individuals. In this unit, a multidisciplinary team (physicians, physiotherapists, psychologists, nurses, nutritionists and kinesiologists) provides optimal health and social support for the elderly.

Patients included in our study were aged ≥ 65 years and did not present any signs of dementia. They were interviewed by a trained nurse who performed all data collection. Information regarding HRQL, daily living activities, and instrumental daily living activities, as well as the mini-mental state examination was obtained. Moreover, they were also submitted to handgrip strength test and timed up and go (TUG) test. The subjects were divided into three groups: institutionalized, community-dwelling elderly living with their relatives, and community-dwelling elderly living alone.

This study was approved by the Clinical Research Ethics Committee of HIAE (process number: 0051.0.028.000-05). Moreover, the procedures were in accordance with the ethical standards of the Hospital's Committee of Ethics for Analysis of Research Projects on Human Experimentation and with the Helsinki Declaration of 1975 (revised in 1983).

Primary outcome

HRQL was assessed based on the Brazilian version of the World Health Organization Quality of Life (WHOQOL). This questionnaire consists of questions regarding four domains: physical health, psychological, social relationships, and environment. The score for each domain varies from 0 to 20, zero being considered the worst and 20 the best quality of life.[7] The participants answered the questionnaire and when asked to help, the researcher was limited to re-reading the questions slowly. If the elderly presented difficulty in reading or understanding the questions, the assessment was conducted by interview.

Secondary outcomes

Daily living activities were assessed using Katz'questionnaire,[8] which includes six items: bathing, getting dressed, going to the bathroom, getting from bed to a chair and vice-versa, maintaining sphincter continence, and eating. Instrumental daily living activities were analyzed using the Lawton-Brody scale[9] that includes eight items: using the telephone, shopping, cooking one's own meals, housecleaning, doing laundry, using transportation, taking medication, and managing finances. The mini-mental state examination was conducted to assess cognitive function, while the level of depression was assessed using a short form of the 15-item Geriatric Depression Scale.[10] Functional capacity was evaluated by handgrip strength test[11] and timed up and go test.[12]

Statistical analysis

Descriptive statistics was performed using frequency distribution and mean±standard deviation. The groups were compared using one-way ANOVA for continuous variables, and Pearson chi-square test for categorical variables. For all inferential analysis, a $p<0.05$ was considered significant.

Results

Figure 1 shows the characteristics of the sample. Men presented higher prevalence of stroke and coronary artery disease, while women presented higher prevalence of depression. Institutionalized men and women were older, had higher prevalence of functional disability, lower cognitive function, and higher prevalence of stroke compared to the other two groups ($p<0.01$). Women living alone presented a higher prevalence of coronary artery disease and depression compared to the other two groups ($p<0.05$). All other variables were similar among the three groups ($p>0.05$).

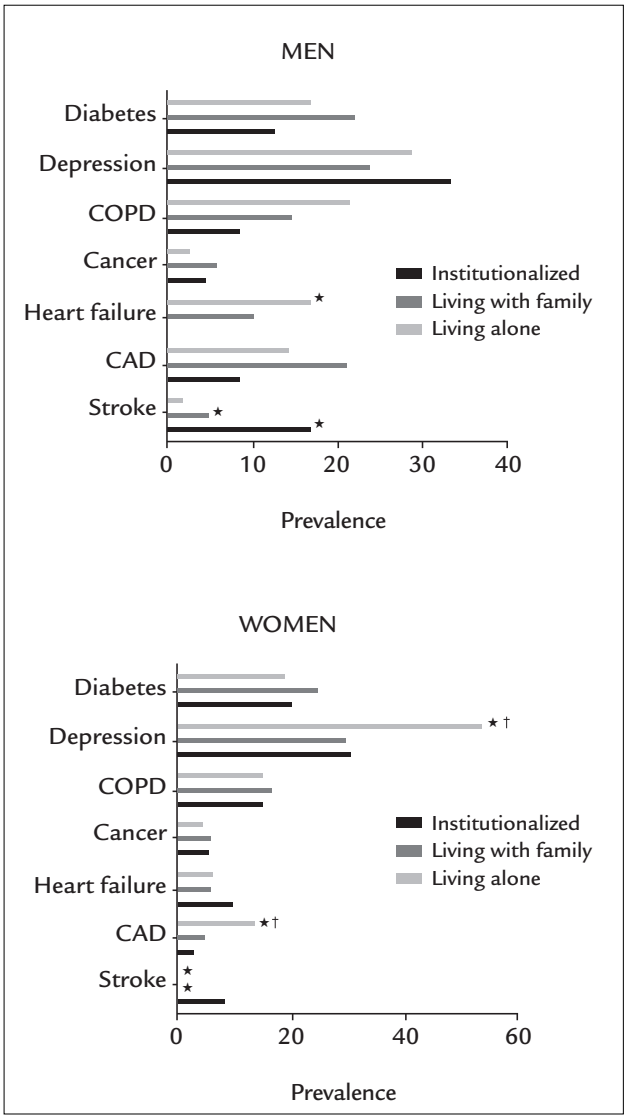

FIGURE 1 Characteristics of the sample.
COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease.
*Difference from institutionalized ($p<0.05$); † difference from living with family ($p<0.05$).

Figure 2 presents the HRQL indicators in elderly men. Institutionalized men presented higher scores in physical and psychological domains compared to elderly men living alone ($p<0.05$). In addition, the score in psychological domain was higher in institutionalized men compared to elderly men living with their families ($p<0.05$).

Figure 3 presents the HRQL in elderly women. The scores in all domains (physical, psychological, relationship, and environment) were similar among the three groups ($p>0.05$).

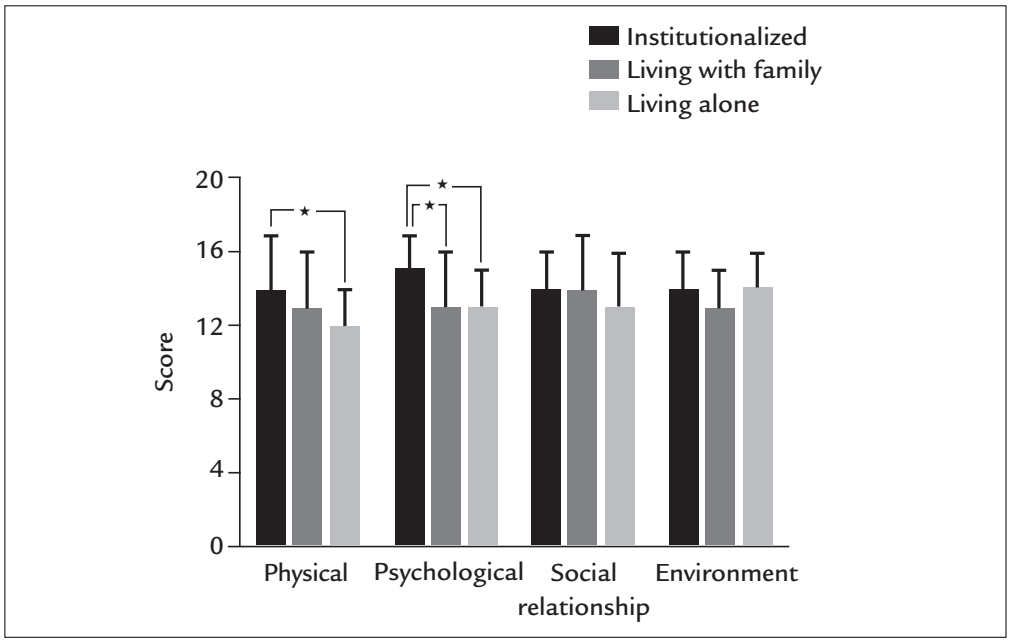

FIGURE 2 Health-related quality of life indicators in elderly men living in institutions (n=24), with family (n=110), or alone (n=42).

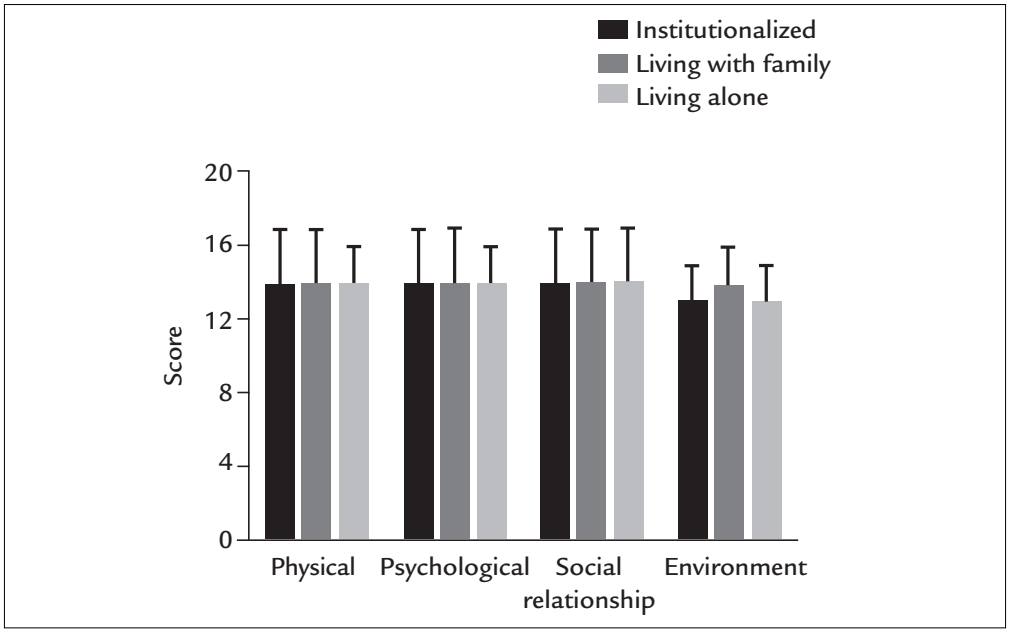

FIGURE 3 Health-related quality of life indicators in elderly women living in institutions (n=75), with family (n=170), or alone (n=75).

Discussion

The main results of this study were: (i) institutionalized elderly presented similar functional performance compared to community-dwelling elderly; (ii) institutionalized elderly men and women were older and presented lower cognitive function compared to community-dwelling elderly; (iii) institutionalized men presented higher scores in physical and psychological of HRQL domains in comparison with community-dwelling elderly; and (iv) both institutionalized and community-dwelling elderly women had similar HRQL.

In the presented study, although institutionalized men and women were older than community-dwelling elderly, they presented similar performance in physical tests, including handgrip strength and timed up and go. These results reflect the rehabilitation program available at the institution, in which a multidisciplinary team (physicians, physiotherapists, psychologists, nurses, nutritionists and kinesiologists) provides optimal health (exercise programs, nutritional counseling) and social support for elderly subjects, with adequate stimulus for improvements in elderly physical capacity. Despite the positive physical profile, the institutionalized elderly participants were less capable of performing basic and instrumental activities of daily living. This was probably caused by the lower cognitive capacity of institutionalized elderly compared to community-dwelling elderly individuals[13] since cognitive functions are strongly related to the capacity to perform basic and instrumental daily activities.[14-16]

Previous studies have suggested an association between dependence and lower perception of HRQL.[17] However, in the present study, despite high dependence, HRQL indicators were similar or better in institutionalized compared to the community-dwelling elderly participants. Factors that included elderly physical fitness and the facilities offered in the institution (e.g. more accessible spaces, short hallways, handrails, and walking path to provide a safety sensation) and the presence of a full-time health staff probably improved their HRQL perception.

The differences in HRQL scores between institutionalized and community-dwelling elderly occurred in a gender-dependent fashion. Institutionalized men showed higher scores in physical and psychological domains compared to community-dwelling elderly, while no significant differences in any domain of health-related quality of life were observed among women. Given that HRQL is related to the perception of life, men probably have a better perception of their physical fitness and cognitive function. Moreover, chronic conditions such as arthritis, back problems, or depression are found more frequently in women[6] and these chronic conditions have a greater effect on HRQL.

The results of the present study reveal some important clinical aspects. First, this study provides further information on HRQL indicators among the elderly living in different settings, and how elderly men and women perceive their HRQL. The similar and/or better results observed in institutionalized elderly compared to community-dwelling elderly suggest that the maintenance of HRQL with aging is possible in elderly individuals living in an adequate environment.

The cross-sectional design is the main limitation of our study, since it does not allow causality, and our results should therefore be confirmed by longitudinal studies. The groups were not matched, as institutionalized elderly were older and presented a lower cognitive function compared to community-dwelling elderly. However, this represents the different profile of institutionalized and community-dwelling elderly populations. The number of institutionalized and community-dwelling men was lower than the number of community-dwelling elderly individuals living with their families, which probably represents the pattern of distribution of elderly men living in different conditions. Finally, the subjects were recruited in a single institution and whether similar results are observed in other places is unknown.

Conclusion

The results of our study indicated that institutionalized elderly men reported better scores in physical and psychological domains of HRQL compared to community-dwelling individuals, while both institutionalized and community-dwelling elderly women presented similar HRQL.

Acknowledgments

The authors wish to extend their grateful thanks to all the patients of the study.

Resumo

Qualidade de vida relacionada à saúde em idosos brasileiros residentes em comunidade e institucionalizados: comparação entre gêneros

Objetivo: comparar os indicadores de qualidade de saúde de vida (QV) entre idosos homens e mulheres institucionalizados e aqueles que vivem na comunidade sozinhos ou com a família.

Método: estudo transversal com amostra composta por 496 idosos homens e mulheres, entrevistados por pesquisadores em um hospital privado que atende idosos institucionalizados e da comunidade. Os indicadores de QV (World Health Organization Quality of Life), atividades da vida diária (Katz *questionnaire*), atividades instrumentais da vida diária (Lawton *questionnaire*), exame do estado mental (mini-mental), teste de força de preensão manual (Handgrip) e capacidade funcional (Timed up to go) foram obtidos.
Resultados: homens institucionalizados apresentaram maiores escores de QV no domínio físico e psicológico em relação aos idosos que vivem na comunidade sozinhos ($p<0,05$). Nas mulheres, os escores em todos os domínios de QV (físico, psicológico, relações sociais e ambientais) foram semelhantes entre as idosas institucionalizadas e as residentes na comunidade, que vivem sozinhas ou com a família.
Conclusão: homens idosos institucionalizados relataram melhores escores de QV nos domínios físico e psicológico em comparação com pares que vivem na comunidade, enquanto, em mulheres, resultados similares foram observados nas idosas institucionalizadas e da comunidade.

Palavras-chave: envelhecimento, institucionalização, função física, cognição.

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Reasons for choosing the profession and profile of newly qualified physicians in Brazil

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Summary

Objective: To evaluate the socio-demographic profile, path to medical school admission and factors affecting the choice of becoming a physician in Brazil.
Method: Application of a structured questionnaire to 4,601 participants among the 16,323 physicians who graduated between 2014 and 2015 that subsequently registered with one of the 27 Regional Boards of Medicine (CRMs).
Results: The average age of participants is 27 years, 77.2% are white, 57% come from families with a monthly income greater than ten times the minimum wage, 65% have fathers who have completed higher education, 79.1% attended a private high school, and 63.5% selected the "will to make a difference in people's lives or do good" as their main reason for choosing medicine, with some differences between the sexes and matriculation at a public or private medical school.
Conclusion: The recent politics for educational diversity and the opening of additional medical schools has not yet had an impact on the socio-demographic profile of graduates, who are mainly white, wealthy individuals.

Keywords: physicians, undergraduate medical education, career choice, demographics.

Introduction

The number of new physicians has reached record levels in several countries in the world that have reformed their training strategies and the provision of such professionals in order to provide a better response to the current needs of these populations and health systems. This progress is more clearly verified in countries that have opened up new courses and increased the number of students admitted to medical schools.[1]

The problem of a widespread insufficiency or shortage of physicians is accompanied by concerns about adequate training, and the profile and motivations of the new generations of professionals who are entering the labor market.

Brazil has also seen a recent significant increase in the amount of qualified physicians, which is a result of programs and policies that aim to focus not only on supply of these professionals, but also their training, distribution and fixation. Law no. 12,871[2] was approved in 2013, and its constituent parts provides for the opening of undergraduate courses in medicine, expansion of medical residency admissions, the provision of physicians in underserved locations and new guidelines for medical training.

Brazil has approximately 425,000 active physicians, which is the equivalent to a rate of around two physicians per 1,000 inhabitants, which is below the average in European countries and distributed unevenly both within the territory and between the public and private health sectors.[3]

For better planning, forecasting and decision-making in relation to the medical workforce, we need to understand the national characteristics and dynamics through multiple sources, including population censuses, surveys with physicians, administrative bases of employers and health services, as well as data relating to medical schools, training, trade associations, licensing and registration.

These efforts could be focused on referential medical demography studies[3-6] that consist of approaching the

population of physicians considering factors such as age, gender, territorial mobility, pay, links, workload, production, inclusion in the health system, behaviors, and the practices of these professionals.

Several national and international studies have outlined the profile of physicians, medical students and former medical school students, highlighting sociodemographic variables such as gender, household income, parental education, training prior to graduation, as well as opinion polls about medical education and career prospects.

In Brazil, in addition to other studies, the characteristics of medical students at State University of Rio Grande do Norte,[7] at the Federal University of Minas Gerais[8] and at the Federal University of Espírito Santo[9] have been studied. A profile has also been outlined of former students graduating from the Medicine Course at the Lutheran University of Brazil – Ulbra, in Porto Alegre,[10] the Medical School of the ABC,[11] the University of São Paulo (USP) Medical School,[12] the Botucatu Medical School,[13] and the medicine course of the State University of Londrina.[14] Meanwhile, the Ministry of Education has produced reports[15] using the data reported by medical students during the National Student Performance Exam (ENADE, in the Portuguese acronym).

However, there is a gap in current national research aimed at outlining the profile, perceptions and motivations of newly qualified physicians. This is the purpose of the following study.

Method

This article is part of the research "Profile and perceptions of new graduates in medicine in Brazil", a survey study aimed at the production of quantitative descriptions of a certain target population.[16] The research has a national scope and involved the application of an optional structured questionnaire, with the eligible and potential participants including all recently qualified physicians registered with one of the 27 Regional Boards of Medicine (CRMs) in Brazil.

The study was performed in two stages. In the State of São Paulo, between September 1, 2014 and August 31, 2015, it followed the registration calendar of new physicians at the Regional Board of Medicine in the State of São Paulo (Cremesp) and had the purpose of testing the operation of the research's online platform on a larger scale, as well as the level of adherence and completeness of the questionnaire. In other units of the Federation the survey took place between November 1, 2014 and October 31, 2015, at the time of registration of new physicians at the CRMs.

The study was approved by the USP Medical School's Research Ethics Committee (CEP) under number (Report 797.424. 9/3/2014).

Instrument

The definition of the format, content and means of applying the questionnaire was based on similar studies[17-24] and methodological manuals[25,26] dealing with this technique. A structured questionnaire was prepared with 104 closed, multiple choice questions grouped into thematic blocks aimed at outlining the demographic profile, as well as studying the perceptions of graduates from medical courses in Brazil about graduation, career, the health system and aspects of medical ethics.

This article includes the results relating to the demographic profile of the new graduates, their entry route, and choice of medical school. The remaining results will be discussed in due course.

After a pilot test with sixth-year medical students, the final version of the questionnaire was deployed in an online platform and applied experimentally in São Paulo for one week, allowing us to assess the actual time requirements and to improve the technical aspects of online completion of the questionnaire.

Data processing

In order to understand the range of new graduates, of whom the participants represented a fraction, we worked with data from the total number of graduates registering with the CRMs in the research period, in accordance with the database provided by the Federal Board of Medicine.

All entries in the database of participants who had no corresponding record in the database of the target population were excluded.

Three stratification variables were used: 1) Sex; 2) Public or private nature of the undergraduate medical school; 3) Major regions of the country, according to the undergraduate medical school.

The number of participants varied between questions and within each stratum. Therefore, we chose to design the analysis equivalent to that of a complex sample (stratified), taking into account the percentage of the different strata in the target population in order to adjust the results. As such, the representativeness of each stratum in the analysis was guaranteed. The confidence intervals for the frequencies were calculated by bootstrapping with 1,000 resamples.

Results

After eliminating inconsistencies such as duplicate taxpayer numbers, registration errors and lack of data regard-

ing the sex or training institution, the target population reached 16,323 eligible newly qualified physicians, all of whom were invited to participate in the study.

The questionnaire was answered by 5,785 individuals. 1,184 participants without registration at the CRMs in the one-year period determined by the study were disregarded. At the end, 4,601 subjects participating in the study were analyzed.

Table 1 presents the distribution of the target population (all new graduates registered at the CRMs) and the participants in the study, according to the strata defined, with the respective confidence intervals. Figure 1 shows the percentage of respondents (joining the study) for each Unit of the Federation in relation to the physicians trained in the same period for each state.

The study allowed us to study the sociodemographic profile of new graduates in medicine in Brazil. These graduates are, on average, 27 years of age, with 16.8% aged up to 24 years, 68.4% aged from 25 to 29 years, and 14.8% aged 30 years or more. Graduates from public universities are significantly younger than those from private universities ($p<0.001$).

Around 91% of new graduates are single and 93.5% do not have children. A total of 85.6% described their situation at the end of medical school as someone who still does not work and is "financed by the family". Around 56% stated they lived with parents or relatives, and 17.8% with friends. A total of 77.2% of respondents consider themselves to be white. This percentage reaches 89.5% in the South region, 80.9% in the Southeast, and falls to 54.2% in the Northeast and 53.7% in the North. Only 1.8% of participants in the study declared themselves to be black, and 16.2% to be pardo (Table 2).

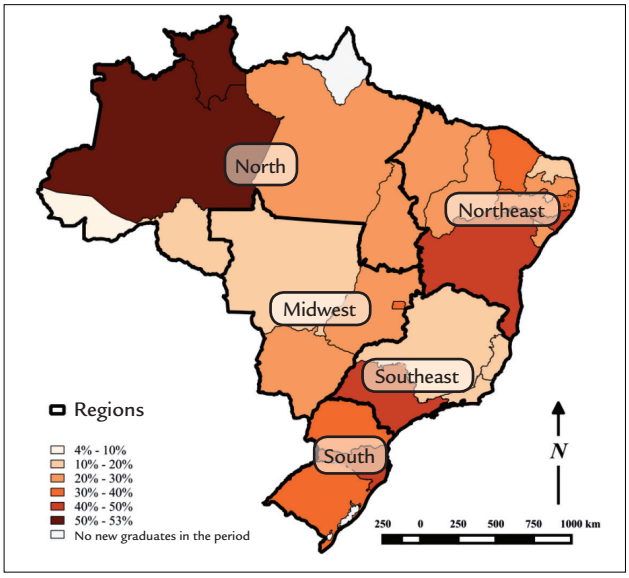

FIGURE 1 Distribution of respondents among the population eligible for the study according to State.

TABLE 1 Distribution of new graduates registered with the CRMs and the participants in the study, according to sex, major region and nature of the undergraduate school.

Strata	N of physicians enrolled with the CRMs	%	N of study participants	% (95CI)
Sex				
Male	7,418	45.4	2,168	47.1% (45.8-48.5)
Female	8,905	54.6	2,433	52.9% (51.5-54.2)
Major region				
South	2,435	14.9	884	19.2% (18.1-20.3)
Southeast	8,172	50.1	1,996	43.4% (42.0-44.8)
Midwest	930	5.7	248	5.4% (4.7-6.1)
North	1,433	8.8	415	9.0% (8.2-9.8)
Northeast	3,353	20.5	1,058	23.0% (21.8-24.2)
Nature of the medical school				
Public	6,294	38.3	2,072	45.0% (43.6-46.6)
Private	10,029	61.4	2,529	55.0% (53.4-56.4)
Total	**16,323**	**100**	**4,601**	**100**

Just over a third of the graduates (35.4%) come from families with a monthly income between three and ten minimum wages (Table 2). The families of the other 29.0% have a monthly income between 11 and 20 minimum wages. More than a quarter (28.3%) are children of families who earn more than 21 minimum wages per month. Among the graduates trained at schools in the North of the country, 14.8% are from families who earn up to three monthly minimum wages. Those who graduated from private medical schools come from families with a higher monthly income: 31.2% of these are above 21 minimum wages, compared to 20.4% of graduates from public medical schools with the same range of family income.

In relation to the level of education of relatives, the fathers of 65% and the mothers of 69.4% had completed higher education (Table 3). Around a third of the graduates (32.6%) had a physician in the family, considering just parents, siblings and/or spouse. Among those educated at public schools, 25.8% have physicians in the family, with the proportion reaching 35.1% among those educated at private schools.

The study verified whether new graduates in medicine attended secondary education at public or private school, and if they attended entry examination preparatory courses (Table 4). A total of 79.1% reported having completed secondary education at private school. Among graduates from private medicine courses, 80.3% completed secondary education at private school, compared with 75.6% of graduates from public medical schools. Only 16.6% did not undergo a preparatory course for the entrance exam. The South region has the highest percentage (88.9%) of students who attended "preparatory courses". In the country as a whole, 43.6% took the "preparatory course" for 2 years, and 18.6% for 3 years or more.

The vast majority of respondents – 88.3% of them – were admitted to the medicine course through the traditional entrance exam. Another 4.1% used the National Secondary Education Exam (ENEM) to complement their score. The Unified Selection System (SISU) and Quota Law were resources cited by 1.7% of those studying at public medical schools.

Less than half of the graduates from private schools (47.6%) received some type of scholarship or funding to cover the cost of the medicine course. In this group, 33.1% were benefited by the Higher Education Student Financing Fund (FIES) and 8.0% by the University for All Program (PROUNI). Around 5.1% received a full or partial scholarship from the medical school itself or an external institution. Among those who attended public medical school, 92.4% did not receive a scholarship, financing or financial aid of any nature during the course.

In the study, the question "why I took Medicine" offered alternative responses and enabled multiple choices (Table 5). The main reason for choosing the profession, as indicated by 63.5% of the new graduates, was "the desire to make a difference in people's lives or to do good", while 54.5% indicated an "interest in the study of the human body and disease".

There is a difference in the expectations of graduates from public and private universities. Among the graduates

TABLE 2 Distribution of new medicine graduates according to self-reported color/race and range of monthly family income.

Do you consider yourself to be?		
White	3,327	77.2%
Black	104	1.8%
Pardo/mulatto	951	16.2%
Yellow/Asian	168	4.4%
Indigenous	22	0.4%
Total	4,572	100%
What is the range of your family's monthly income?		
Up to 3 minimum wages	350	7.3%
3 to 10 minimum wages	1,601	35.4%
11 to 20 minimum wages	1,329	29.0%
21 to 30 minimum wages	612	15.1%
More than 30 minimum wages	544	13.2%
Total	4,436	100%

TABLE 3 Distribution of new graduates in medicine according to father and mother's level of education.

	Father's level of education		Mother's level of education	
No schooling	29	0.5%	12	0.3%
Elementary from 1st to 4th years	246	5.3%	134	2.8%
Elementary from 5th to 8th years	299	6.5%	202	4.5%
High school	1,115	22.9%	1,115	23.0%
Higher education	2,806	64.8%	3,039	69.4%
Total	**4,495**	**100%**	**4,502**	**100%**

at public medical schools, 36.4% stated they had studied medicine "due to the potential pay" of the profession. Among graduates at private schools, this percentage drops to 25.2%. When the answers are grouped by sex, we can see that women responded more to the choices "to do good" (66.2% *versus* 59.3% among men) and "interest in the physician/patient relationship" (45.3% *versus* 35.4%). Male participants attributed the choice more to the "prestige of the profession" and the "potential pay" – with the latter justification cited by 37.5% of men *versus* 22.2% of women.

There is a difference in the motivations indicated to choose the profession according to level of income. The reasons "due to family influence or advice" and "interest itself/intellectual challenge" were more common among higher income graduates (p<0.001 and p=0.021). Meanwhile, "interest in the study of the human body and disease" was indicated more by lower income graduates (p=0.010). The reason "due to family influence or advice" was more common among graduates who have a physician in the family (p<0.001). Graduates without a physician in the family were more likely to indicate the reasons "interest in the study of the human body and disease" (p=0.014) and "desire to make a difference in people's lives or to do good" (p=0.010).

All of the indicators raised in the study were stratified by sex, major regions and according to the public or private nature of the medical schools.

Discussion

Newly qualified physicians in Brazil are whiter and richer than the general population, and the vast majority is

TABLE 4 Distribution of new graduates in medicine according to the public and private nature of the undergraduate school and the school where they completed secondary education, and according to the attendance at the entrance exam preparatory course.

	Educated at public school		Educated at private school		Total	
	n	Freq.	n	Freq.	n	Freq.
What kind of secondary education school did you attend?						
All or mostly public school	431	19.8%	345	13.4%	776	15.1%
Half in public school and half in private school	18	0.8%	15	0.7%	33	0.8%
All or mostly private school	1,542	79.4%	2,044	85.9%	3,586	84.2%
Total	1,991	100%	2,404	100%	4,395	100%
Did you attend an entrance exam preparatory course?						
I did not attend a preparatory course	268	13.7%	440	17.7%	708	16.6%
Yes, I attended the course for 1 year or less	663	31.9%	1,021	42.5%	1,684	39.7%
Yes, I attended the course for 2 years or more	1,055	54.5%	942	39.8%	1,997	43.6%
Total	1,986	100%	2,403	100%	4,389	100%

TABLE 5 Distribution of new graduates in medicine, according to reason for choosing the profession.

Reason for choosing medicine	Female	Male	p-value	Public	Private	p-value	Total
Due to the desire to make a difference in people's lives or to do good	1,554 (66.2%)	1,196 (59.3%)	<0.001	1,249 (64.1%)	1,501 (63.3%)	>0.050	2,750 (63.5%)
Due to the interest in studying the human body and disease	1,285 (55.6%)	1,040 (52.8%)	>0.050	1,086 (56.8%)	1,239 (53.7%)	>0.050	2,325 (54.5%)
Due to the interest in the physician/patient relationship	1,022 (45.3%)	711 (35.4%)	<0.001	759 (40.0%)	974 (42.0%)	>0.050	1,733 (41.5%)
Due to the interest itself/intellectual challenge	884 (35.0%)	1,009 (45.7%)	>0.050	979 (49.7%)	914 (35.4%)	0.002	1,893 (39.2%)
Due to the potential of pay	553 (22.2%)	797 (37.5%)	<0.001	696 (36.4%)	654 (25.2%)	0.047	1,350 (28.2%)
Due to the prestige of the profession	410 (17.5%)	636 (31.2%)	<0.001	508 (26.6%)	538 (21.4%)	>0.050	1,046 (22.8%)

young, single and has no children, and is financially dependent on their parents and still living with them. A third of new graduates have medical "lineage", that is, they have a physician in the family, corroborating studies conducted with medical students in the country.[9,27] In accordance with self-reported race/color, only 1.8% of newly qualified physician in Brazil declared themselves to be black, and 16.2% pardo. The scenario is quite different from that observed in the population, in which 7.6 and 43.1% declare themselves to be black and pardo, respectively.[28] Among newly qualified physicians, 77% are white, which is around 20% more than the 48% of the Brazilian population that declare themselves to be white.[28]

Studies[7,9,27] have already indicated that medical students are, for the most part, proportionately whiter than the population. The situation is different, for example, than that of South Africa[29] and Colombia,[30] where the profile of medical students is closer to the ethnic distribution of the general population.

In Brazil, other undergraduate courses such as Law, Dentistry, Psychology and Veterinary Medicine also have a proportion of whites above that recorded in the general population.[31] Meanwhile, among participants in the ENEM as a whole, the ethnic distribution has been increasingly similar to that of the population.[32]

Certain socioeconomic indicators of new graduates in medicine are concordant: most come from families with a high monthly income, completed secondary education at private school, took a private preparatory course for the entrance exam, and have parents who completed higher education.

57.3% of the participants in the study have a household income of over 10 minimum salaries, a proportion that is eight times higher than in the general population, where 7.6% are in this income range.[33]

Another factor revealing inequality is the percentage of newly qualified physicians (merely 20%) who completed secondary education at public school. In Brazil, secondary education is predominantly public and represents 87% of enrollments.[34]

In higher education in Brazil, in general, students are predominantly from public schools but study undergraduate courses at private education institutions.[15] The pattern is therefore distinct in medicine.

The traditional entrance exam was the predominant mode of admission for the medicine course (to 88%), almost always proceeded by a preparatory course. Only 17% did not take the "preparatory course" and 60% did so for 2 or more years.

Various policies are currently underway in Brazil seeking to promote inclusion in higher education. Aimed at the private education sector, since 2001 there has been the Higher Education Student Financing Fund (FIES) and the University for All Program (ProUni) launched in 2005, which provides full or partial scholarships to students with a low family income of up to 3 minimum wages. Meanwhile, the SISU was created in 2010 as an alternative to the traditional entrance exam at public universities, using the results of the ENEM as selection criteria, as well as other affirmative measures. Furthermore, Law no. 12.711/ 2012[35] determined that federal universities must reserve at least 50% of their admissions for students coming from public schools and low income students.

Among newly qualified physicians at public medicine courses, only 1.6% was benefited by the SISU or the Quota Law. Meanwhile, among graduates at private medical schools, 33.1% used the FIES and 8.0% used the ProUni. It is worth noting that the participants in this study, who graduated in 2014 and 2015, began their studies 6 years earlier, when these inclusion mechanisms were still not widely practiced or did not include medicine courses. However, these measures have limitations, given that the quota policy is restricted to public education, students shoulder disproportionate costs to their conditions under the FIES, and the ProUni, which is restricted to tax exemption linked to the scholarships granted, has expanded much less than the demand.[31,36] It is possible to adjust the academic metrics to increase socioeconomic, racial and ethnic diversity among undergraduate students of medicine.[37]

By analyzing the motivations for choosing the medical profession, it can be noted that there was a prevailing consent for humanitarian issues among the new graduates, such as "helping people", "doing good" and the "physician/patient relationship". To a lesser extent, there is reference to the "potential pay" of the profession and the "prestige of the profession".

It is noteworthy that new graduates from public schools expressed a greater interest in the financial return of the profession than their peers educated in private courses. Historically linked to the social rise of popular strata,[38] in contrast, the medical profession is currently chosen by individuals located in higher income strata who, as can be seen, mainly studied secondary education at private schools, with many completing their medical degree at public universities.

When the responses are grouped by sex, we see that the choice of medicine by new graduates that are women has a greater social component. They are more likely to indicate "doing good" and the "interest in physician/patient relation-

ship" while reported the "prestige of the profession" and "potential pay" more often. As such, it is worth noting that studies using gender theory outline the traditional female identity as more accustomed to caring and being concerned about the care of others when compared to male identity. The male gender is indicated by the literature as having a dominant pattern linked to competitiveness, and the condition of provider to women, children or the elderly. Thus, men tend to focus on issues of professional success, competing more in the market, or concern with gaining the income they deem necessary.[39-43]

There are also other gender and generational effects on the choice of medicine, which have repercussions on the definition of career and professional realization.[44] For example, young female physicians acknowledge motivations and practices also aimed at including better reconciliation between personal and professional life.[45] Changes in how medical work is conceived, organized and valued have been identified as being necessary to combat gender inequalities in medicine, which are translated into lower pay and a lower presence of women in medical specialties and leadership positions in medicine.[46]

In the study's target population, women are the majority (54.6%) among new graduates, in keeping with historical patterns worldwide towards a progressive reduction in quantitative differences in education and employment in general.[47] In Brazil, around 7% of physicians are male, but since 2011 the number of women has surpassed men among the total registrations of new physicians,[3] following a trend towards feminization of medicine already recorded by various countries.[48] However, this trend is not homogeneous. In studies with medical students, the female presence ranges from 22.4% in the medical course at the Federal University of Espírito Santo[14] to 50.2% at the State University of Londrina,[9] while in foreign studies this ranges from 48% in the United States[49] to 67.1% in the United Kingdom.[50]

Given the different values expressed by women and men in relation to their reasons for choosing the profession, the study raises new investigations into the possible impacts of the feminization of medicine in Brazil. Will medicine become a profession focused more on care and less valued for professional success? Or will women tend towards the more traditional male values that have prevailed in the profession throughout their careers, given the fact that until recently this was a male profession?

There are limitations in the study. There are significant differences between the frequency of the strata in the target population and between participants, which required adjustments. However, there is no way to estimate the possibility of bias, considering the different adhesion rates between strata. There was also a significant amount of participants in the study with no correspondence in the target population database and who were therefore disregarded. These improper entries may possibly be attributed to those registered with the CRMs and who answered the questionnaire but were not new graduates but rather physicians that were ineligible for the study and had requested secondary registration due to transfer of their state of domicile.

Conclusion

Entry into medicine in Brazil privileges white individuals and those who have a better socioeconomic situation. Although there has been a significant increase in the number of medical courses and admissions in recent years, reconciling this expansion with the democratization of access to medical education is a major challenge.

Educational policies of inclusion, quotas and affirmative measures that aim to promote equal access to higher education have not yet had an impact on changing the profile of physicians trained in Brazil. Medical training remains elitist and inaccessible to certain strata of the population, partly for being more competitive or expensive, among other factors, as well as being marked by competition in entrance exams for public courses and high tuition fees in private courses.

Now the majority of new graduates, women have different characteristics and motivations than those expressed by men, which places the feminization of medicine as a relevant topic for future research.

It is hoped that the elements raised by this study can contribute to outlining a broader research agenda aimed at a better understanding of the dynamics of the medical profession which, ultimately, has repercussions on the organization and operation of the health system.

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Resumo

Motivos de escolha da profissão e perfil de médicos recém-graduados no Brasil

Objetivo: traçar o perfil sócio-demográfico de recém-graduados em medicina no Brasil, a forma de ingresso na graduação e os motivos de escolha da profissão médica.

Método: aplicação de questionário estruturado em 4.601 participantes, dentre 16.323 médicos formados entre 2014 e 2015, que se registraram em um dos 27 Conselhos Regionais de Medicina (CRM), considerados a população-alvo do estudo.
Resultados: a idade média dos recém-graduados é de 27 anos, 77,2% são brancos, 57% vêm de famílias com renda mensal acima de dez salários mínimos, 65% têm pais com educação superior, 79,1% cursaram ensino médio em escola particular e 63,5% apontaram a "vontade de fazer diferença na vida das pessoas ou fazer o bem" como principal razão para a escolha da medicina, com diferenças entre sexo e natureza pública ou privada da escola de graduação.
Conclusão: as políticas no Brasil de inclusão educacional e de abertura de escolas médicas ainda não tiveram impacto no perfil dos recém-formados em medicina, em sua maioria indivíduos brancos e de maior nível socioeconômico.

Palavras-chave: médicos, educação de graduação em medicina, escolha da profissão, demografia.

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Evidences of autologous fat grafting for the treatment of keloids and hypertrophic scars

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Summary

Introduction: Since the 1980s, the use of autologous fat grafting has been growing in plastic surgery. Recently, this procedure has come to be used as a treatment for keloids and hypertrophic scars mainly due to the lack of satisfactory results with other techniques. So far, however, it lacks more consistent scientific evidence to recommend its use. The aim of this study was to review the current state of autologous fat grafting for the treatment of keloids and hypertrophic scars, their benefits and scientific evidences in the literature.

Method: A review in the Pubmed database was performed using the keywords "fat grafting and scar", "fat grafting and keloid scar" and "fat grafting and hypertrophic scar." Inclusion criteria were articles written in English and published in the last 10 years, resulting in 15 studies.

Results: These articles indicate that autologous fat grafting carried out at sites with pathological scars leads to a reduction of the fibrosis and pain, an increased range of movement in areas of scar contraction, an increase in their flexibility, resulting in a better quality of scars.

Conclusion: So far, evidences suggest that autologous fat grafting for the treatment of keloids and hypertrophic scars is associated with a better quality of scars, leading to esthetic and functional benefits. However, this review has limitations and these findings should be treated with reservations, since they mostly came from studies with low levels of evidence.

Keywords: cicatrix, keloid, cicatrix hypertrophic, transplantation autologous, adipose tissue.

Study conducted at the Plastic Surgery Division of the Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (FMRP-USP), Ribeirão Preto, SP, Brazil

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Introduction

Autologous fat grafts have been used since the beginning of the last century to fill in defects in subcutaneous tissue. In the mid-1980s, the technique of liposuction boosted its use by facilitating its acquisition and application. Since then, the number of procedures using autologous fat grafting has grown in several areas, especially in plastic surgery.

Due to the large number of patients with hypertrophic scars and keloids that did not show improvement with the treatments available at the time, new techniques have been used in order to promote scar maturation and obtain esthetic and functional benefits. In this context, autologous fat grafting represents another therapeutic option and has been used on unsightly and retracted scars,[1,2] burn sequelae,[3] and in reconstructive and cosmetic surgeries (to improve body contour, with the intention of filling and increasing volume).

Previous studies have shown that there are stem cells derived from adipose tissue in the product of liposuction (ADSC: "adipose-derived stem cell"). These cells produce mediators that stimulate the wound healing process and tissue regeneration, and may lead to obtaining a resulting scar of better quality.[4]

Recently, there has been greater promotion of autologous fat grafting at scientific events in our country in order to improve the appearance of keloids and hypertrophic scars, in addition to other benefits. However, currently there is a lack of consistent scientific evidence to recommend autologous fat grafting as a treatment of pathological scars.

The objective of this study was to conduct a review of the current state of autologous fat grafting for the treatment of keloids and hypertrophic scars, its benefits, and scientific evidence present in the literature.

Method

The research was conducted at the Plastic Surgery Division of the Hospital das Clínicas, University of São Paulo's Ribeirão Preto Medical School (ORDERS-USP), from May 2015 to January 2016. A review of articles relating to the topic on the Pubmed/Medline database was conducted, cross-referencing the following descriptors: "fat grafting and scar", "fat grafting and keloid scar" and "fat grafting and hypertrophic scar".

We found 291 articles related to the topic. The inclusion criteria were articles written in English containing the descriptors stated above and published over the last 10 years, resulting in 15 articles (the most relevant articles were selected by their level of evidence or the data contained therein). Case reports were excluded. In each study the authors sought information concerning the role of autologous fat grafting in the treatment of pathological scars, as well as the evidence for such, and esthetic/functional benefits. The inclusion and exclusion criteria are given in Table 1.

The articles were classified according to their level in the evidence pyramid,[5] which varies in descending order from I to V, as can be seen in Table 2. Certain studies cannot be classified based on this classification, as is the case of animal studies, cadaver studies, review articles, letters and editorials.

TABLE 1 Articles inclusion and exclusion criteria.

Inclusion criteria
Articles accessed in the Pubmed database
Articles containing the keywords "fat grafting and scar", "fat grafting and keloid scar" and "fat grafting and hypertrofic scar"
Articles written in English
Articles published in the last 10 years
Exclusion criteria
Case reports
Articles with no data on the use of autologous fat grafting for the treatment of pathological scars

Results

The articles selected for this review point to the results and conclusions presented in Table 3.[1-4,6-16]

Nine of the 15 studies were classified as level IV (case series), two as level III (a retrospective cohort and a comparative clinical study), one as level II (prospective cohort study), and three were not classified (for dealing with animal studies or review articles). No level I studies were found, that is, those with the strongest evidence (controlled and randomized clinical trials).

Animal and *in vitro* studies revealed that fat grafting also stimulates angiogenesis due to the presence of growth factors such as insulin-like growth factor 1 (IGF-1), platelet derived growth factor (PDGF) and, principally, vascular endothelium growth factor (VEGF), which is critical for angiogenesis and fibrotic tissue replacement. During fat grafting, ADSC have been found, which may regulate vessel density, the granulation process and thickness of collagen, leading to an improved appearance of pathological scars.[6]

There was some variability between the authors as to the inclusion criteria for patient selection. These criteria included hypertrophic scars and keloids without improvement after clinical treatment, burns without improvement after three weeks of treatment and ulcers of various etiologies. As exclusion criteria, some authors used the realization of previous surgeries on the site,[6] scars over bony prominences and *diabetes mellitus*,[7] as well as areas with neoplasia due to the theoretical risk of producing new growth factors at the fat grafting site, in addition to VEGF, which could potentially promote tumor growth and invasion.[8]

Fat grafting was also used in patients with painful and retracted scars,[7] in post-mastectomy breast reconstructions (showing a reduction of esthetic sequelae such as cicatricial retraction and deformities),[8] in cicatricial

TABLE 2 Level of evidence of the types of scientific study.

Level of evidence	Type of scientific study (Treatment)
I	High quality randomized controlled clinical trial
II	Prospective cohort; prospective comparative study
III	Retrospective cohort; retrospective comparative study; case-control study
IV	Case series with pre- and post-test or only post-test
V	Case report; opinions developed through consensus

TABLE 3 Selected articles, types of study and level of evidence.

Author / Year	Conclusion of the article regarding autologous fat grafting	Type of study	Level of evidence
Piccolo NS et al., 2015[3]	Decreased fibrosis and hypertrophic scars Increase elasticity and scar malleability	Case series	IV
Huang SH et al., 2015[12]	Relief of cicatricial neuropathic pain due to improved quality of pathological healing	Case series	IV
Kato H et al., 2014[13]	Dynamic remodeling of the cicatricial area after fat grafting	Experimental animal study	-
Maione L et al., 2014[7]	Decreased consistency and size of the pathological scar Increased range of movement of the pathological scar	Case series	IV
Balkin DM et al., 2014[4]	Decreased scar size Improvement of scar color Increased malleability of scar	Case series	IV
Pallua N et al., 2014[6]	Improvement of the quality, color and malleability of the pathological scar	Case series	IV
Moltó Garcia R et al., 2014[8]	Decreased retractions in pathological scars	Case series	IV
Maione L et al., 2014[9]	Decreased pain during treatment, and decreased surgical complications Remodeling of the scar architecture	Comparative clinical study	III
Mazzola IC et al., 2013[10]	Improvement in esthetics and function of the area with pathological healing Low rate of surgical complications	Case series	IV
Viard R et at., 2012[14]	Increased softness of the pathological scar Remodeling in areas with lack of subcutaneous volume	Case series	IV
Guisantes E et al., 2012[1]	Decreased scar retraction Improvement of pathological scar depression	Case series	IV
Sultan SM et al., 2011[11]	Decreased scar fibrosis Improvement of cicatricial quality with increased revascularization	Experimental animal study	-
Caviggioli F et al., 2011[15]	Improvement of quality, and improvement of cicatricial pain	Prospective cohort study	II
Clauser LC et al., 2011[16]	Esthetic and functional improvement of the pathological scar	Retrospective cohort study	III
Patel N, 2008[2]	Improvement of texture and elasticity in the pathological scar	Review	-

sequelae associated with chronic pain,[9] in post-traumatic pathological cicatricial deformities (with important benefits in tissue texture and elasticity),[2] in hypertrophic scars after tracheostomy (with better esthetic and functional quality)[10] and, lastly, in hypertrophic scars and keloids after burns (demonstrating correction of retracted or depressed scars).[1]

Discussion

In this review, certain authors suggest that fat grafting in cicatricial areas has been used due to the benefits of the ADSC with potential for differentiation in other tissues. In the last decade, recognition of the regenerative potential of fatty tissue has indicated clinical improvement of hypertrophic scars in burn patients.[11] The use of fat grafting has been extended even for the treatment of neuropathic pain originating from scar tissue, with improvement in the postoperative period of such patients.[12]

In most of the articles analyzed, the Coleman technique[17] was used as the standard for obtaining the fatty tissue for realization of the autologous fat graft. Generally speaking, the procedure presented a low rate of surgical complications and satisfactory evolution in the postoperative period.[15] A study by Moltó Garcia et al. showed a rate of 3.35% for early complications from fat grafting, such as pain at the application site, seroma and

infection of the surgical wound. In relation to late-onset complications, this study indicated the presence of cysts at the fat grafting site (16.2% of cases) and calcifications (10.8% of cases).[8]

Some studies suggest that autologous fat grafting improves the quality of hypertrophic scars and keloids by presenting a large amount of stem cells and growth factors. As such, this could contribute to decreased fibrosis and increased elasticity, promoting increased malleability of pathological scars.[3] In addition, there is evidence of benefits to scars that have pathological retractions, resulting in clinical improvement and a gain in the amplitude of movements.[7] However, since these studies[3,7] are classified as case series (level IV), any conclusions remain limited by the low level of evidence.

According to some studies, the benefit of ADSC does not appear to be merely theoretical, as they promote increased angiogenesis, the formation of granulation tissue and re-epithelialization, improve color, and may lead to less visible scarring (Figure 1) and increased malleability of the scar.[4,9] Histological studies carried out in areas of fat grafting have indicated that mesenchymal stem cells promote architectural remodeling in the scar tissue, as well as angiogenesis and improved local hydration, leading to increased malleability of the scar.[9]

In relation to hypertrophic scars and keloids in burn patients, fat grafting resulted in accelerated revascularization of the scar tissue associated with decreased fibrosis. This improvement may be related to an increase in VEGF, with a reduction of fibrosis markers verified using ELISA and PCR. This early revascularization could be a protective factor of the wound due to increased tissue transforming growth factor beta 1 (TGF-β1), resulting in a breakdown in the synthesis of collagen in the beginning of the pathological scar formation.[11]

One of the limitations of this review is that most of the studies analyzed (nine articles out of a total of 15) were classified as cases series (evidence level IV). This indicates that most of the data relating to autologous fat grafting in the treatment of pathological scars originated from studies located in the lower levels of the evidence pyramid, meaning that the results and conclusions should be analyzed critically and with some reservation. For this reason, we believe that there is a lack of more consistent evidence for the recommendation of autologous fat grafting in the treatment of keloids and hypertrophic scars.

Finally, new studies with the strongest level of evidence (randomized and controlled clinical trials, prospective cohort studies, and comparative studies with control groups) are required in order to elucidate some of the gaps in our knowledge concerning the role of autologous fat grafting in pathological scars, for example, the standardization of surgical indication, more prolonged postoperative monitoring assessment of late-onset results, the systematization of conduct and proof of the role of ADSC in the promotion of cicatricial improvement.

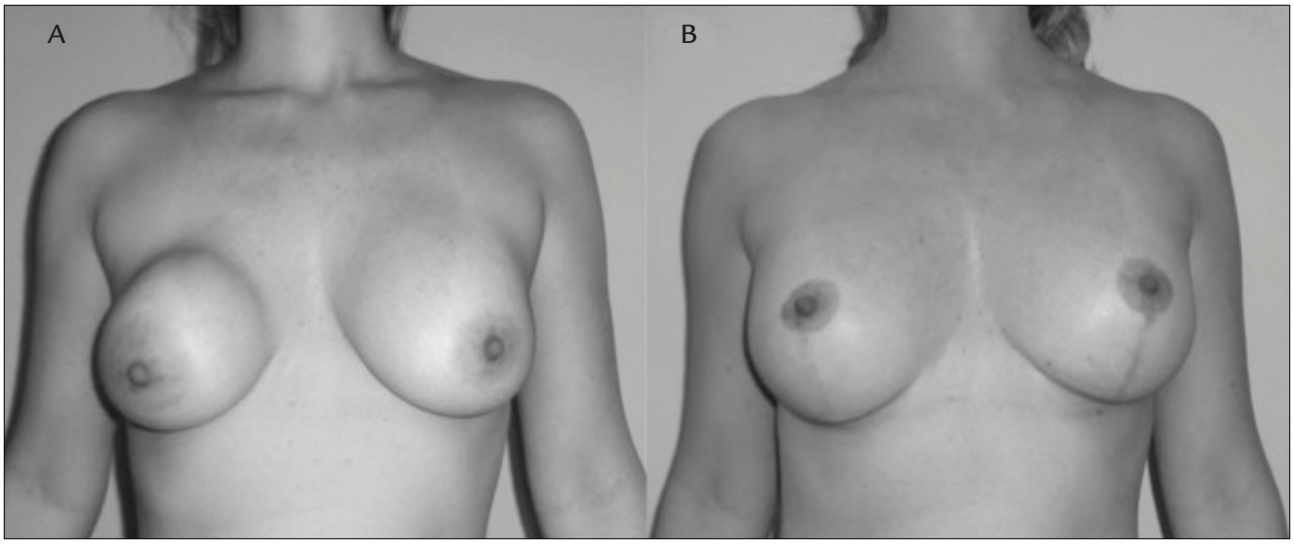

FIGURE 1 A. A 40-year-old female patient who underwent mammoplasty 10 years before and developed capsular contracture on the right. B. She was submitted to a change of implant and bilateral mastopexy associated with fat grafting (60 mL) to the right breast only, in order to improve the contour. Note the improved quality of the scars on the right breast, which are less evident in relation to the left.

Conclusion

Up to now, the evidence indicates that autologous fat grafting for the treatment of hypertrophic scars and keloids is associated with decreased local fibrosis, increased scar malleability and greater range of motion in areas of cicatricial retraction, leading to esthetic and functional benefits. However, this review has limitations and the findings must be noted with reservations, given that the majority of these findings originated from studies with low levels of evidence.

Resumo

Evidências da lipoenxertia autóloga para o tratamento de queloides e cicatrizes hipertróficas

Introdução: a partir da década de 1980, o uso da lipoenxertia autóloga tem crescido na cirurgia plástica. Recentemente, esse procedimento passou a ser utilizado como tratamento de queloides e cicatrizes hipertróficas, principalmente em decorrência da falta de resultados satisfatórios com outras técnicas. No entanto, até o momento, faltam evidências científicas mais consistentes que recomendem seu uso. O objetivo deste estudo foi realizar uma revisão do estado atual da lipoenxertia autóloga no tratamento de queloides e cicatrizes hipertróficas, os benefícios e as evidências científicas presentes na literatura.
Método: foi realizada uma revisão na base de dados Pubmed com os descritores "fat grafting and scar", "fat grafting and keloid scar" e "fat grafting and hypertrofic scar". Os critérios de inclusão foram artigos escritos em inglês e publicados nos últimos 10 anos, resultando em 15 estudos.
Resultados: os artigos indicam que a lipoenxertia autóloga realizada em locais com cicatrizes patológicas leva a uma diminuição da fibrose e da dor, à maior amplitude de movimentos em áreas de retração cicatricial, ao aumento de sua maleabilidade, resultando na melhor qualidade das cicatrizes.
Conclusão: até o momento, as evidências sugerem que a lipoenxertia autóloga para o tratamento das queloides e cicatrizes hipertróficas está associada à uma melhor qualidade das cicatrizes, levando a benefícios estéticos e funcionais. Contudo, esta revisão possui limitações e os achados devem ser analisados com ressalvas, já que a maioria provem de estudos com baixos níveis de evidência.

Palavras-chave: cicatriz, queloide, cicatriz hipertrófica, transplante autólogo, tecido adiposo.

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Current aspects of polycystic ovary syndrome: A literature review

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Summary

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder with variable prevalence, affecting about one in every 15 women worldwide. The diagnosis of polycystic ovary syndrome requires at least two of the following criteria: oligoovulation and/or anovulation, clinical and/or biochemical evidence of hyperandrogenism and morphology of polycystic ovaries. Women with PCOS appear to have a higher risk of developing metabolic disorders, hypertension and cardiovascular disorders. The aim of this article was to present a review of the literature by searching the databases Pubmed and Scielo, focusing on publications related to polycystic ovaries, including its pathogenesis, clinical manifestations, diagnosis and therapeutic aspects, as well as its association with cardiovascular and arterial hypertensive disorders.

Keywords: polycystic ovary syndrome, hyperandrogenism, cardiovascular disorders, arterial hypertension.

Introduction

Polycystic ovary syndrome (PCOS) is a common gynecological endocrine disorder of unknown etiology, with a prevalence ranging from 8.7 to 17.8% in women of reproductive age.[1] Evidence suggests that PCOS phenotype may vary widely and is most commonly observed in the post-pubertal period.[2] Despite a diversity of phenotypes, women with PCOS are characterized by polycystic ovaries, chronic anovulation, hyperandrogenism and gonadotropin abnormalities.[3,4]

In addition to the characteristics that are inherent in PCOS, it is a common occurrence of metabolic and hormonal abnormalities associated with obesity, type 2 *diabetes mellitus* and dyslipidemia.[5] A combination of these characteristics lead to metabolic syndrome.[6] The variety of metabolic disturbances in PCOS may be related to a higher risk of developing cardiovascular disease.[7] This fact may explain a predisposition to arterial hypertension in women suffering from the syndrome.[8] Although the association between changes in arterial blood pressure and PCOS has still not been fully elucidated, the increased risk of hypertensive state may be explained by insulin resistance and hyperandrogenism, even when adjusted for age, body mass index and other anthropometric parameters.[9]

The study of PCOS is one of the most important topics in female reproductive endocrinology, subject that has the experience of our research group with studies in rats in persistent estrus mimicking state of chronic anovulation.[3] Although the syndrome has been widely investigated, its definition and pathophysiological aspects are still highly controversial. Therefore, the aim of the current study was to conduct a non-systematic review of published literature through PubMed and SciELO search. Publications were related to polycystic ovaries, including the pathogenesis, clinical manifestations, diagnosis and therapeutic aspects of the disease, as well as its association with cardiovascular disease and arterial hypertension. The current study may also contribute to raise awareness about the risk of hypertension in patients with polycystic ovary syndrome.

Etiology and pathophysiology

Polycystic ovary syndrome is a chronic disorder with unknown etiology that was first described in 1935 by Stein

and Leventhal. It is a reproductive, heterogeneous and metabolic disorder.[10] The prevalence of the disorder ranges from 8.7 to 17.8% in women of reproductive age.[1] The first clinical manifestations of PCOS are present in adolescence. However, there is evidence that the disease has its origin in the intrauterine environment, indicating genetic involvement.[11] Some studies including a study by Soter et al.,[12] have demonstrated a definite influence of interleukin-6 and interleukin-10 gene polymorphisms, interferon-c and transforming growth factor-beta1 in the development of PCOS, although no clear pattern of inheritance has been identified.[12] Other causal factors are epigenetic exposures, highlighting the association between intrauterine exposure and maternal androgens and phenotypes related to the syndrome.[13] Ethnic variations in PCOS may be associated with environmental factors, such as socioeconomic conditions and lifestyle.[14]

Despite a large number of research studies, pathogenesis of PCOS still needs further elucidation.[15] However, some pathophysiological mechanisms are known, e.g. alterations in the secretion of gonadotropin-releasing hormone, defect in androgen synthesis and development of insulin resistance.[16] One of the numerous theories proposed to explain pathogenesis of the syndrome is the disturbance of the hypothalamic-pituitary axis, resulting in disarranged gonadotropin secretion by the hypothalamus with a consequent elevation of luteinizing hormone (LH) levels and normal and/or low follicle-stimulating hormone (FSH) levels.[14]

A number of studies have also indicated that insulin resistance is the key pathophysiological element for development of the syndrome. Insulin acts synergistically with LH to increase androgen production in the theca cell of the ovary.[17] Another site for androgen production is the adrenal cortex, due to abnormalities in cortical stereoidogenesis promoted by stimulation of adrenocorticotropic hormone.[18] And these excess androgen levels, mainly testosterone, androstenedione and dehydroepiandrosterone sulfate, cause premature atresia of ovarian follicles, forming multiple cysts and anovulation with persistent estrogen levels resulting from aromatization of androgens to estrogens without opposition of progesterone and associated with an increased risk of endometrial carcinoma.[19,20]

Clinical manifestations and diagnosis

In the Rotterdam Consensus, it was defined that at least two of the following three findings are required for diagnosis of PCOS: oligoovulation or chronic anovulation, clinical and/or laboratory evidence of hyperandrogenism, and pelvic ultrasonography indicative of polycystic ovaries.[10] These criteria recognize that PCOS is a diagnosis of exclusion.[21] Therefore, to confirm this syndrome, disorders that mimic the clinical characteristics of PCOS must be excluded, such as thyroid disorders, hyperprolactinemia and non-classical congenital adrenal hyperplasia.[22]

Although PCOS has been traditionally considered a disorder that affects women in their reproductive years, clinical manifestations may be observed at menarche.[23] In addition, clinical complications vary according to different phenotypes, age, ethnicity and body weight.[24]

According to research studies, the classical PCOS phenotype is linked to hyperandrogenism, anovulation and polycystic ovaries. Symptoms usually worsen with time.[25] Among these characteristics, hyperandrogenism is considered a cardinal element for diagnosing this condition and to define a patient as hyperandrogenic may be of major clinical significance.[26] The clinical manifestation of hyperandrogenism in these women varies in different ethnic groups, with external manifestations like oily skin, acne, hirsutism, central obesity, and even androgenetic alopecia.[22,27]

The cardiovascular system of women with PCOS is affected, regardless of obesity, due to metabolic disturbance associated with the respective syndrome.[28] Factors such as dyslipidemia, diabetes and obesity are all potent risk factors for cardiovascular disease, explaining why women with PCOS are more predisposed to hypertension.[8]

PCOS and hypertension

In general, systemic arterial hypertension (SAH) is more common in PCOS patients. A study carried out by Stener-Victorin et al.[28] showed that the prevalence of hypertension was about 40% in this group of women. Insulin resistance is a potential determinant of the association between PCOS and hypertension. It plays a central role not only in the development of PCOS, but also in the development of cardiovascular disease.[29]

Researchers have invested in research studies to discover the underlying relationship between hypertension and endocrine disorder. One of the most well-accepted hypotheses is that such alterations are stimulated by insulin resistance.[28] Some authors demonstrated an inverse association between insulin sensitivity and systolic arterial pressure in the group of women with PCOS.[30]

Insulin resistance leads to hyperinsulinemia and amplification of LH action in theca cells, with a consequent increase in androgen levels (Figure 1).[19,20] In experimental models, some authors have also demonstrated that the

adrenal gland of the rat in persistent estrus resembles PCOS. A higher proliferative activity occurred in the reticular zone of the adrenal gland, producer of androgens in humans, in comparison to controls.[3] Androgen levels may directly regulate the renin-angiotensin system of the proximal renal tubule and increase reabsorption flow rate, thus increasing extracellular volume and blood pressure.[7,31]

A long-term follow-up study carried out by Wild et al.[32] suggested an increased prevalence of hypertension in patients with PCOS. However, it did not evaluate the association between PCOS syndrome and the increased risk of morbidity and mortality from coronary artery disease.[33,34] Nevertheless, these results suggest that women with polycystic ovary syndrome should be screened for hypertension at a younger age.[35]

Animal model

A study of women with polycystic ovaries has some ethical limitations. Therefore, there has been a search for appropriate experimental models that mimic PCOS.[36] During the last decades, researchers have used diverse animal models, such as rats, mice, hamsters, guinea pigs and subhuman primates to study the reproductive cycle, ovarian morphology and hormonal changes.[37] However, the animal model that has the morphology and endocrinology most similar to humans is the rat.[38]

Rats are polyestrous animals, i.e., these animals have regular and consecutive estrous cycles, manifested by morphological changes in the ovaries, uterus, vagina and mammary glands. These cycles last from 4 to 6 days and are easily observed, including proestrus, estrus, metaestrus and anestrus, with a mean pregnancy period of 21 days.[39,40]

Nevertheless, interruption of the rat estrous cycle, characterized by persistent vaginal keratinization or persistent estrus, is different from the short period of sexual receptivity named estrus or heat. The rat model was more widely studied by Barraclough in 1961, who characterized the period of most intense hypothalamic sensitivity. That author used only a subcutaneous injection of androgen (testosterone propionate at a dose of 1.25 mg). Thus, a simple s.c. injection of 1.25 mg of testosterone propionate administered to female rats during the first 5 days of live induced persistent estrus in all animals.[39,41,42]

These animals in adulthood present anovulation, higher LH secretion, polycystic ovaries and aggressive behavior when in contact with males, thus there is a resemblance to the human condition of polycystic ovary syndrome.[18,40] Furthermore, rats in persistent estrus may have hypertension, as shown in a study conducted by Gontijo et al.[8] Those authors showed that rats in persistent estrus had a significant increase in arterial pressure, in comparison to rats in the control group.[8]

Treatment

Regarding treatment, it is recommended to start with aggressive diet/lifestyle modifications which may lead to weight loss, improve anovulation and indirectly cause a reduction in systolic arterial pressure.[33] If weight loss is insufficient to correct anovulation and decrease arterial pressure, drug treatment should be administered in order

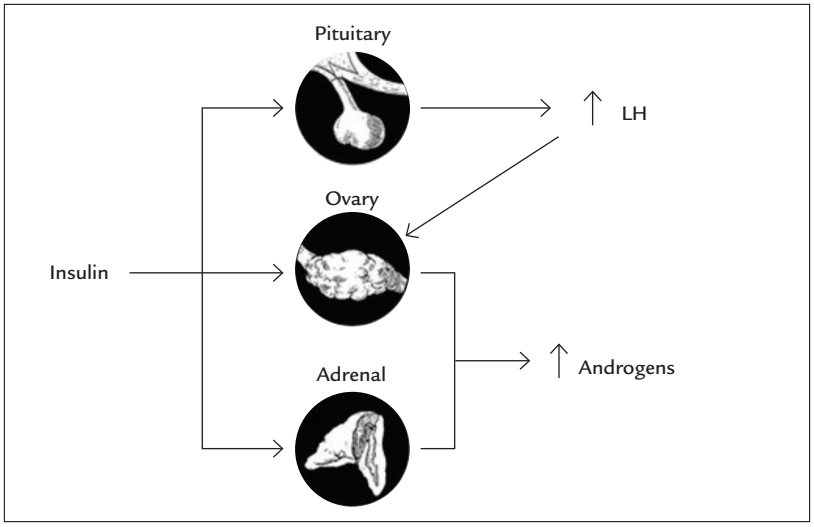

FIGURE 1 The influence of insulin in the amplification of LH and increase in androgen levels.

Source: Adapted from Dunaif.[19]

to correct the signs and symptoms. Despite a lack of consensus on the treatment of cardiovascular disease in women with PCOS, target therapy for hypertension in the PCOS population is similar to treatment given to patients without the syndrome.[25]

Conclusion

Women with PCOS, in addition to anovulation and infertility, have an increased risk of developing hypertension and cardiovascular disease in association with metabolic syndrome. The diagnosis of PCOS is fundamentally clinical. Treatment of PCOS is limited to management of signs and symptoms since the etiology of the disorder is unknown. There is a need for further studies to understand the pathophysiology of PCOS and the development of high blood pressure in women suffering from the disorder.

Resumo

Aspectos atuais da síndrome do ovário policístico: uma revisão da literatura

A síndrome dos ovários policísticos (SOP) é uma desordem endócrina heterogênea com prevalência variável, que afeta cerca de uma em cada 15 mulheres no mundo. O diagnóstico da SOP requer, pelo menos, dois dos seguintes critérios: oligo-ovulação e/ou anovulação, evidência clínica e/ou bioquímica de hiperandrogenemia e morfologia dos ovários policísticos. As mulheres com SOP parecem ter um risco mais elevado de desenvolver distúrbios metabólicos, hipertensão e doenças cardiovasculares. O objetivo deste artigo foi apresentar uma revisão da literatura por meio de pesquisa nas bases de dados PubMed e Scielo, focada em publicações relacionadas com ovários policísticos, incluindo patogênese, manifestações clínicas, diagnóstico e aspectos terapêuticos, bem como associação com doenças cardiovasculares e hipertensão arterial.

Palavras-chave: síndrome do ovário policístico, hiperandrogenismo, distúrbios cardiovasculares, hipertensão arterial.

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Current management of non-alcoholic fatty liver disease

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Summary

Non-alcoholic fatty liver disease (NAFLD) is characterized by hepatic accumulation of lipid in patients who do not consume alcohol in amounts generally considered harmful to the liver. NAFLD is becoming a major liver disease in Eastern countries and it is related to insulin resistance and metabolic syndrome. Treatment has focused on improving insulin sensitivity, protecting the liver from oxidative stress, decreasing obesity and improving *diabetes mellitus*, dyslipidemia, hepatic inflammation and fibrosis. Lifestyle modification involving diet and enhanced physical activity associated with the treatment of underlying metabolic are the main stain in the current management of NAFLD. Insulin-sensitizing agents and antioxidants, especially thiazolidinediones and vitamin E, seem to be the most promising pharmacologic treatment for non-alcoholic steatohepatitis, but further long-term multicenter studies to assess safety are recommended.

Keywords: non-alcoholic fatty liver disease, steatosis, steatohepatitis, metabolic syndrome, obesity.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinical/pathological condition characterized by significant lipid deposition in the hepatocytes (steatosis) after the exclusion of significant alcohol intake, viral infection, or other specific liver disease. Steatosis is usually diagnosed using imaging examinations, which may or not be associated with necroinflammatory changes and fibrosis (steatohepatitis) diagnosed by liver biopsy. This disease encompasses a spectrum of changes ranging from steatosis and steatohepatitis to fibrosis and hepatic cirrhosis, and is associated with a higher frequency of hepatocellular carcinoma.[1,2]

NAFLD is considered the hepatic manifestation of metabolic syndrome (MetS),[1] which is defined by the presence of at least three of the following factors: central obesity, hypertension, hypertriglyceridemia, reduced high-density lipoprotein (HDL) cholesterol, and hyperglycemia.[2] The strong association between NAFLD and insulin resistance (IR) and MetS is well documented in the literature.[3] This condition is currently recognized as the most prevalent liver disease in Western populations with average rates estimated at 20 to 30%.

Treatment of NAFLD

NAFLD treatment aims to reduce insulin resistance and oxidative stress, control the associated conditions (obesity, *diabetes mellitus*, dyslipidemia), and also reduce inflammation and fibrosis of the liver. Considering all patients with NAFLD, the treatment focuses on lifestyle modifications, including a change of eating habits and the regular practice of physical activities, associated with the treatment of all the components of metabolic syndrome. Discontinuation of the use of hepatotoxic drugs is also recommended.

Patients with non-alcoholic steatohepatitis (NASH) should be the main target of treatment given that this group has a higher risk of mortality related to the disease. Among the causes of death in patients with NASH, cardiovascular diseases are in first place, followed by complications from cirrhosis and hepatocellular carcinoma. The ideal management of these patients is not yet well established. Clinical trials currently in progress are focusing on this population. Lifestyle modifications with diet and physical activity, bariatric surgery, drug therapy to improve IR and the use of antioxidants are the therapies

that have been studied the most. Other treatment approaches have aimed at inhibiting proinflammatory or fibrotic pathways.[4,5]

Diet and physical activity

NAFLD is a manifestation of obesity and of MetS, usually associated with excess calorie intake and a lack of physical activity. Weight loss is widely accepted as part of treatment for patients with NAFLD, although there is still a lack of data to provide guidance on how, in what amount of time and how much weight the patient should lose.[6,7] The lack of data makes it difficult to elaborate evidence-based recommendations for the modification of diet and the practice of physical exercise in the treatment of NAFLD. It is recommended to perform exercises for at least 250 minutes per week.[8] In general, 5 to 10% reduction in body weight in obese or overweight people over 6 to 12 months has been advocated through changes to eating habits and the practice of physical activity. This recommendation is based on short-term studies that showed an improvement in IR and in liver histology with gradual weight loss, as shown in Table 1.

Bariatric surgery

In patients with morbid obesity or obese patients of greater severity (BMI > 40 or BMI between 35 and 40 with comorbidities), bariatric surgery induces long-term maintenance of weight loss and has been recommended by the researchers for motivated candidates. Whatever the surgical procedure, 14 to 25% weight loss is observed 10 years after surgery, associated with improvement in IR, remission of *diabetes mellitus* and few cardiovascular events.[15,16]

In terms of liver damage, various studies have shown improvement of the steatosis after bariatric surgery. A meta-analysis in 2008 that included 15 studies and 766 paired liver biopsies of patients undergoing bariatric surgery showed significant improvement of all NAFLD components: reduction of steatosis in 93%, reduction of steatohepatitis in 82% and reduction of fibrosis in 73%.[17] Other recent studies have suggested potential benefits of

TABLE 1 Recently published clinical trials on the effect of diet associated with physical activity in patients with NAFLD.

Author/year	Diagnosis	n	Intervention	Results
Baba et al., 2006[9]	Biopsy	65	Moderate calorie restriction in obese individuals + PA (40' walk 3-4 times per week, 60 to 70% maximum HR)	Beneficial effect limited to patients who fulfilled the dietary programs and PA (n=44)
Thamer et al., 2007[10]	MRI	112	Reduction of fat intake up to 30% of total calories, reduction of saturated fatty acids up to 10% of total calories, increased daily dose of fiber intake to 15 g/1,000 kcal, and increased PA to 3h/week for 9 months	Reduction of IR and fat in the liver
Albu et al., 2010[11]	MRI	58	Decreased calorie intake (-500 kcal/day) and increased PA (≥ 175 min/week), during 12 months	Reduction of fasting blood glucose and fat in the liver
Promrat et al., 2010[12]	Biopsy	65	Caloric restriction (1,000-1,200 kcal/day if baseline weight < 200 lb or 1,200-1,500/day if initial weight > 200 lb) and a daily fat target of 25% and 200 minutes of moderately intense PA per week for 12 months	Significant improvement in steatosis, lobular inflammation, hepatocyte ballooning and NAS in patients with a decrease of at least 7% of total body weight
Lazo et al., 2010[13]	MRI	5,145	Moderate caloric restriction (1,200-1,500 kcal/day for individuals weighing < 114 kg and 1,500-1,800 kcal/day for those weighing > 114 kg) and increased physical activity with a target of 175 min of moderately intense PA per week for 12 months	Reduction in liver fat
Oh et al., 2014[8]	Fibroscan	169 (obese)	Calorie restriction of 1,680 kcal/day and PA for less than 250 min per week or 250 min or more per week	Reduction of serum ferritin and adiponectin and reduction of liver fat
Vilar-Gomez et al., 2015[14]	Biopsy	293	Low-calorie diet (750 kcal/day less than the calculated daily energy need) and PA for 200 min a week for 52 weeks	Histological improvement, including fibrosis, when weight loss was greater than or equal to 10%

PA: physical activity; HR: heart rate; NAS: NAFLD Activity Score; MRI: magnetic resonance imaging.

bariatric surgery.[18-21] However, there is a lack of randomized studies assessing the effect of this procedure on NASH. Therefore, performing bariatric surgery specifically for the treatment of this condition is not recommended.[22] It should be considered that although bariatric surgery may play a role in the treatment of patients with morbid obesity and NASH, the recommendation of this procedure must be individualized and conducted at specialized medical centers with a multidisciplinary approach due to the potential complications, which vary depending on the center where the procedure is performed (mean mortality of 0.3% and morbidity of 10%).

Antioxidants

Antioxidants, especially vitamin E, have been studied in patients with NAFLD because oxidative stress is considered a key mechanism in the pathophysiology of NASH, leading to hepatocellular injury and progression of the disease.

Vitamin E

Vitamin E is a fat-soluble vitamin with antioxidant properties. Two recently published, large-scale, randomized and controlled studies (PIVENS and TONIC) have assessed its effect on NAFLD in adults and children, respectively.[23,24] In the PIVENS study, a significant histological improvement (a reduction of at least 2 points in the inflammatory activity score – NAS) was noted in patients who received vitamin E compared to patients treated with a placebo (43 *vs.* 19%, p=0.001).[23] In children with hepatic steatosis, both vitamin E associated with metformin and the isolated use of vitamin E were not superior to the placebo in reducing alanine aminotransferase (ALT) levels in the TONIC study. However, the children treated with vitamin E that presented NASH proven via biopsy had significant histological improvement.[24]

Some data suggests potential safety concerns with the long-term use of vitamin E, though. A meta-analysis that included 11 trials that tested the effect of vitamin E supplementation in humans showed that high-dose supplementation (400 U/day) was associated with increased mortality due to any cause.[25]

Cytoprotective agents

Drugs classified as cytoprotective agents prevent apoptosis and inhibit the inflammatory cascade, two central mechanisms in the pathogenesis of NASH.

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is an excellent example of a cytoprotective agent that has been investigated in the treatment of NASH. The largest study that evaluated UDCA *versus* a placebo showed similar improvement in both groups, despite a high dropout rate and an unexpectedly high rate of improvement in the placebo group.[26] A randomized and controlled study with 147 patients treated with a placebo *versus* UDCA at 23-28 mg/kg/day only found an improvement of ALT serum levels and lobular inflammation, with the absence of a significant overall histological improvement.[27] A study of 126 patients comparing high doses of UDCA with a placebo showed an improvement in the level of aminotransferase, serum markers of fibrosis (FibroTest) and IR after 12 months, although liver histology was not assessed.[28] These controversial results, associated with recent concerns about the increased mortality from all causes with high doses of UDCA in primary sclerosing cholangitis has led to a decrease in research with patients with NAFLD.

Pentoxifylline

Another approach to the treatment of NAFLD involves using anti-TNF-α drugs, given that this cytokine induces both necroinflammation as well as IR.[29] Pentoxifylline is a TNF-α inhibitor, and has been used in animal models[30] and in patients with NASH. A meta-analysis assessing five randomized, placebo-controlled studies, including only 157 patients, showed that pentoxifylline can reduce transaminase activity and improve histological parameters in NAFLD patients.[31]

A more recent study not included in this meta-analysis and involving 55 NASH patients showed an average improvement of 1.6 points in the NAS score *vs.* 0.1 points in the placebo group. The reduction in fibrosis was not statistically significant, although it occurred in 35% of patients in the pentoxifylline group *vs.* 15% in the placebo group.[32] Therapy with this medication appears to be well tolerated, although other studies are needed before it can be recommended as a therapy for NASH.

Hypolipidemic agents

Hypolipidemic medication such as statins and omega-3 fatty acids are seen as potential options for the treatment of NAFLD due to their effects on hypertriglyceridemia and low levels of HDL cholesterol, which are common changes in patients with MetS.

Statins

With antioxidant and anti-inflammatory properties, in addition to the frequent coexistence of NAFLD and dyslipidemia, and the increased cardiovascular risk of these patients, statins appear as an attractive therapeutic option

in NAFLD. Important evidence indicates the use of statins in order to reduce cardiovascular disease in patients with dyslipidemia.[33] However, data on the effectiveness of statins for the treatment of NAFLD is scarce. A pilot study in which 16 participants with NASH proven via biopsy were randomized to receive 40 mg of simvastatin or a placebo for 12 months found a significant improvement in the level of aminotransferase in the simvastatin group. Liver histology was not significantly affected by the simvastatin.[34] Similarly, another study using atorvastatin 24 mg/day *versus* a placebo revealed that there was a significant improvement in serum transaminase in the statins group. Furthermore, there was an increase in aminotransferase in the placebo group. Histological changes were not assessed.[35] At the present time, when there is still a lack of evidence of any histological benefit, therapy with statins may not be recommended as a primary therapy for NAFLD but as a treatment for associated hyperlipidemia.

Omega-3 fatty acids

Omega 3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are potent activators of nuclear receptor proteins such as PPARα and PPARγ, which regulate various genes involved in the stimulation of fatty acid oxidation, regulate pro-inflammatory genes, such as TNF-α and IL-6, and improve insulin sensitivity.[36,37] In relation to the effects on NAFLD, a recent systematic review and meta-analysis found heterogeneity between the studies and concluded that, although omega-3 supplementation may decrease fat in the liver (without effects on transaminase levels), the optimal dose has not yet been established.[38] A subsequent randomized, double-blind study assessed supplementation with an EPA compound in individuals with NASH confirmed via biopsy. After 12 months, there was no improvement in the histological characteristics of the NASH. A possible explanation for the negative results of this study is that the dose of EPA was not sufficiently suitable for the population (only 2.7 g/day). Furthermore, the response rate to the placebo in this trial was higher than previously reported in other studies.[39] Thus, additional studies are needed to support the routine use of omega-3 in patients with NAFLD, with its use currently restricted to the treatment of hypertriglyceridemia.

Insulin sensitizers

Given the importance of IR in the pathogenesis of NASH, insulin sensitizers such as metformin and thiazolidinediones (TZDs) have been extensively studied in the treatment of NASH.

Metformin

Metformin is a biguanide that improves IR and hyperinsulinemia by reducing hepatic glucose production, increasing peripheral glucose uptake by the muscles and reversing IR induced by tumor necrosis factor.[40] However, recent meta-analyses have concluded that the use of metformin did not promote a consistent benefit in patients with hepatic steatosis.[41,42] Therefore, its use is reserved for the management of patients with fatty liver and associated type 2 diabetes as it improves the metabolic parameters and promotes moderate weight loss.[43]

Thiazolidinediones

Thiazolidinediones improve insulin sensitivity in adipose tissue, activating nuclear transcription factor PPARγ.[44] The two drugs in this class that have been studied in the treatment of NASH are pioglitazone and rosiglitazone. A series of well-designed randomized clinical trials has shown the efficacy of these medications in the improvement of fatty liver, inflammation, cell ballooning, and possibly fibrosis.[45-47]

In the multicenter, randomized PIVENS (Study of Pioglitazone *versus* Vitamin E *versus* Placebo for the Treatment of Non-Diabetic Patients with Hepatic Steatosis) study, 247 adults with NASH and without diabetes were randomized to receive one of three treatments (placebo, n=83; vitamin E 800 IU/day, n=84, or pioglitazone 30 mg/day, n=80) for 96 weeks. Although pioglitazone did not achieve its main objective, it improved insulin sensitivity and decreased steatohepatitis (34 *vs.* 19%; p=0.04) compared to the placebo.[23] A recent meta-analysis assessing four randomized clinical trials (three with pioglitazone and one with rosiglitazone) showed improvement in steatosis, inflammation and cell ballooning, but no improvement in fibrosis. However, by limiting the analysis to studies with pioglitazone, a significant improvement in fibrosis is observed (OR 1.68, 95CI 1.02-2.77).[48]

TZD therapy is not free of side effects, which may limit its clinical usefulness. Both pioglitazone and rosiglitazone are associated with an average weight gain of 3 to 4 kg with long-term treatment, and retrospective assessments have linked TZD therapy to decreased bone mineral density and fractures.[49] Recent evidence has associated the use of rosiglitazone with increased rates of myocardial infarction, which has reduced this agent being indicated as a therapeutic option.[50,51] However, piogli-

tazone remains available and is considered as a potential treatment for patients with NASH.

New approaches and treatment summary

Obeticolic acid

Obeticolic acid (OCA), a derivative of chenodeoxycholic acid, is a selective agonist of the farnesoid X receptor (FXR), which is a nuclear hormone receptor that regulates glucose and lipid metabolism. Several preclinical studies have shown that OCA increases sensitivity to insulin and regulates glucose homeostasis, modulates lipid metabolism, and exerts anti-inflammatory and fibrotic effects on the liver, kidney and intestine, the main organs expressing FXR.[52]

A recent multicenter, double-blind, controlled and randomized study has evaluated the effectiveness of OCA in non-cirrhotic NASH patients. Patients were randomly distributed 1:1 to receive the treatment administered orally with OCA (25 mg/day) or a placebo for 72 weeks. OCA was associated with improvement of the histological characteristics of NASH in comparison with the placebo.[53] More studies are required to prove the benefits of this drug in the long term and its actual safety, especially in relation to changes in the lipid profile.

Table 2 presents the main options for the treatment of NAFLD.

Conclusion

Lifestyle intervention remains the cornerstone of NAFLD treatment. However, it is well recognized that lifestyle changes in diet and exercise are difficult to achieve and maintain in the long term. Current guidelines recommend that pioglitazone and vitamin E may be used to treat steatohepatitis in non-diabetic patients, despite inconclusive data about their long-term safety. Other conditions associated with NAFLD must also be controlled, such as *diabetes mellitus* and dyslipidemia. Large studies should be performed to better assess the efficacy and safety of antioxidant or cytoprotective drugs and to find possible

TABLE 2 Treatment options in non-alcoholic fatty liver disease.

Modality	Effect	Comments
Diet		
Weight loss of 5-10%. Moderate calorie restriction. Reduce 500-750 kcal/day	Improves histology in NASH	Only 40% of patients are able to achieve these goals. A loss of at least 10% is necessary to decrease fibrosis
Eliminate or significantly reduce saturated fats and fructose in the diet	Fructose increases lipogenesis through activation of pyruvate dehydrogenase	Prospective studies have shown that fructose consumption is a risk factor for NAFLD
Consider omega-3 supplementation	May decrease hepatic steatosis. Decreases triglyceride levels	The optimal dose is unclear, but some benefit may be achieved with a dose of 1 g/day
Physical activity		
≥ 250 min/week	Decreases insulin resistance and decreases hepatic steatosis	Benefits with aerobic or anaerobic physical activity. Best results associated with diet
Pharmacological treatment		
Vitamin E 800 IU/day	Improves histology in NASH	Benefits must be validated in diabetics and various ethnic groups. May increase the risk of prostate cancer
Pioglitazone 30 mg/day	Improves histology in NASH	Associated with weight gain. Possible increased risk of CHF and osteoporosis
Metformin	Improves metabolic parameters and promote moderate weight loss	No direct improvement in NAFLD. Its use is reserved for the management of patients with fatty liver and associated type 2 diabetes
Statins	Limited data relating to histological improvement	Safe in patients with NAFLD. Decreases the risk of cardiovascular diseases
Bariatric surgery		
Roux-en-Y gastric bypass; adjustable gastric band; vertical gastrectomy	Improves histology in NASH in up to 80% cases, including fibrosis	Few randomized and controlled studies; caution in patients with cirrhosis; lifestyle change should be attempted first

Adapted from Torres et al.[5]
NASH: non-alcoholic steatohepatitis; NAFLD: non-alcoholic fatty liver disease; CHF: congestive heart failure.

medication that could directly affect the pathophysiology of hepatic steatosis.

Resumo

Atualidades no tratamento da doença hepática gordurosa não alcoólica

A doença hepática gordurosa não alcoólica (DHGNA) é caracterizada pela deposição significativa de lipídios nos hepatócitos de pacientes que não apresentam história de ingestão alcoólica significativa. É a doença do fígado mais prevalente em populações ocidentais e existe forte associação da DHGNA com a resistência à insulina (RI) e com a síndrome metabólica. O tratamento objetiva reduzir a RI, o estresse oxidativo, a obesidade, a dislipidemia bem como a inflamação e a fibrose hepáticas. O tratamento atual baseia-se principalmente em modificações do estilo de vida, que incluem dieta e prática regular de exercícios físicos, associadas ao tratamento de todos os componentes da síndrome metabólica. Quanto ao tratamento medicamentoso da esteato-hepatite não alcoólica, os agentes insulino-sensibilizantes e os antioxidantes parecem os mais promissores, especialmente as tiazolidinodionas e a vitamina E, mas faltam estudos multicêntricos avaliando sua segurança a longo prazo.

Palavras-chave: hepatopatia gordurosa não alcoólica, esteatose hepática, esteato-hepatite, síndrome metabólica, obesidade.

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Atrial fibrillation with high ventricular rate in emergency room: What's the best strategy for treatment?

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Summary

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and can lead to significant decline in functional status and quality of life among affected patients. The risk of developing AF increases with age and the presence of structural heart disease. Thus, the attendance of patients with high ventricular response to AF is common, which makes knowledge of its management mandatory. In this context, the choice of heart rate and/or rhythm control therapy is fundamental and complex, with multiple possibilities. Thus, this review aims to assist in the management of these patients, systematizing their care.

Keywords: atrial fibrillation, emergency, arrhythmia.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is characterized by the absence of P waves and irregular interval between QRS complexes on the electrocardiogram (ECG).[1-3]

AF can lead to a significant reduction in the functional status and quality of life of the affected patients. It increases mortality between 1.5 and 1.9 times on the account of hemodynamic deterioration caused by increased heart rate (HR), loss of atrioventricular (AV) synchrony and progressive dysfunction of the left atrium and ventricle, in addition to increasing the risk of stroke and other embolic events triggered by atrial thrombi.[1-5]

The risk of developing AF increases with age and with the presence of structural heart disease. Prevalence increases from 0.1% in adults less than 55 years to 8% in those aged 80 years or older. It is higher among men compared with women (1.1% x 0.8%); and among white compared with black individuals (2.2% x 1.5%).[2,4,5]

Arterial hypertension (SAH) and coronary artery disease (CAD) (post acute myocardial infarction or ischemic cardiomyopathy) are the most common comorbidities present in patients with AF in developed countries. Rheumatic heart disease, although currently uncommon in developed countries, has a much greater association with AF. AF is an infrequent form of manifestation of acute myocardial infarction or ischemia in the absence of other signs and symptoms of CAD.[1-5]

AF and heart failure (HF) often occur together, and a cause and effect relationship between the two is common. In addition, AF is associated with pulmonary disorders including chronic obstructive pulmonary disease (COPD) and pulmonary embolism. Similarly, both the clinical and subclinical forms of hyperthyroidism are associated with an increased risk of AF. Other risk factors related to AF include chronic renal failure, genetic factors, autonomic dysfunction, hypomagnesemia, alcohol consumption, and drugs such as theophylline, adenosine and digitalis.[1-5]

The classification proposed by the ACC/AHA/ESC for AF divides it into five subtypes:[1-3]

- First detected or diagnosed episode independent of its duration and presence of any symptoms.
- Paroxysmal: recurrent (more than two episodes) that terminate spontaneously lasting up to 7 days (usually ceases within 24 hours).
- Persistent: Episodes lasting longer than 7 days that require pharmacological or electrical cardioversion to return to sinus rhythm.
- Long-lasting persistent: the same as persistent AF, but lasting for one year or longer.

- Permanent: when it is not possible to maintain sinus rhythm after cardioversion, or when it has been decided not to attempt cardioversion for several factors (e.g. elderly, asymptomatic, AF with low or normal ventricular response and large left atrium).

Thus, the presence of a patient with high ventricular response AF is frequent, and makes the knowledge of its management compulsory. In this context, the choice of heart rate and/or rhythm control therapy is fundamental and complex, with multiple possibilities. This review therefore aims at assisting in the approach of these patients, systematizing their care.

Clinical picture

Not all patients with AF are symptomatic and among those who are, there is a wide variety of symptoms. Information such as onset of symptoms, timing of diagnosis, frequency and duration of episodes and severity of symptoms is very important for the therapeutic decision. Episodes can be precipitated by exercise, emotions or acute intake of large amounts of alcohol. In other cases, they may be precipitated during sleep or after a meal.[1-5]

The typical symptoms associated with AF are palpitations, tachycardia, fatigue, weakness, dizziness, reduced exercise capacity, increased urinary volume, dyspnea.[1-3] Follow-up studies of patients with AF have shown that approximately 90% of these individuals have recurrent episodes of AF, although more than 90% of the events are not recognized by them. Nevertheless, asymptomatic episodes lasting more than 48 hours are not uncommon, occurring in 17% of patients.[4,5]

More severe symptoms include restless dyspnea, angina, pre-syncope, syncope (infrequent). Some patients may also have thromboembolic events and/or stroke as their first presentation.[4,5]

Five steps for the systematic approach of AF in the emergency room

1) Recognize/ward off clinical instability related to AF

It is not always easy to recognize whether AF is the main cause of clinical instability presented by the patient. Anamnesis and physical examination should be performed in all patients with AF, seeking signs of hemodynamic instability (hypotension, significant pulmonary congestion, history of syncope, mental confusion, angina/chest pain), adequate use of medications, signs/symptoms of infection, time of onset of symptoms, presence of structural heart changes (systolic HF and/or left ventricular hypertrophy) and coronary artery disease.[1-3]

Those presenting signs of hemodynamic instability at baseline (hypotension, significant pulmonary congestion, history of syncope, mental confusion, angina/chest pain – these being attributable to arrhythmia [usually in HR greater than 150 to 160 beats per minute]) should be taken to the emergency room for peripheral venous access, continuous monitoring and oxygen therapy, and promptly submitted to synchronized electrical cardioversion with 100 to 200 J, regardless of the time of onset. A bolus dose of 10,000 units of unfractionated heparin is recommended prior to this emergency cardioversion. In such cases, after the reversal, associated diseases such as CAD, valvopathy and ventricular dysfunction should always be investigated. The same is true for patients with AF and pre-excitation with elevated HR or hemodynamic instability.[1-3]

2) Remove secondary causes that induce high ventricular response

The main cause for high ventricular response AF should always be evaluated, especially in those patients with refractory HR control or who already have permanent/persistent AF and presented recent lack of HR control even while correctly using the medications. When drug adherence is appropriate, drug or alcohol use, hyperthyroidism, anemia, hydroelectrolytic disorders (especially hypo or hyperkalemia and hypomagnesemia), infections and pulmonary thromboembolism should always be considered. In these cases, all patients should perform a chest x-ray and, in women, even if asymptomatic, the collection of type I urine and uroculture must be performed.[1-3]

A recently published retrospective study evaluated the management of patients with high ventricular response AF in the ER, either according to the rhythm control or reversal strategy or not, when the patient arrives at the site. In about 30% of patients, the cause of high ventricular response AF was sepsis. The rate of adverse events among patients undergoing control/reversal strategies *versus* uncontrolled strategy was 40.7% x 7.1%, and only about 20% of patients achieved adequate control with therapy when a secondary cause was present. This reinforces the idea of investigating the secondary cause before adopting complementary measures in the initial approach, unless the patient presents with hemodynamic instability.[6]

3) Obtain proper control of HR

There are two main strategies for managing the symptoms of patients with AF: control of HR using AV node blockers, or rhythm control (reversion to sinus rhythm followed by maintenance), either with antiarrhythmic drugs or by catheter ablation.[1-3]

The results of two large multicentric studies, AFFIRM and RACE, demonstrated that both rhythm control and ventricular rate control strategies are associated with similar rates of mortality and severe comorbidities. Generally, the choice of one or another strategy takes into account factors such as the age of the patient and the presence of symptoms associated with AF with an impact on the quality of life, and reduction of the left ventricular systolic function attributed to the presence of the arrhythmia.[7,8]

Thus, theoretically, the initial and main objective adopted in the care of patients in the emergency room who do not present clinical instability related to AF is HR control, especially in those with more than 48 hours of symptoms, multiple comorbidities or heart disease (left ventricular dysfunction, left ventricular hypertrophy and left atrium > 50 mm).[1-3] When controlling HR, unrestricted control maintenance (HR < 110 bpm) proved to be similar to the restricted control (HR < 80 bpm), and the most flexible measure was also adopted in the emergency sector approach.[7] Exception is made for patients with left ventricular dysfunction, symptomatic mitral stenosis or coronary stenosis, in whom HR control should be more rigorous due to underlying heart disease.[1-3]

A heart rate control strategy generally requires drugs that reduce AV node conduction, such as B-blockers, non-dihydropyridine calcium channel blockers or digoxin, either alone or in combination (Table 1).[1-3]

B-blockers and/or calcium channel blockers (diltiazen and verapamil) are generally the drugs of choice for initiation of therapy. It has been proven that drugs such as diltiazen, esmolol, metoprolol and verapamil are superior in the control of HR compared to digitalis and amiodarone.[9-13] In patients without ventricular dysfunction we may use intravenous metoprolol (maximum dose of 15 mg), diltiazen 0.25 mg intravenously (repeat 0.35 mg/kg if necessary), or verapamil 5 to 10 mg intravenously.[9-13]

Digoxin may also be used, but it is not as effective in controlling HR during physical activity.[1-3,14] In patients with ventricular dysfunction, the use of C-lanatoside, 0.4 mg intravenously (maximum dose of 0.8 mg), or amiodarone, 150 mg intravenously in 10 minutes, is considered as the first option.[1-3] The fact that amiodarone can lead to the reversal of the rhythm in up to 28% of the patients, predisposing them to the occurrence of embolic events, is highlighted.[15]

In patients with hemodynamic shock and AF, heart rate control should be done only when HR exceeds 130 to 150 beats per minute and preferably amiodarone via continuous infusion pump (450 to 1,200 mg daily) depending on the chronotropic response of the patient. In these cases, the HR target is usually around 120 beats per minute, without damaging the compensatory response to shock, and its indication should be reviewed daily and individually.[1-3]

4) Consider heart rate control/AF reversal

Although HR control is the main target in the treatment of high ventricular response AF in the emergency room, there are some situations in which the rhythm control strategy should be considered: if the symptoms have clearly started less than 48 hours; persistent symptoms despite adequate HR control; inability to achieve adequate HR control (ruling out secondary causes); young patients with a first episode of AF diagnosed or those in whom arrhythmia had a recent onset and the risk of recurrence appears to be lower; and, in the latter case, according to the patient's preference.[1-3]

If cardioversion is chosen, it may be chemical (using antiarrhythmic drugs) or electric (Figure 1). In such cases, the patient's HR should be kept preferably high, since after the reversal the risk of sinus bradycardia associated with clinical instability becomes lower.[1-3]

For chemical reversal, the recommended medications are: flecainide, dofetilide, ibutilide, propafenone and amiodarone. The first three are not available in Brazil. Before administering antiarrhythmic medication for cardioversion, a B-blocker or a calcium channel blocker should be given to prevent rapid AV conduction.[1-3]

TABLE 1 Main drugs used to control HR in patients with high ventricular response AF.

Medication	Dose	Contraindication
Metoprolol	5 mg IV in 5 min. (max. 15 mg)	BCS, low blood pressure, heart failure
Diltiazem	0.25 mg/kg IV / Can be repeated at a dose of 0.35 mg/kg	Heart failure, low blood pressure
Verapamil	5 to 10 mg IV	Heart failure, low blood pressure
C-lanatoside	0.4 mg IV (max. 0.8 mg)	
Amiodarone	150 mg IV in 10 min. (max. 2.2 g in 24 h)	

IV: intravenous; BCS: bronchospasm.

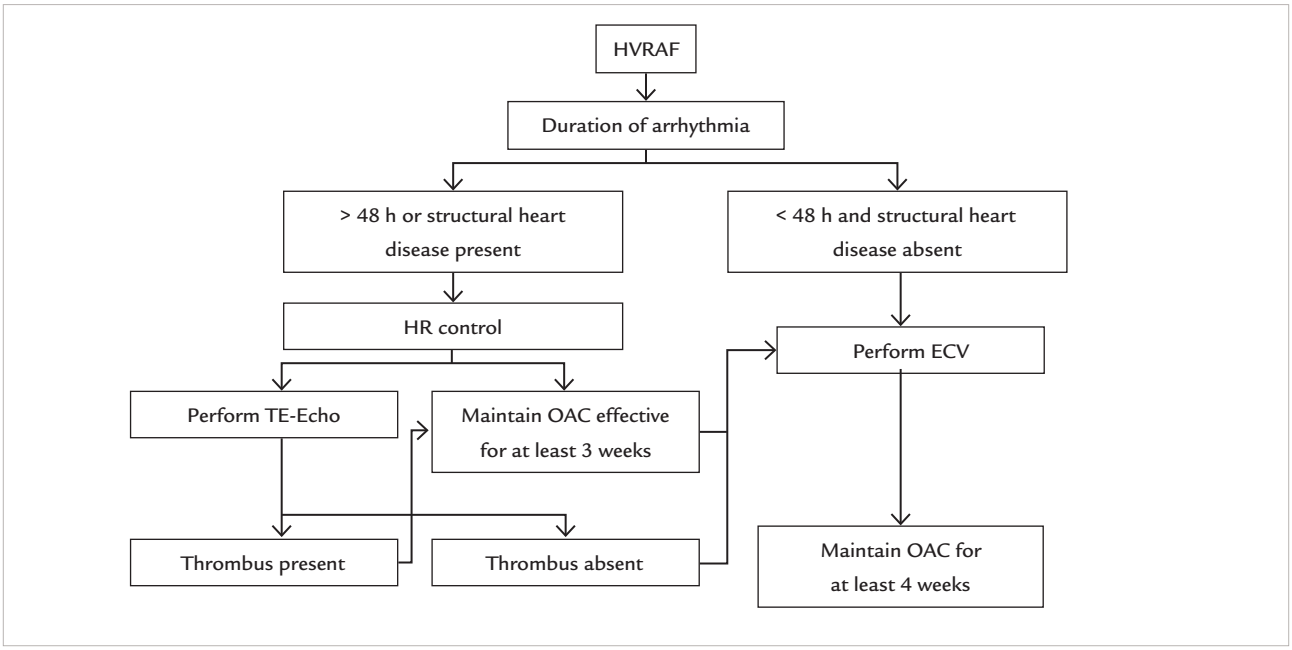

FIGURE 1 Algorithm for evaluation of patients with high ventricular AF for ECV.
HVRAF: high ventricular response AF; HR: heart rate; TE-Echo: transesophageal echocardiography; OAC: oral anticoagulation; ECV: synchronized electrical cardioversion.

In patients without structural heart disease, the option of choice is propafenone. In the first event, it should be administered in hospital orally at a dose of 450 mg (if the patient's weight is less than 70 kg) or 600 mg (weight 70 kg or more). If the treatment is well tolerated and effective, the patient can be discharged with the guidance of home use at the same dose, if there is recurrence, in a strategy called *pill in the pocket*. In these cases, the probability of AF reversion in up to 6 hours is around 94% of cases. This strategy should be done only in cases of AF with few recurrences (up to 2 every 6 months).[1-3]

In patients with structural heart disease [left ventricular hypertrophy (septum and posterior wall thickness > 1.2 cm), ischemia, valvular disease and/or ventricular dysfunction], amiodarone is the best option for chemical cardioversion. Amiodarone should be given at a dose of 150 mg intravenously in 10 minutes, or 5-7 mg/kg in 1 hour (up to a maximum dose of 2.2 g in 24 hours). Amiodarone is associated with higher rates of maintenance of sinus rhythm, but is also associated with a greater number of adverse effects in the long term.[1-3]

Sotalol may be beneficial in patients with paroxysmal AF also in sinus rhythm, provided that the patient has minimal structural disease or normal heart, and QTc < 460 ms. It is the antiarrhythmic drug of choice in patients with AF and CAD who do not have left ventricular systolic dysfunction. In this situation, propafenone is contraindicated.[1-3]

If electric cardioversion is chosen, it should be done with the administration of shock initially synchronized at 100 to 200 J in a single-phase defibrillator or 100 J in a biphasic defibrillator, after explaining the procedure and adequate sedation to the patient. Administration of amiodarone prior to electrical cardioversion increases the chance of success and may prevent immediate recurrence of AF.[1-3]

Finally, radiofrequency ablation (RFA) is also useful in maintaining sinus rhythm mainly in symptomatic patients with paroxysmal AF who have failed an antiarrhythmic, have normal or slightly increased left atrium, and normal or discreetly decreased function of the left ventricle. However, its use should be considered an exception when it comes to patients seen in emergency units.[1-3]

If there is structural heart disease, after the reversal, the patient should be discharged with amiodarone prescribed at a dose of 200 mg orally, three times a day for 2 weeks, followed by 200 mg twice daily for another 2 weeks. Thereafter, amiodarone at 200 mg daily. In the absence of evidence of structural heart disease, amiodarone should preferably be replaced with propafenone, 150 to 300 mg every 12 hours.[1-3]

In all cases with more than 48 hours of AF or in those with structural heart disease, if reversion is chosen, it is mandatory that the patient be anti-coagulated for at least 3 weeks.[1-3] In the case of warfarin, the weekly INR control should show values between 2.0 and 3.0. Currently one

option is to use one of the new anticoagulants. In a prospective study, rivaroxaban was validated and showed the same level of safety of warfarin related to electrical cardioversion (ECV).[16] Apixaban and dabigatran, on the other hand, also showed the same safety profile of warfarin in subanalyses.[17,18] Thus, the guidelines release their use when choosing to reverse the patient's rhythm. After reversion, any of the anticoagulants used should be maintained for a minimum period of 4 weeks, and may be extended indefinitely if the patient presents risk factors for AF recurrence (ventricular dysfunction and/or structural heart disease, atrial dilatation, previous episodes, etc).[1-3]

In those without oral anticoagulant use for at least three continuous weeks, transesophageal echocardiography must be performed. In the absence of thrombi, the patient may be cardioverted with synchronized electrical therapy or chemical therapy.[1-3]

If a thrombus is seen, only HR control should be performed and the patient is discharged with oral anticoagulation prescription to schedule the procedure after at least 3 weeks at an outpatient clinic.[1-3]

5) Define the indication for oral anticoagulation

All patients with AF should be evaluated for the need for anticoagulation and this is done by applying the CHADS2 and/or CHA2DS2VASC scores. The latter is a refinement of the former and has been the most used in recent years because it identifies patients with actual "low risk" more accurately. For the evaluation of bleeding risk, the most commonly used criterion is HAS-BLED, which serves as a guideline for the rational and cautious choice of anticoagulation. However, it should not contraindicate it.[1-3,19]

There are two indications of anticoagulation in AF. In the short term, in patients with low thromboembolic risk in which the strategy of rhythm control is chosen and cardioversion is performed to the sinus rhythm, and in the long term, patients that meet criteria for chronic anticoagulation.[1-3]

Antithrombotic therapy to prevent thromboembolism should be indicated for all patients with AF, except for those with isolated AF without other risk factors, and those with a contraindication to it. Anticoagulation is recommended for patients at high risk of thromboembolic event (two or more risk factors considering the CHA2DS2VASC score). If the CHA2DS2VASC criterion only scores for the female sex, chronic oral anticoagulation is not mandatory.[1-3]

The selection of the anticoagulant agent should be based on the absolute risk of stroke and bleeding and the risk/benefit ratio to the patient. In patients with significant heart valve disease, mechanical valvular prostheses and/or chronic renal insufficiency (CrCl < 30 mL/min), the option is warfarin. The target INR is 2.0 to 3.0, except for mitral and aortic mechanical prostheses, in which case the target varies between 2.5 and 3.5.[1-3]

In the remaining patients, warfarin or any of the new anticoagulants (apixaban, rivaroxaban or dabigatran) may be used.[1-3,20-22]

The association of ASA and clopidogrel to reduce the risk of thromboembolic events may be considered for patients with AF in case of possible inadequate anticoagulation with warfarin, either at the choice of the patient or when the attending physician is not sure of the safety for the patient. In this case, the level of evidence is lower and comes from simple non-multicentre studies.[2]

When the patient with AF remains hospitalized for another reason, the use of warfarin should be routinely withdrawn at least in the initial phase. Although there is limited evidence in hospitalized patients, when INR is below 2.0, anticoagulation should be initiated with subcutaneous enoxaparin, 1 mg/kg every 12 hours, or unfractionated heparin via continuous infusion.[2]

Conclusion

Management of patients with high ventricular response AF in the emergency room is complex. Identifying factors that cause AF is critical to correct treatment. When possible, heart rate control is the priority. At the time of hospital discharge, the patient should be evaluated for indication and possibility of oral anticoagulation. In a simplified manner, the algorithm for conduct is shown in Figure 2.

Resumo

Fibrilação atrial de alta resposta ventricular na sala de emergência: qual é a melhor estratégia de tratamento?

A fibrilação atrial (AF) é a arritmia mais comum da prática clínica e pode levar à redução significativa do estado funcional e da qualidade de vida dos pacientes acometidos. O risco de desenvolvimento de AF aumenta com a idade e com a presença de doença cardíaca estrutural. Dessa forma, o comparecimento de paciente com AF de alta resposta ventricular é frequente, o que torna o conhecimento de seu manejo obrigatório. Nesse âmbito, a escolha da terapia de controle de frequência cardíaca e/ou ritmo é fundamental e complexa, com múltiplas possibilidades. Esta revisão tem o objetivo de auxiliar a abordagem desses pacientes, sistematizando o atendimento.

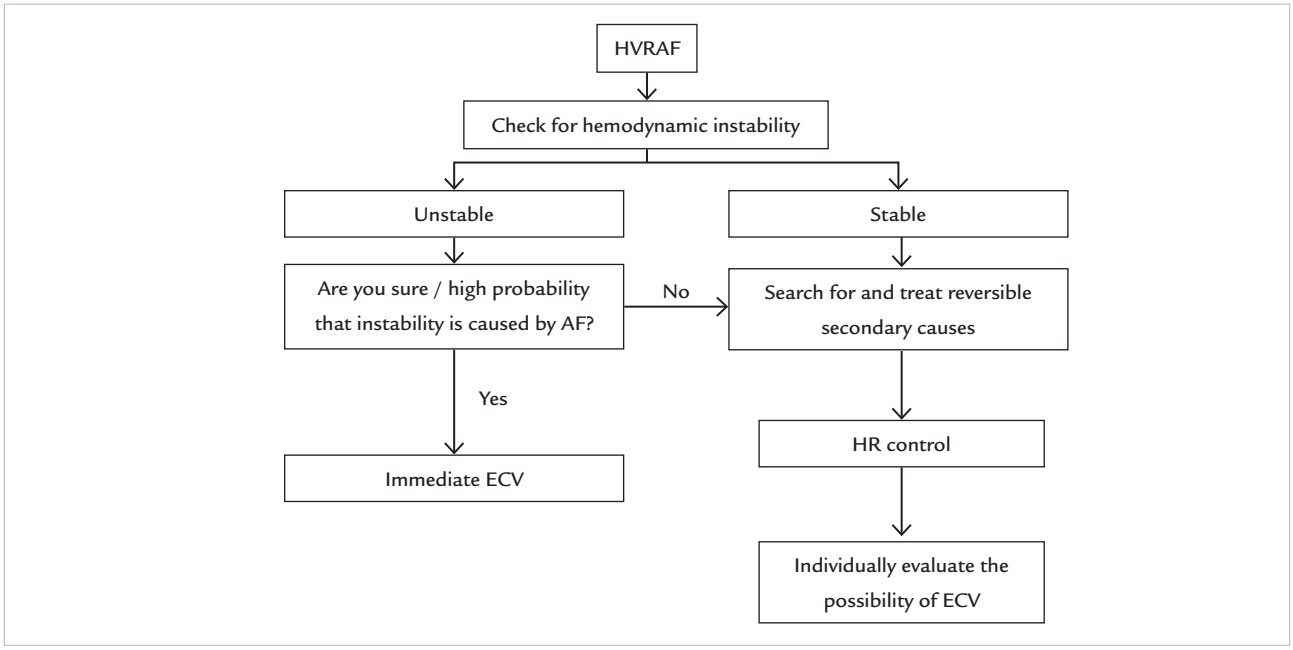

FIGURE 2 General algorithm for approaching patients with high ventricular response AF in the emergency unit.
HVRAF: high ventricular response atrial fibrillation; ECV: synchronized electrical cardioversion; HR: heart rate.

Palavras-chave: fibrilação atrial, emergência, arritmia.

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Management of degenerative cervical myelopathy – An update

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Summary

Introduction: Degenerative cervical myelopathy (DCM) is the most common cause of spinal cord dysfunction in adult patients. Patients generally present with a slow, progressive neurological decline or a stepwise deterioration pattern. In this paper, we discuss the most important factors involved in the management of DCM, including a discussion about the surgical approaches.
Method: The authors performed an extensive review of the peer-reviewed literature addressing the aforementioned objectives.
Results: Although the diagnosis is clinical, magnetic resonance imaging (MRI) is the study of choice to confirm stenosis and also to exclude the differential diagnosis. The severity the clinical symptoms of DCM are evaluated by different scales, but the modified Japanese Orthopedic Association (mJOA) and the Nürick scale are probably the most commonly used. Spontaneous clinical improvement is rare and surgery is the main treatment form in an attempt to prevent further neurological deterioration and, potentially, to provide some improvement in symptoms and function. Anterior, posterior or combined cervical approaches are used to decompress the spinal cord, with adjunctive fusion being commonly performed. The choice of one approach over the other depends on patient characteristics (such as number of involved levels, site of compression, cervical alignment, previous surgeries, bone quality, presence of instability, among others) as well as surgeon preference and experience.
Conclusion: Spine surgeons must understand the advantages and disadvantages of all surgical techniques to choose the best procedure for their patients. Further comparative studies are necessary to establish the superiority of one approach over the other when multiple options are available.

Keywords: cervical myelopathy, spondylotic myelopathy, surgical approach, anterior approach, posterior approach.

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Introduction

Chronic cervical degeneration or spondylosis (CS) is a natural consequence of aging, resulting in arthritic changes in the intervertebral discs, facet joints, ligaments and vertebral bodies.[1,2] These include abnormal bony spurs on the vertebrae, disc and joints degeneration, ligament hypertrophy and ossification. However, although the vast majority of the general population will have cervical spondylosis, only the minority of patients will have clinical symptoms.[2]

Degenerative cervical myelopathy (DCM) is the most common cause of spinal cord dysfunction in adult patients and a clinical presentation of spondylosis resulting in spinal cord compression.[2-4] The degenerative changes, at times in concert with a developmentally narrow canal, lead to chronic cord compression, which may then become symptomatic. These changes are generally unique for each patient, resulting in a wide range of radiological presentations and clinical scenarios. For this reason, the surgical

approach is generally individualized according to many factors involved in each case and surgeon's experience.[5]

In this paper, we discuss the most important factors involved in the surgical management of DCM, including the approaches.

Natural history

The clinical history of patients is quite variable, similarly to its radiological presentation.[2] Some patients may present with a slow and progressive neurological decline, whereas others may have a stepwise pattern with periods of quiescent disease prior to deterioration.[2,5,6] An acute presentation is not common, with exception for cervical trauma or acute disc herniation.[2]

It is well known that patients with symptoms will be unlikely to improve without surgical treatment. Non operative management techniques, while utilized to address concurrent neck pain, do not improve the underlying disease state of compression, demyelination, macro and micro-vascular architecture changes, neuronal and oligodendrocyte apoptosis and destruction of the blood-spinal cord barrier. Under chronic pressure, necrosis of white and gray matter ensues in the cervical spinal cord.[2,6] Finally, almost all patients untreated surgically will worsen and, in some reports, over 50% will progress to severe clinical disability.[7-10]

Clinical presentation

Physical examination of a DCM patient may include at least one long-tract sign localized to the cervical spinal cord (Babinski, Oppenheim and Hoffman signs, clonus, hyperreflexia, crossed abductor sign, coordination impairment and gait dysfunction). Symptomatically, patients can complain of tingling and numbness in the arms and hands, muscle weakness, gait difficulty, neck and arm pain, loss of coordination, heavy feelings in the legs, and deterioration in fine motor skills (such as buttoning a shirt).[11] Neck pain and stiffness are also common, with restriction to movements. Finally, some patients may uncommonly present with bladder dysfunction.

The two most common systems used to evaluate the severity of DCM are the Nürick grade system (Table 1) and the Japanese Orthopedic Association (JOA).[12,13] Of note, a modified version of the JOA has been proposed and validated for western cultures (Table 2).[14]

The JOA scale is an objecting assessment scale of the severity of DCM.[12] It is based on six domain scores: 1) Motor dysfunction of the upper extremities; 2) Motor dysfunction of the lower extremities; 3) Sensory dysfunction in the upper extremities; 4) Sensory function in the trunk; 5) Sensory function in the lower extremities and 6) Bladder function.

The JOA score can range from 0 to a maximum of 17 points. Yonenobu et al. defined the myelopathy as mild if the JOA is larger than 12, moderate from 9 to 13 and severe when the JOA is less than 9 points.[15]

A modified JOA score, which improves applicability towards Western cultures, replaces the use of chopsticks with a spoon to evaluate motor function in the upper extremities, assessing only motor dysfunction in the upper and lower extremities, sensory function in the upper extremities and bladder function, excluding sensory function in the trunk and lower extremities (four domain scores).[14] Each one of the four scales varies, respectively, from 0 to 5, 7, 3 and 3, ranging from 0 to 18 points. Fehlings et al. proposed classifying the severity of the myelopathy using the mJOA as mild (15 or more), moderate (12 to 14) and severe (less than 12).[16] Of note, a score of 17 in the JOA scale or 18 in the mJOA scale reflects a normal neurological function.

Finally, Kato et al. performed a prospective multicenter study and reported that the both JOA and the mJOA have a good correlation, but it was not ideal to use them interchangeably.[17]

TABLE 1 The Nürick grade system – Six grades of severity based on "difficulty in walking".

Grade	Characteristics
0	signs or symptoms of root involvement but without evidence of spinal cord disease
1	signs of spinal cord disease but no difficulty in walking
2	slight difficulty in walking which does not prevent full-time employment
3	difficulty in walking which prevented full time employment or the ability to do all housework, but which was not so severe as to require someone else's help to walk
4	to walk only with someone else's help or with the aid of a frame
5	chair-bound or bedridden

TABLE 2 The modified JOA scoring system for evaluating the severity of DCM.

Score	Description
Motor dysfunction of upper extremity	
0	Unable to move hands
1	Unable to eat with a spoon but able to move hands
2	Unable to button shirt but able to eat with a spoon
3	Able to button shirt with great difficulty
4	Able to button shirt with slight difficulty
5	No dysfunction
Motor dysfunction of lower extremity	
0	Complete loss of motor and sensory function
1	Sensory preservation without ability to move legs
2	Able to move legs but unable to walk
3	Able to walk on flat floor with a walking aid (cane or crutch)
4	Able to walk up- and/or downstairs w/aid of a handrail
5	Moderate-to-significant lack of stability but able to walk up- and/or downstairs without handrail
6	Mild lack of stability but able to walk unaided with smooth reciprocation
7	No dysfunction
Sensory dysfunction	
0	Complete loss of hand sensation
1	Severe sensory loss or pain
2	Mild sensory loss
3	No sensory loss
Sphincter dysfunction	
0	Unable to micturate voluntarily
1	Marked difficulty in micturition
2	Mild-to-moderate difficulty in micturition
3	Normal micturition

Additional work-up

Plain radiographies

Initial investigation of DCM is based on simple plain cervical radiographs, including flexion-extension exams to detect occult instability.[18] CS is characterized by osteophyte formation, loss of cervical disc space, loss of normal cervical alignment, uncovertebral and facet joints hypertrophy.

The Pavlov ratio is measured based on simple plain cervical radiographies to estimate congenital narrowing of the spinal canal, a major risk of DCM.[19,20] Using the lateral incidence, the spinal canal / vertebral body ratio is determined (a/b), where "a" is the distance from the posterior surface of the vertebral body to the nearest point of the spinal laminar line and "b" is defined as the midpoint between the anterior surface and the posterior surface of the vertebral body. A normal Pavlov ratio is about 1.0, whereas < 0.8 suggests congenital cervical stenosis, and spondylotic compression occurs when < 0.4. Although the ratio is useful for screening, further radiological investigation is needed when the ratio is < 0.8, as large vertebral bodies may skew the final ratio and yield false positive results.[21]

Also useful information obtained with plain cervical radiography is the mean value of the spinal canal in the antero-posterior (AP) diameter. In normal adult males, the mean value of the AP diameter of the spinal canal measured on lateral cervical radiograph is 17 to 18 mm at C3-5 and 12 to 14 mm at C6-7. Severe cervical stenosis is presumed when the diameter is less than 10 mm in the lower cervical spine and 10 to 13 in the upper cervical spine.[22]

Additionally, in cases where cervical deformity is present, measuring the C2-7 sagittal vertical axis (SVA) is important for outcome purposes. The horizontal distance from two plumb lines, one from the mid-vertebral body of C2 and the second from the posterior superior corner of the C7 vertebral body, greater than 4 cm postoperatively is associated with poor neck disability scores.[18]

Finally, 36 inch long cassette X-rays may be useful for assessment of global sagittal balance in patients with severe cervical deformity and concordant thoracolumbar deformity and dynamic flexion-extension x-rays are also used for detecting segmental instability and also assessment of cervical flexibility.[18]

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is the modality of choice to evaluate the neural elements, with multiplanar images and a high accuracy in detecting spinal cord compression secondary to degenerative changes. It is the gold standard modality for confirming the diagnosis of DCM. In addition to diagnosis, MRI can provide prognostic information: patients with high T2 signal intensity and concomitant a low T1 signal intensity in the spinal cord generally have unfavorable outcomes. Some new studies using new MRI techniques, such as diffusion tensor imaging (DTI) and fiber tractography can demonstrate spinal cord changes and DCM earlier than conventional sequences.[23]

CT scan

Conventional CT scan can demonstrate a small diameter of the spinal canal, osteophytes and degenerative changes but has a poor visualization of the spinal cord. It provides detailed information of the bone anatomy, with superiority when compared to X-rays and even MRI.[24] CT scan is important for surgical planning when spinal instrumentation will be required for preoperative anatomical study including that of the upper cervical spine.

In patients with contra-indications for an MRI study or those with previous surgeries and spinal instrumentation that may affect image quality, CT myelography can demonstrate indirect cord and nerve root compression.[24,25] CT myelography can also be used for calculating the compression ratio, a relationship between the smallest sagittal diameter of the spinal canal / transverse diameter x 100 (%). A compression rate of less than 0.4 correlates with clinical evidence of DCM and with a less favorable clinical outcome. By this reasons, some authors proposed that surgery should be indicated before this degree of deformation occurs into the spinal cord.[26]

Electromyography

Although limited in the assessment myelopathy, electromyography (EMG) may demonstrate radiculopathy.[27] It is, however, most useful in assessing differential diagnoses, such as motor neuron diseases (such as amyotrophic lateral sclerosis) and peripheral neuropathy. Additionally, EMG may offer some prognostic information: patients without myelopathy (mJOA scale of 18 or normal) but with severe stenosis and abnormal findings on the EMG have been shown in one study to eventually develop symptomatic DCM.[26]

Somatosensory and motor evoked potential (SSEP and MEP)

In patients with cervical cord compression, the somatosensory evoked potential (SSEP) are delayed or have low amplitude.[26] Cortical motor evoked potential (MEP) are more sensitive than SSEP in assessing early spinal cord dysfunction.[28] Bednarik et al. demonstrated that patients with cervical stenosis without clinical myelopathy who had abnormal SSEP had statistically more chances of developed DCM than those with normal SSEP, suggesting a predictable importance of this exam.[26]

Normal cervical alignment

Assessment of cervical alignment is important for planning surgical treatment in DCM. The normal cervical lordosis between C2 to C7 range from 20 to 35 degrees, but these measures depends on patient's population, age, radiological modality, etc.[29] Benzel et al. proposed that cervical kyphosis can be diagnosed if any vertebra from C3 to C6 crosses a line drawn from the posteroinferior aspect of the body of C2 in the midsagittal plane to the posteroinferior aspect of the body of C7.[30] Maintenance of cervical alignment is important, once it is associated with patient's outcome.

Lastly, in the cervical spine, about two thirds of the weight-bearing axis lies posterior to the vertebral bodies in the posterior column.[30] This emphasizes the importance of the integrity of the posterior ligamentous and bony structures in the maintenance of cervical alignment.

Differential diagnosis

Differential diagnosis of DCM may include:[31] primary spinal cord tumors; syringomyelia; extramedullary lesions (primary tumors, metastases); congenital myelopathies; normal pressure hydrocephalus; spinal cord infarction or infection; bilateral carpal tunnel syndrome; neurological diseases (amyotrophic lateral sclerosis, myasthenia gravis, multiple sclerosis, etc)

A thorough clinical examination, an adequate assessment of patient medical history, and the MRI is critical for differential diagnosis of DCM and other pathologies.

Surgical treatment

In cases with moderate or severe DCM, surgical treatment is clearly indicated as non-operative management will lead to continued, and possibly irreversible, neurological decline. Additionally, although recovery of lost function after surgery is generally uncertain, the best surgical results are generally associated with patients with mild DCM and early symptoms.[26] Considering these points, some authors have proposed surgery for all patients with diagnosis of DCM. However, Kadanka et al. have demonstrated that patients with mild DCM were successfully treat (no significant deterioration in the mJOA score, recovery ratio, or timed 10 m walk within either group during the 2 years of follow-up) with close clinical observation in one randomized controlled study comparing conservative *versus* surgery in spondylotic cervical myelopathy.[32] Of note, a limitation of this study is that, although patients did not deteriorate, they did not have any clinical improvement with clinical treatment.

The main goals of surgical treatment in DCM are to decompress the spinal cord, maintain or restore cervical alignment and stabilize the involved segments when needed. To achieve these goals, many different surgical techniques were proposed, using anterior, posterior or combined approaches. The choice of each one is based on patient characteristics (age, clinical symptoms, number of involved levels, site of compression, cervical alignment, previous surgeries, patients functional status, bone quality, presence of instability, among others), surgeon's preference and analysis of risk and benefits of each approach over the other considering the case.

Surgical approaches

Considering all the surgical goals, we discussed the key components of the most common surgical approaches used to treat DCM, summarized in Table 3.

Anterior cervical approaches

Anterior cervical surgery is one of the most frequent spinal surgeries performed in the US, mostly commonly used to treat DCM in one, two, or three level disease. The anterior cervical approach was described by Smith and Robinson in 1955.[33] It allows an excellent exposure of the ventral aspect of the spinal cord without touching the neural elements. With the anterior cervical approach, it is also possible to perform disc space distraction that can enlarge the neural foramen and the spinal canal, with direct decompression and restoring cervical lordosis.[34,35] The use of autografts or allografts into the disc space is important to achieve fusion.[34,35] Fusion is important to maintain the disc space height without collapse, maintaining cervical lordosis, and also for stabilization of the involved segments, avoiding further new compression.[34,35]

In cases where ventral cord compression involves a significant component of the vertebral body, beyond the disc boundaries, a cervical corpectomy is necessary to adequately decompress the spinal cord, followed by reconstruction and stabilization. An interbody device such as a titanium, PEEK, allograft or autograft (harvest from the iliac crest or fibula) is used for reconstruction and fusion.[34,35] A combination of discectomies and corpectomies can be used according to patient need and sites of compression.[35-37]

TABLE 3 Main surgical approaches and their variations for treating DCM.

Anterior cervical approaches
Discectomy(ies)
Corpectomy(ies)
Combined discectomy(ies) and corpectomy(ies)
Cervical arthroplasty
Posterior cervical approaches
Laminectomy
Laminectomy and fusion (instrumented or not)
Laminoplasty
Open-door or unilateral technique
Double door laminoplasty (also known as French door laminoplasty, spinous process-splitting, midline opening or T-saw laminoplasty)

DCM: degenerative cervical myelopathy.

Comparison of anterior discectomies *versus* corpectomy

Clinical outcomes [JOA, visual analog sclace (VAS) for arm and neck pain] for two levels discectomies were comparable with one level corpectomy when both options are feasible.[38] However, anterior cervical corpectomy and fusion (ACCF) had a higher operative time and bleeding amount compared with discectomies.[38] Additionally, discectomies obtained better improvements in segmental height and postoperative cervical lordosis when compared with corpectomy.[38,39] Of note, although corpectomies may have a lower rate of pseudoarthrosis than multilevel discectomies, because of the fewer bone graft interfaces, there was a higher stress on bone screws compared with discectomy. The choice of one approach over the other depends on surgeons' preference and patient's radiological findings.

Cervical arthroplasty

Cervical arthroplasty is also an alternative for treating one or even two levels DCM secondary to degenerative disc disease, especially those secondary to disc herniation. The best surgical candidates are younger patients, without facet joints arthritis and preserved cervical motion.[40] The rationale for performing a cervical arthroplasty instead of fusion is to preserve segmental motion and avoid adjacent level disease, even though this has been questioned since heterotopic ossification may occur in up to 50% of the cases and ASD has not been shown to be decreased by cervical arthroplasty in long term outcomes. Both anterior cervical anterior discectomy and fusion (ACDF) and cervical arthroplasty are effective to treat disc herniation in DCM.[40] When performing a cervical arthroplasty, surgeons may be aware that an inadequate decompression may lead to recurrence of myelopathic symptoms.

Posterior cervical approaches

The posterior cervical approach is a straightforward alternative to decompress the spinal cord and nerve roots with direct visualization.[41] However, unlike the anterior cervical approach, posterior approaches require a preoperative lordotic or straight cervical alignment.[41] Rigid local or global kyphosis is a contraindication for posterior decompression, as the spinal cord remains compressed and stretched by the anterior elements.[41] Posterior approaches avoid certain complications that are more common with anterior approaches, such as dysphagia, dysphonia and injury to the esophagus and carotid sheath contents.[41]

Cervical laminectomy

The oldest and most traditional posterior cervical surgery is a decompressive laminectomy.[41] It is based on direct decompression of the spinal canal, enlarging its anteroposterior diameter. Posterior approaches can directly decompress the posterior elements such as the ligamentum flavum, posterior bone, facet hypertrophy and also indirectly decompress the ventral elements, shifting the spinal cord posteriorly.[41,42]

However, as stated previously, the main disadvantages of cervical laminectomy are the inability to access ventral pathologies, such as disc herniation and anterior osteophytes, and the high risk of cervical deformity (post-operative kyphosis), which can result in cervical pain and late neurological deterioration.[41] Another complication of an isolated cervical laminectomy is post-laminectomy membrane that may cause recurrent stenosis.

Cervical laminectomy and instrumented fusion

The incidence of post-operative kyphosis after cervical laminectomy may be as high as 50%, and dependent on many factors, such as preoperative deformity, the presence of segmental instability, removal C2 and/or C7 lamina, extensive laminectomies, wide facetectomies and younger age.[41,43] Due to the risk of post-operative instability, concomitant instrumented fusion is advocated as a prophylactic maneuver for avoiding deformity and its consequences, especially when treating multilevel spinal cord compression.[41,42]

Similarly to a standard laminectomy, posterior instrumentation requires a lordotic or at least straight cervical spine alignment. A wide range of modern surgical techniques of instrumentation were described for the cervical spine, such as lateral mass and pedicle screws, laminar screws, pars screws for C2, among many others.[41,44] Cervical instrumentation may also avoid a new compression due to instability in the decompressed site. Disadvantages may include increasing surgical time and cost, implant related complications and loss of cervical range of motion, potentially increasing the chances of adjacent level disease below and above the fixed levels.[41]

Cervical laminoplasty

Laminoplasty is a surgical technique proposed in the early 1970's by Japanese surgeons for the treatment of ossification of the posterior longitudinal ligaments (OPLL) and congenital cervical stenosis.[45,46] The goal is to enlarge the cervical spine canal and avoid post-operative kyphosis but also to preserve motion at the treated levels. This motion preservation is the potential advantage of laminoplasty compared with laminectomy and instrumented fusion, which can potentially avoid the complications associated with arthrodesis.

A multitude of surgical procedures for expandable laminoplasty were described, but we can group them in two main techniques:[45,46]

1. open-door or unilateral technique; and
2. double door laminoplasty (also known as French door, spinous process-splitting, midline opening or T-saw laminoplasty).

The open door technique is based on open the lamina in one side (generally the most symptomatic one or with radicular symptoms) and hinge the contra-lateral side, wherein a greenstick fracture is performed. The lamina can be maintained in the open position with sutures or miniplates (that offers immediate stability). In contrast, the double door expands the spinal cord symmetrically by opening the midline with a split of the spinous processes and hinging both the left and right hemilaminae. The midline laminar splits can be opened with laminar spreaders or bone graft.[41,45,46]

While laminoplasty offers advantages over cervical fusion, it is not indicated for all patients. It does not address neck pain and may even cause worsening symptoms compared with anterior approaches, with extensive posterior muscle denervation. It is contra-indicated in patients with loss of cervical lordosis and with segmental instability. Complications of laminoplasty may include C5 palsy (5 to 12%), cervical axial pain, decreasing in cervical range of motion (ROM), and progression of OPLL.[28,41,46]

Interestingly, although C5 palsy is associated classically with posterior decompression, Gandhoke reported that the incidence of C5 palsy was similar comparing anterior cervical corpectomy (31 cases) *versus* posterior laminoplasty (31 cases as well).[47] There were two cases of C5 nerve root pareses in each group (p=1). There was no differences between the complication or reoperation rates between the two groups (p=0.184 and p=0.238, respectively). This study, however, was underpowered to assess different complication rates.

Finally, laminoplasty requires some stabilization to maintain the lamina in a new expanded position. The hardware for laminar fixation may increase the cost of the procedure (such as titanium implants) and also add potential complications (such as lamina migration, non union, hardware subsidence, etc). Lastly, there is a risk of laminar door closure with recurrence of neurological symptoms.

Comparison of anterior *versus* posterior approaches for multilevel DCM

Both anterior and posterior approaches are associated with improvement in patients' final neurological outcomes in DCM. Some systematic reviews reported that there was a trend towards better postoperative neural function with anterior approaches, possibly explained by the fact that anterior surgery is generally proposed for several forms of the disease. However, the recovery rate was similar between both according to systematic reviews with meta-analysis.[48] Of note, multilevel anterior cervical decompression and fusion had a higher rate of complications compared with posterior surgery.[48]

Fehlings et al. performed a prospective observational multicenter study of 264 patients comparing the anterior and posterior surgical approaches to treat DCM.[49] The choice of each approach was at the discretion of the surgeon and a follow-up rate of 87% was obtained. Outcome measures included the mJOA scale, Nürick scale, the Neck Disability Index and SF-36 Health Survey *version* 2 Physical and Mental Component Scores. A total of 169 patients were treated anteriorly and 95 received a posterior cervical surgery. DCM patients who underwent anteriorly cervical surgery were younger and had less severe myelopathy (as defined by the mJOA and Nürick scores). Both groups had similar baseline Neck Disability Index and SF-36, but the mJOA was lower in the posterior approach group. The extent of improvement in the Nürick scale, Neck Disability Index, SF-36 *version* 2 Physical Component Score, and SF-36 *version* 2 Mental Component Score were similar between the groups, although the mJOA improvement was lower in the anterior group (2.47 *vs.* 3.62, respectively, p<0.01). They concluded that, although patients who underwent anterior cervical approach were younger and had less severe DCM, both treatments had similar efficacy in the treatment of DCM.

Combined anterior-posterior approaches

In selected cases, a combined anterior-posterior or posterior-anterior approach can be used. The indications for combined approaches include patients requiring osteotomies for releasing the spine, patients with high risk for hardware failure, such as those with severe osteoporosis, and patients with a failure of a previous surgical approach (generally an anterior approach).[41,50-52] Combined approaches may add morbidity of both anterior and posterior surgeries, but must be considered in some challenging cases to successfully achieve the goals of surgery (decompression, stability and good cervical alignment). Of note, patients with 2-stage surgery are at an increased risk of experiencing major complications as they typically have more extensive degenerative pathology.

Conclusion

Cervical spondylotic myelopathy is the most common cause of spinal cord dysfunction in adult patients. The

diagnosis is made clinically and confirmed with a cervical MRI. The severity of the DCM can be objectively assessed using the mJOA and the Nürick scale, the most commonly used scoring for cervical myelopathy.

Surgical treatment is the main treatment modality. The main goals of surgery are to decompress the spinal cord, maintain stability and achieve a good cervical alignment with an anticipated outcome of neurological preservation or improvement. The choice of one approach over the other depends on patient's characteristics (such as number of involved levels, site of compression, cervical alignment, previous surgeries, bone quality, presence of instability, among others) and surgeon's preference.

Spine surgeons must understand the advantages and disadvantages of all surgical techniques to choose the best surgery for each patient to optimize the final outcome. Further comparative studies are necessary to attest the superiority and differential risks of one approach over the other when multiple options are available.

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Resumo

Manejo da mielopatia cervical degeneratiiva – Uma atualização

Introdução: a mielopatia cervical degenerativa (MCD) é uma das causas mais comuns de disfunção medular em adultos. Os pacientes em geral apresentam declínio neurológico lento e progressivo, ou deterioração escalonada. No presente artigo, discutimos os mais importantes fatores envolvidos no manejo da MCD, incluindo considerações sobre os aspectos relacionados à escolha da abordagem cirúrgica.
Método: realizou-se extensa revisão da literatura de artigos *peer-reviewed* relacionados ao tema.
Resultados: embora o diagnóstico seja realizado clinicamente, a ressonância magnética (RM) é o estudo de imagem de escolha para confirmá-lo e excluir eventuais diagnósticos diferenciais. A gravidade do quadro clínico pode ser avaliado utilizando-se diferentes escalas, como a modified Japanese Orthopedic Association (mJOA) ou a de Nürick, provavelmente as mais comuns. Uma vez que a melhora clínica espontânea é rara, a cirurgia é a principal forma de tratamento, em uma tentativa de evitar dano neurológico adicional ou deterioração e, potencialmente, aliviar alguns sintomas e melhorar a função dos pacientes. Abordagens cirúrgicas por via anterior, posterior ou combinada podem ser usadas para descomprimir o canal, concomitantemente a técnicas de fusão. A escolha da abordagem depende das características dos pacientes (número de segmentos envolvidos, local de compressão, alinhamento cervical, cirurgias prévias, qualidade óssea, presença de instabilidade, entre outras), além da preferência e experiência do cirurgião.
Conclusão: os cirurgiões de coluna devem compreender as vantagens e desvantagens de todas as técnicas cirúrgicas para escolher o melhor procedimento para seus pacientes. Estudos futuros comparando as abordagens são necessários para orientar o cirurgião quando múltiplas opções forem possíveis.

Palavras-chave: mielopatia cervical, mielopatia espondilótica, abordagem cirúrgica, abordagem anterior, abordagem posterior.

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Microscopic colitis: A literature review

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Summary

Microscopic colitis (MC) refers to chronic inflammation of the colon which is characterized by histologic changes at the level of a radiologically and endoscopically normal mucosa. It is a common cause of chronic non-bloody diarrhea that occurs primarily in older individuals; however, there are few studies in the literature with strong scientific evidence compared to other inflammatory bowel diseases (IBD), which limits the knowledge of physicians and pathologists. This article aims to review the information on MC, describing diagnostic methods and drugs available for treatment. We conducted a search of the Pubmed database and CAPES Portal using the keywords "microscopic colitis", "collagenous colitis", "lymphocytic colitis", and "review" for selection of articles published between 1996 and 2015 related to the topic. Based on the studies discussed in this review, we conclude that MC is a relatively new gastrointestinal disorder, most studies are incipient particularly with respect to pathophysiology and immunology, and budesonide is the best documented short-term treatment. However, further studies are needed to elucidate the best strategy for treatment in the long term.

Keywords: microscopic colitis, collagenous colitis, lymphocytic colitis, review.

Introduction

Microscopic colitis (MC) refers to chronic inflammation of the colon which is characterized by histologic changes at the level of a radiologically and endoscopically normal mucosa. It is a common cause of chronic non-bloody diarrhea that occurs primarily in older individuals, accounting for 10 to 20% of cases.[1]

Collagenous colitis (CC) was described in 1976 by Lindstrom and Freeman with clinical and histological features similar to MC, except for the presence of a thick band of subepithelial collagen. The term MC was used in 1980 to describe patients with chronic watery diarrhea and normal findings on sigmoidoscopy and barium enema but with microscopic inflammation on colon biopsy. It is unclear whether these two conditions represent separate diseases or are phenotypes of the same disease.[2]

Currently, MC includes two subsets: CC, with a thick band of subepithelial collagen, and lymphocytic colitis (LC), without collagen thickening and with an increase in the number of intraepithelial lymphocytes (≥ 20/100 epithelial cells).[2,3]

Method

The literature review was adopted for the preparation of this article on MC. Data was collected from articles published between 1996 and 2015 in journals indexed in the Pubmed and CAPES Portal search engines. The keywords used were "microscopic colitis", "collagenous colitis", "lymphocytic colitis" and "review" for the selection of articles related to the topic. The search included original articles and literature reviews published in English. The research was also complemented by articles referenced in other publications already selected. The investigation was only concluded when signs of theoretical saturation of the research topic emerged.

Epidemiology

Several risk factors have been described for MC, the main ones including: female, advanced age, autoimmune dis-

eases, past or current diagnosis of malignancy and history of solid organ transplants.[3]

Recent studies in the US have shown an MC incidence rate of 7.1 per 100,000 individuals/year for CC, and 12.6 per 100,000 individuals/year for LC.[4] The global prevalence of MC was observed at 103.0 per 100,000 individuals, with 39.3 per 100,000 individuals for CC and 63.7 per 100,000 individuals for LC. These figures are similar to the data obtained for classic inflammatory bowel diseases (IBD).[3]

MC is typically a disease of the elderly, with an average age at diagnosis of 65 years.[5] CC is around 20 times more frequent in women, while LC is equally distributed between men and women.[4] MC is a rare phenomenon in children and 25% of patients with MC are aged less than 45 years, which reflects the need for investigation in young patients with chronic diarrhea.[5]

Pathogenesis

The pathophysiology of MC is still unknown, but it is believed that it is due to a multifactorial etiology, involving an exacerbated immune response to harmful luminal agents in the mucosa of these individuals.[1,3,4]

There is strong evidence of an autoimmune basis for CC and LC, both of which are associated with diseases such as celiac disease (12%), thyroid diseases (10.3%), Sjögren's syndrome (3.4%) and *diabetes mellitus* (1.7%).[3-5] Various autoantibodies and phenotypes can be found along with MC, including the DR3 phenotype of human leukocyte antigen (HLA). However, no specific autoantibody has been identified as relevant in the diagnosis.[3,4]

Several luminal factors have an important role in the pathogenesis of MC. Many drugs are cited, such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), sertraline, ranitidine, simvastatin, carbamazepine, and more. These medications should be stopped when MC is diagnosed, which may result in improvement of the symptoms reported by the patient.[3,4]

Malabsorption of bile acids was found in up to 60% of patients with LC and 44% of patients with CC, supporting the idea that this may be the cause of MC.[3,4] Increases were also reported in interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1 β), and a profile of Th1 cytokines, which are suggested to be involved in the inflammatory process.[3,4]

As for environmental factors, the major etiologic role is played by cigarettes. Smoking is more prevalent among patients with MC, and studies indicate an association with lung cancer. It has also been demonstrated that MC involvement in individuals that smoke occurs around 10 years earlier, increasing the relevance of this habit.[3-5]

Clinical presentation

LC and CC are not distinguishable from each other based on symptoms and clinical presentation. Differentiation between the two is undertaken through histology only.[1,3,4,6]

The main symptom noted is chronic, typically aqueous, non-bloody diarrhea; nocturnal diarrhea is common (50%), as well as urgency (70%) and fecal incontinence (40%).[1,3-10]

Abdominal pain is a common symptom and may be present in up to 50% of patients. A differential diagnosis with irritable bowel syndrome (IBS) should therefore be investigated.[1,3,5,6] Weight loss is also observed during active disease in almost half of patients. Celiac disease should be investigated and discarded in patients with marked weight loss, steatorrhea, iron deficiency anemia, and those who do not respond to the usual therapy.[1,5]

The presence of fever, vomiting, or hematochezia should indicate the possibility of an alternative diagnosis.[8]

Laboratory and imaging diagnosis

The diagnosis of MC depends on a proper medical history, with the exclusion of other diseases, normal radiological/endoscopic findings and endoscopic biopsies with histopathological findings consistent with MC.[4]

Medical history helps to rule out other etiologies that can cause a similar clinical presentation, such as IBD, celiac disease and IBS. Laboratory and radiographic examinations also rule out other pathologies, but are typically normal.[4] Only non-specific changes may be found, such as moderately high C-reactive protein and anemia. A stool examination usually reveals the absence of pathological microorganisms. The diagnostic accuracy of calprotectin and fecal lactoferrin is low.[11]

Barium enema and colonoscopy are usually normal, although subtle changes may be observed in the mucosa, such as edema, enanthem and abnormal vascular pattern, occasionally seen during colonoscopy.[12]

Histological diagnosis

The diagnosis of MC is based solely on results of typical microscopic changes in mucosal biopsies of the colon. In CC (Figure 1) we can observe thickening of the subepithelial collagen layer together with chronic mononuclear inflammation in the lamina propria and damaged epithelial cells with an occasional increase in the number of intraepithelial lymphocytes. The enlargement of the subepithelial collagen layer is greater than 10 µm, in contrast with the normal basal membrane which measures less than 3 µm.[13]

The thickening of the collagen layer can vary and is most prominent in the ascending and transverse colon; it

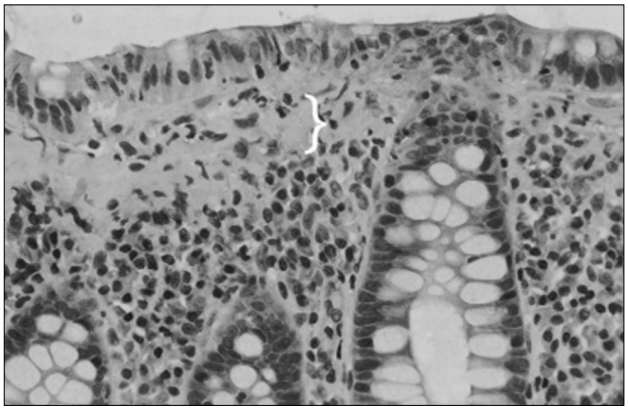

FIGURE 1 Collagenous colitis. In addition to the inflammatory infiltrate, a thick band of subepithelial collagen can be observed (brace).
Source: adapted from Pardi DS et al.[2]

may be absent in biopsies of the sigmoid colon or rectum, emphasizing the importance of obtaining proximal colon biopsies for the diagnosis of CC. In general, histopathological changes are restricted to the large intestine, although thickening of the collagen layer may infrequently be found in the stomach, duodenum or terminal ileum.[13]

Meanwhile, in LC (Figure 2), we can observe an increase in the number of intraepithelial lymphocytes (≥ 20/100 surface epithelial cells), in conjunction with damage to the surface of the epithelial cells and infiltration of lymphocytes and plasma cells in the lamina propria. The collagen layer, however, remains normal. In doubtful cases, immunolabeling of CD3 T lymphocytes facilitates the assessment of the amount of intraepithelial lymphocytes.[3,13]

There are histological similarities between the two forms of colitis, such as inflammation in the lamina propria essentially consisting of an increase in the number of lymphocytes and plasma cells and epithelial damage.[4]

Treatment

The first step in treating patients with MC is to search for exacerbating factors, such as dietary history in order to search for foods that contribute to cause diarrhea, such as dairy products in patients with lactose intolerance or excessive consumption of dietetic products like caffeine and alcohol.[1,2,13,14]

It is also important to review the medication currently used by the patient in order to search for drugs or substances that are causing or exacerbating the diarrhea in MC.[1,5,8,14] Stopping smoking should be considered, although the evidence for such is still weak.[5] Nevertheless, most patients with MC require treatment.[1]

Treatment of MC must take into account the severity of the symptoms, the impact on the patient's quality of life and the availability of data about the results of randomized clinical trials. The main objective is to achieve clinical remission and improve the patient's quality of life. It is not currently known whether histological remission is relevant to the recurrence rate. Therefore, it is unclear if this should be an important goal.[7]

Antidiarrheal drugs such as loperamide are often used in MC empirically in patients with mild diarrhea, but have never been formally tested in randomized placebo controlled trials. Clinical remission is rarely achieved and an impact on colon inflammation is unlikely.[1,5,7]

In 1998, Fine et al.[15] suggested the use of three bismuth subsalicylate tablets (262 mg/each), three times/day in patients with mild symptoms or those that do not respond to loperamide. However, in 2001, Pardi et al.[16] showed that most patients treated with this medication showed a partial response.

Steroids are the most effective treatment in patients with more intense symptoms and nonresponders to bismuth, with the use of budesonide as the best-documented treatment.[1,9]

Baert et al.,[17] Bonderup et al.[18] and Miehlke et al.[19] showed the efficacy of budesonide at a dose of 9 mg/day for 6 to 8 weeks for the induction of clinical remission in randomized placebo-controlled clinical trials on CC. Most patients responded quickly to budesonide, and presented a substantial improvement in quality of life and clinical symptoms after 2 to 4 weeks of treatment. In a Cochrane meta-analysis conducted in 2009 by Chande et

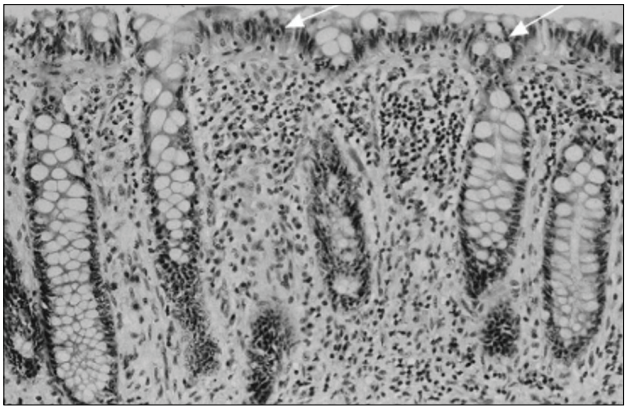

FIGURE 2 Lymphocytic colitis. Intraepithelial lymphocytosis (arrows) can be observed, and mixed inflammatory infiltrate in the lamina propria. With regard to the distinction between ulcerative colitis and Crohn's colitis, the architecture of the crypts is normal.
Source: adapted from Pardi DS et al.[2]

al.[20] the *odds ratio* for clinical response to budesonide compared to a placebo was 12.32 (95CI 5.53-27.46), with an 81% response rate.

The same efficacy of budesonide at the dose of 9 mg/day has been demonstrated in the treatment of LC by two placebo-controlled studies conducted in 2009 by Miehlke et al.[21] and Pardi et al.[22] Both studies also showed substantial improvement in colon inflammation.[21,22] Two other randomized placebo-controlled trials conducted by Bonderup et al.[23] and Miehlke et al.[24] showed that clinical remission and histological response could be maintained in most patients with budesonide at a dose of 6 mg/day for 6 months, with an 83% response rate.

After stopping treatment with budesonide, relapse of symptoms may occur in 60 to 80% of patients, most of which respond to retreatment.[1,5,7,9,25] Many patients therefore become steroid-dependent. As such, before starting budesonide, the diagnosis should be reviewed and differential diagnoses ruled out, such as celiac disease and hyperthyroidism.[1,2]

Patients treated with long-term budesonide should be monitored for side effects associated with the use of steroids, such as hypertension, hyperglycemia and changes in bone metabolism, among other factors. Furthermore, they should avoid consuming grapes, grape juice and any other cytochrome P450 inhibitors that interfere with the metabolism of budesonide and predispose to side effects.[1]

The main advantage of budesonide in relation to conventional corticosteroids is its limited systemic absorption, which leads to better long-term tolerance.[25] Furthermore, it presents fewer side effects than prednisone, with higher efficacy demonstrated in 2013 by Gentile et al.[26] in an uncontrolled study. Therefore, unless cost is a major concern, budesonide is generally used when corticotherapy is required.[1]

Prednisolone has been analyzed in retrospective studies conducted by Olesen et al.,[27] Bohr et al.[28] and Pardi et al.[29] and in a randomized placebo-controlled trial carried out by Munck et al.[30] In the comparison, patients using budesonide showed lower recurrence than those treated with prednisolone. Therefore, prednisolone does not appear to be of value in the treatment of patients who do not respond to budesonide.[5]

Sulfasalazine or mesalazine have been widely used in MC, but have not been strictly evaluated in randomized placebo-controlled trials.[9] In the treatment of MC, mesalazine has mainly been reported in retrospective studies carried out in 1996 by Bohr et al.[28] and in 2004 by Olesen et al.,[27] suggesting a therapeutic response in about half of patients. In 2008, Chande et al.[31] conducted an uncontrolled prospective study that showed greater efficacy of mesalazine when administered over a period of 6 months. Due to the lack of control groups, the true value of the use of mesalazine when treating MC remains inconclusive.[7,32]

Calabrese et al.[33] conducted a randomized study with 23 patients with CC and 41 with LC who received 2.4 g/day of mesalazine monotherapy, or in combination with 4 g/day of cholestyramine for 6 months. Disease remission was noted in 91% of the patients with CC and 85% of the patients with LC after 6 months of treatment. Combined therapy presented the best responses.

Immunosuppressive therapies, such as azathioprine, 6-mercaptopurine or methotrexate, may be useful in steroid-dependent or steroid-refractory patients.[1,5,7-9,14]

There are only a few reports of the use of anti-TNF (tumor necrosis factor inhibitors) agents in patients with CC at similar doses to those for IBD. However, a risk-benefit analysis should be completed, and regular monitoring is necessary.[5]

Probiotics *Lactobacillus acidophilus* LA-5 and *Bifidobacterium animalis* subsp. *lactis* BB12 (AB-Cap-10) did not show any benefit over the placebo with regard to clinical response, histological improvement or quality of life when administered for 12 weeks.[34]

Pentoxifylline, verapamil and subcutaneous octreotide could be treatment options, but their use has not yet been recommended.[14] Metronidazole and erythromycin may be beneficial in some patients, although diarrhea may occur again when the medication is withdrawn.[2,9]

Surgical intervention in patients with MC should be considered as a last resort in cases refractory to all interventions. Ileostomy with or without colectomy or ileal pouch-anal anastomosis have been successfully performed in some cases.[1,2,5,7-9]

Prognosis

The natural history of MC is benign and variable, with many self-limited cases. However, patients can be severely affected. It is possible to have periods of spontaneous remission and relapse, as well as an ongoing pattern.[4]

Some cases of MC have been reported as progressing into Crohn's disease or ulcerative colitis, but there are still no studies to demonstrate such involvement.[4] The risk of cancer and mortality is similar to that of the population.[5]

The long-term prognosis of MC is generally good. In a follow-up study on CC conducted by Goff et al.,[35] 63% of patients remained in remission after 3.5 years. Meanwhile, in another cohort study conducted by Bonner et

al.,[36] all 25 patients showed improvement after 47 months of diagnosis, with 29% requiring continuous medication.

Final considerations

MC is a common, relatively new and under-diagnosed cause of chronic watery diarrhea, which may be confused with IBS, celiac disease, IBD and other disorders. The peak incidence occurs in middle-aged women and it is usually associated with other autoimmune disorders. Diagnosis is based on histopathological analysis of colonic mucosal biopsies, which should always be obtained in the investigation of chronic diarrhea.

The choice of initial drug therapy depends on the intensity of the patient's symptoms. In patients with mild symptoms, treatment can be attempted with antidiarrheal medications and bismuth subsalicylate. However, steroid or immunosuppressive drugs are necessary in refractory cases and those with more intense symptoms, with budesonide as the drug of choice for short-term treatment. Surgical intervention is the latest treatment option in cases refractory to all medical therapies. The prognosis is good and the disease does not increase the risk of occurrence of colorectal cancer.

It is necessary to take a multidisciplinary and individualized approach, always considering MC as a possible diagnosis in patients who present chronic diarrhea.

We conclude that there is a need for further randomized placebo-controlled studies, especially with regard to immunomodulators and anti-TNF drugs, as experience with such is still limited, in order to provide better long-term therapeutic strategies and, consequently, better clinical management of the patient.

Resumo

Colite microscópica: uma revisão da literatura

Colite microscópica (CM) corresponde à inflamação crônica do cólon que se manifesta por modificações histológicas em nível de uma mucosa radiológica e endoscopicamente normal. É uma causa comum de diarreia crônica não sanguinolenta que ocorre principalmente em indivíduos idosos; porém, há poucos trabalhos na literatura com forte evidência científica quando comparada à de outras doenças inflamatórias intestinais (DII), o que limita seu conhecimento por médicos e patologistas. Este artigo tem como objetivo revisar as informações referentes à CM descrevendo os meios diagnósticos e os medicamentos disponíveis para o tratamento. Foi realizada uma pesquisa na base de dados Pubmed e no Portal da CAPES entre 1996 e 2015 utilizando as palavras-chave "colite microscópica", "colite colagenosa", "colite linfocítica" e "revisão" para seleção de artigos relacionados ao tema. Diante dos trabalhos analisados, conclui-se que a CM é uma desordem gastrointestinal relativamente nova, a maioria dos estudos são incipientes, principalmente quanto à imunologia e fisiopatologia, e a budesonida é o tratamento em curto prazo mais bem documentado. Todavia são necessários novos estudos para elucidar qual é a melhor estratégia em longo prazo.

Palavras-chave: colite microscópica, colite colagenosa, colite linfocítica, revisão.

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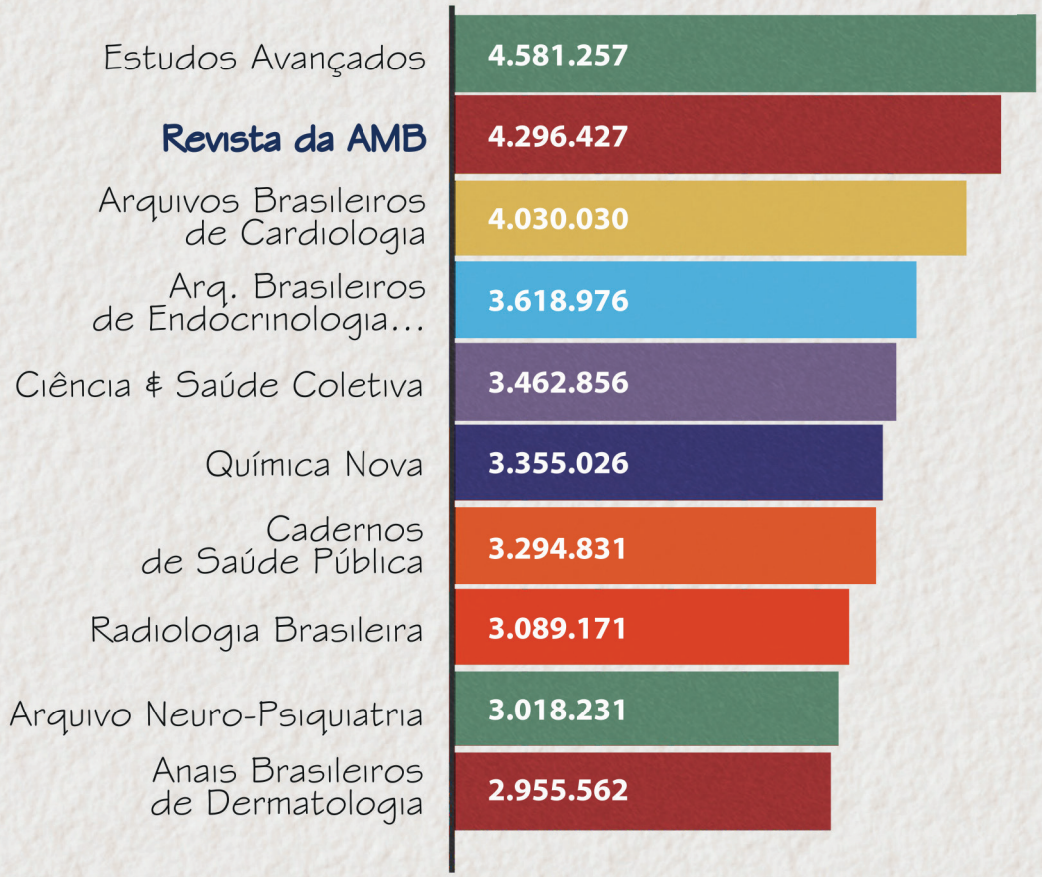

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