Laryngeal sarcoidosis: Literature review

Sarcoidose laríngea: Revisão de literatura

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Summary

Introduction: Laryngeal sarcoidosis is a granulomatous disease representing a challenge as regards diagnosis and treatment.
Method: In this review, all aspects of the disease are involved, including etiology, clinical manifestations in adults and children, diagnosis, and treatment, by searching through Medline, Lilacs and Scielo databases, as well as English and Portuguese articles published from 1973 to 2008.
Final Comments: Despite the breakthroughs in its diagnosis and treatment, sarcoidosis is a disease that remains without a clear etiology and physiopathology, becoming an exclusion diagnosis due to both the lack of precise exams and its likely multifactor background. Laryngeal impairment, however infrequent, is a suspicion mainly when there is a precedent history of systemic sarcoidosis, and the research for differentiated diagnosis must be wide-ranging so as to prevent severe diseases like malign neoplasia from being unnoticed.
Keywords: laryngeal disease, sarcoidosis, larynx, positron emission tomography.

Resumo

Introdução: A sarcoidose laríngea é uma doença granulomatosa que representa um desafio em relação ao diagnóstico e o tratamento.
Método: Nesta revisão são abordados todos os aspectos da doença, incluindo etiologia, manifestações clínicas em adultos e crianças, diagnóstico e tratamento, a partir da base de dados Medline, Lilacs e Scielo, incluindo-se artigos de língua inglesa e portuguesa publicados no período de 1973 a 2008.
Comentários Finais: Apesar dos avanços ocorridos na investigação e tratamento da sarcoidose, é uma doença que ainda se mantém sem etiologia e fisiopatologia definidas, constituindo um diagnóstico de exclusão pela ausência de exames específicos e por sua provável origem multifatorial. O acometimento laríngeo, apesar de raro, é suspeitado principalmente diante de história prévia de sarcoidose sistêmica, e a pesquisa dos diagnósticos diferenciais deve ser extensa para não passarem desapercebidas doenças graves como neoplasias malignas.
Palavras-chave: doenças da laringe, sarcoidose, laringe, tomografia por emissão de pósitrons.

INTRODUCTION

Granulomatoses are systemic diseases integrating the differentiated diagnosis of numerous affections of the respiratory tract, on one hand due to the preference for this system, on the other hand for the polymorphism of their clinical manifestations. In this group, there are sarcoidosis, chronic inflammatory disease of undetermined etiology, which, in most cases, impairs the lungs, visceral and parietal pleura, hilar and mediastinal lymph nodes. In the head and neck area, they can cause lymphadenopathy, facial palsy, parotid swelling, eye, and nose and larynx lesions, however rare in a separate way.

Laryngeal sarcoidosis is an underdiagnosed disease, whether for lack of specific detecting tests, turning the diagnosis into an exclusion one, or for the diversity of criteria to be analyzed, so that the diagnostic suspicion can be confirmed (1). The clinical features vary from the asymptomatic form to severe cases, mainly when there is an obstruction of the airways. Differences in the characteristics of the disease are observed according to age, and a lower frequency of the isolated laryngeal impairment and a more evident symptomatology are seen during the pediatric age group.

New technologies have been used for a diagnosis, such as PET/CT (positron-emission tomography), widely used in malign neoplasias, but since it is not a specific tumor exam, it can be used to detect benign conditions like sarcoidosis.

The objective of this review is to update the sarcoidosis data, from etiology to treatment, by emphasizing the laryngeal impairment scarcely described in literature and approaching an exhaustive investigation in its differentiated diagnosis.

METHOD

This review was performed by searching subject describers 'sarcoidosis', 'laryngeal diseases' and 'larynx' on Medline, Lilacs and Scielo databases, including English and Portuguese articles published between 1973 and 2008. From the primary selection, new relevant scientific works found in the references were added.

LITERATURE REVIEW

Epidemiology

Sarcoidosis happens to people at all ages, sexes and races, however there are some differences in the characteristics and frequency for likely genetic and environmental factors involved. Typically, it occurs in young adults aged between 20 and 40, and it is discreetly prevalent in women. In the USA, a higher prevalence was identified in the black (35.5/100,000 inhabitants) compared with the white population (10.9/100,000). As to the African continent, it is noticed there is a higher prevalence in the black, however at lower ratios. In the Scandinavian countries, the highest prevalence is found around 64/100,000 in Sweden and 26.7/100,000 in Norway (2). In Brazil, the prevalence in the general population was estimated around 10/100,000 inhabitants (3). The laryngeal involvement occurs in around 0.5-8.3% of the patients, and its isolated presence in this organ is still scarcer.

Etiology

A number of etiologic factors have been associated with likely causes of sarcoidosis, considering the possibility that environmental infectious or non-infectious agents do not unleash a series of immunological and inflammatory events, with a final transformation of macrophages into giant cells and epithelioids composing granuloma blocks and characterizing the disease in genetically susceptible people (6, 7).

Sarcoidosis usually occurs in individuals exposed to environments in which other granulomatoses are proven to occur, particularly, occupational exposure to insecticides, agricultural jobs, bird raising and humid and musty places, typically associated with the exposture to bioaerosol (8).

The genetic susceptibility is demonstrated by the evidence of a higher prevalence in the family and a correlation of some genotypes with the severity and chronic feature of the disease (9, 10), as well as the demonstration of the association with some HLA alleles (DRB1 and DQB1), (11, 12).

Due to the similarity of the clinical and histological features with diseases caused by fungi and microbacteria, the likelihood of transmission in transplanted patients, an increase in antibodies and the detection in tissues of some agents like *Propionibacter acnes* suggests an infectious case for sarcoidosis (13, 14).

Clinical Manifestations

Three clinical standards are identified in patients diagnosed of sarcoidosis: without symptoms, unspecific constitutional symptoms and organ-specific symptoms (1). The asymptomatic patients have an investigation

starting from alterations found in the routine thoracic x-ray and are around 30-50% of the total (15, 16). The symptomatic patients show unspecific complaints such as fatigue, fever and loss of weight; or associated with organ-specific symptoms. Regarding larynx, the most common signals and symptoms are pharyngeal globe, dyspnea, dysphonia, dysphagia and dry cough. Most severe cases can evolve with a stridor and an obstruction of the airway, sometimes requiring a tracheotomy (11, 17).

Laryngeal sarcoidosis patients do not necessarily show the systemic form: in BENJAMIN et al's review (18), out of five patients with laryngeal lesions, only one showed a generalized disease; in NEEL AND MCDONALD's reports (4), out of thirteen patients having laryngeal lesions, seven showed an impairment of other organs.

The laryngoscopy findings are shown as edematous, elevated and pale mucosa, in the following sites in a decreasing frequency order: Epiglottis, arytenoid, aryepiglottic folds and vestibular folds (19). This major impairment of the supraglottis probably occurs due to the big amount of lymphatic vases in this area, which are stretchered by replacing the architecture by sarcoid deposits or subcutaneous foci of the disease (Figure 1) (20). More rarely, it can involve subglottis and in 24% of the cases, vocal folds, also causing their immobility, whether for an impairment of the vagum nerve or their fixation by sarcoid infiltration in the crycoaritenoid joint, a diagnosis sometimes hard to be made by electromyography (21,22).

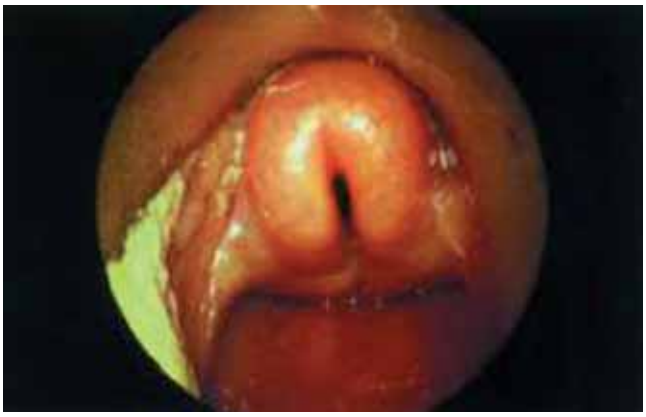

Figure 1. Laryngeal sarcoidosis - Image provided by Dr. Enric Massana.

Pediatric Sarcoidosis

This is an uncommon disease in the pediatric age group, having an approximate 1.02/100,000 ratio (23). It is usually shown more symptomatically than in adults, probably because the disease is more detected in asymptomatic adults by a routine thoracic x-ray, what is not usually performed in children (24). The most common symptoms are lethargy and fatigue, but cough, fever and loss weight are also frequent (25).

Its extrapulmonary characteristic is more frequent than in adults; however the isolated laryngeal impairment is more infrequent as related by KENNY et al. (26). The laryngeal involvement happens in both the pre-pubertal and in the post-pubertal age group and dyspnea, cough and hoarseness are frequent (27).

Diagnosis

For a sarcoidosis diagnosis, 3 criteria must be met: compatible clinical-radiological findings, histological sample represented by non-necrotizing granulomas and exclusion of other granulomatoses or diseases having similar findings.

The thoracic x-ray images usually show a hilar lymphadenopathy and a pulmonary infiltrate (6). The larynx images are more unspecific, among which are sideface cervical X-ray, what can show an increase in epiglottis similar to "the thumb sign" of the acute epiglottis, or the computed tomography showing a dense mass of soft parts in the impaired topography, usually supraglottis (18,28).

Another exam that has been mostly recently used is FDG PET (positron emission tomography), which has identified an increase in detecting fluoro-deoxy-glycolysis not only in malign lesions but in granulomatous lesions with sarcoidosis (29, 30).

BRAUN et al. (31) demonstrated an 85% sensitivity of PET/CT to detect active sites of laryngeal-pharyngeal sarcoidosis proven by a biopsy. Additionally, it can be a useful method to warn about the presence of the laryngeal involvement in patients with a previous history of sarcoidosis without typical symptoms (29).

Evidence of laryngeal lesion associated with the histological sample of another site (e.g., lung) compatible with sarcoidosis are not sufficient to determine a laryngeal impairment by sarcoidosis, because in literature cases of pulmonary sarcoidosis associated with a laryngeal carcinoma are described (32). Therefore, in order to reach a diagnosis of laryngeal sarcoidosis, a biopsy of the lesion in this topography must be performed, and the result is shown as non-necrotizing epithelioid granuloma (1, 3, 2).

In order to exclude other diseases integrating the differentiated diagnosis, a survey of alcohol-acid-resistant

Table 1. Differentiated diagnosis of sarcoidosis.

Infectious	Inhalation	Undetermined	Miscellaneous
Tuberculosis			
Leprosy	Silicosis		
Syphilis		Wegener	Hypothyreoidism
Paracoccidioidomicosis	Asbestosis		
Histoplasmosis			
Rhinoscleroma	Berylliosis	Amyloidosis	Squamocellular carcinoma
Actinomicosis			

fungi and bacillus, as well as a culture for bacteria and fungi from the biopsied specimen; survey of syphilis (VDRL), Wegner's granulomatous (cANCA), tuberculkosis (PPD) and a serology for histoplasmosis and paracoccidioidomicosis (1,18).

Differentiated Diagnosis

Since sarcoidosis is an exclusion diagnosis (1, 21), all the supplementary methods must be used to investigate diseases having similar manifestations in the clinical, radiological and, especially, histological features (Table 1).

Treatment

The clinical course of sarcoidosis is very diversified: 60-70% of patients showing a spontaneous remission, 10-20% showing permanent sequels and the mortality is 1-5% usually for pulmonary, cardiological and neurological complications (1). The treatment of choice is systemic corticotherapy; usually the drug used is prednisone at a dose of 40-60 mg/day in adults and mug/kg/day in children, for a total period of 6-12 months (34, 35). In the immune cases or with an intention of reducing the side effects of corticoids, cytotoxic agents, such as methotrexate and azathioprine, can be used effectively, and only in resistant cases, more toxic drugs, such as cyclophosphamide and chlorambucil can be used (36,37).

When there is no satisfactory improvement of laryngeal lesions with a systemic treatment and the patient appears to be symptomatic, an option is an intraregional corticoid injection (triamcinolone or methylprednisolone), which will reach high local concentrations with reduced side effects (26). The results are diverse, but in some cases of airway obstructions, decannulation of tracheostomy is achieved by this therapy (27). When there is an imminent of respiratory insufficiency for a high obstructon, tracheostomy must be performed beforehand and, if there is no response, injectable corticotherapy is chosen for resection of obstructive lesions, in most cases, partial resection of epiglottis through CO2 laser or cold instruments (26). A radiotherapy treatment is also described for these lesions with the disadvantage of a likely local carcinogenic effect (38).

Conclusion

In this review, the breakthroughs in the diagnosis and treatment of sarcoidosis are shown; however it is a disease that remains without a clear etiology and physiopathology, becoming an exclusion diagnosis due to both the lack of precise exams and its likely multifactor background. Laryngeal impairment, however infrequent, is a suspicion mainly when there is a precedent history of systemic sarcoidosis, and the research for differentiated diagnosis must be wide-ranging so as to prevent severe diseases like malign neoplasia from being unnoticed.

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