Respiratory Medicine 113 (2016) 42–49

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Review article

The three tiers of screening for sarcoidosis organ involvement

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ARTICLE INFO

Article history:
Received 9 November 2015
Received in revised form
22 February 2016
Accepted 22 February 2016
Available online 23 February 2016

Keywords:
Sarcoidosis
Organ involvement
Symptoms
Screening
Diagnosis

ABSTRACT

Sarcoidosis may involve any organ in the body. Organ involvement with sarcoidosis may go undetected. This manuscript addresses a suggested approach to screening for sarcoidosis organ involvement. As sarcoidosis organ involvement may never cause symptoms or clinical problems, it is not always necessary to expend the time or expense to detect all organs involved with sarcoidosis. On the other hand, some forms of sarcoidosis organ involvement may have potentially severe consequences such as permanent vision impairment from eye sarcoidosis and sudden death from cardiac sarcoidosis. We believe it useful to describe three tiers of screening for sarcoidosis organ involvement. The first tier of screening involves eliciting a medical history and performing a physical examination. This is a useful screen for all organs. The second tier of screening involves performing specific laboratory tests to search for specific sarcoidosis organ involvement, even if there is no clinical sign or symptom to suggest involvement of that organ. Such screening is only recommended for a limited number of specific organs. The third tier of screening is complex and involves the performance of multiple tests/algorithms or examinations by subspecialists to search for specific organ involvement. The third tier of screening is used to evaluate eye sarcoidosis, vitamin D dysregulation associated with sarcoidosis, and cardiac sarcoidosis. It is hoped that this approach to screening for sarcoidosis organ involvement will be a springboard for rigorous examination of this process that is likely to benefit sarcoidosis patients.

Contents

1. Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology that may affect any organ system. Sarcoidosis organ involvement may not cause any symptoms and, therefore, may evade clinical detection. It is not always necessary to expend the time or effort to identify an organ with sarcoid granulomatous inflammation if this process is unlikely to have an impact of the patient's quality of life, level of functioning, or prognosis. Fig. 1 shows the frequency of sarcoidosis organ involvement and the frequency of treatment for each organ in a large sarcoidosis clinic in the United States [1]. This figure demonstrates that there is a poor correlation between the frequency of an organ being involved with sarcoidosis and the need for treatment, and that the presence of sarcoidosis involvement in an organ does not mandate treatment.

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http://dx.doi.org/10.1016/j.rmed.2016.02.011
0954-6111/

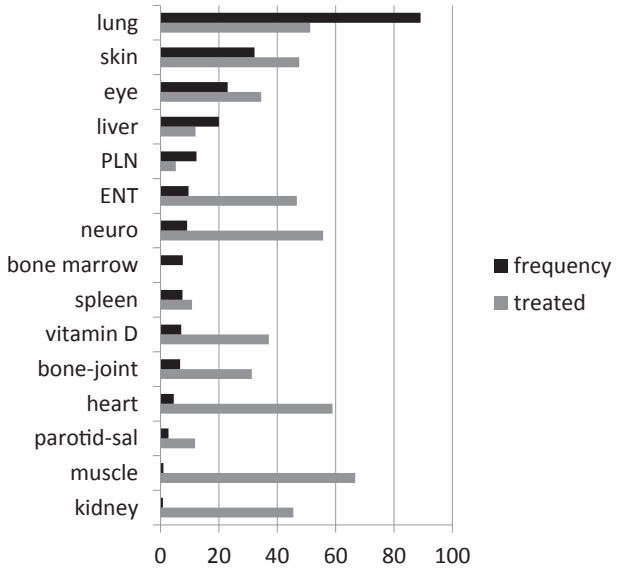

Fig. 1. The frequency (%) of sarcoidosis organ involvement (black bars) and the frequency (%) of the organ requiring a treatment intervention (grey bars) in 1248 sarcoidosis clinic patients (reference [1]) organ involvement was defined using "definite" or "probable" A Case Control Etiologic Study of Sarcoidosis (ACCESS) criteria (reference [39]).

These data imply that patient care is not optimized by identifying every possible organ involved with sarcoidosis, which may require expensive and/or invasive testing and have no significant benefit. Rather, the impetus to detect sarcoidosis organ involvement depends on the potential for quality of life impairment, functional impairment, organ dysfunction, significant morbidity and/or mortality. Additional factors that need to be considered in determining the aggressiveness of screening for organ involvement include a) the clinical importance of monitoring organ function once organ involvement has been detected; and b) the degree of danger in waiting until overt symptoms or signs of organ involvement before organ involvement has been detected. Therefore, screening for sarcoidosis organ involvement does not necessarily require a highly sensitive test to detect every organ with granulomatous inflammation. Rather, the goal of sarcoidosis screening is to detect organ involvement that is clinically relevant and could potentially benefit the patient by being detected.

In this manuscript, we will outline the approach to screening for sarcoidosis in various organs, assuming that the patient has had a secure diagnosis of sarcoidosis previously established. We believe that it is useful for the clinician to divide the screening of sarcoidosis into three tiers of screening: a) using the medical history and physical examination; b) using laboratory data; c) complex screening using algorithms requiring both historical and laboratory information.

2. The first tier of screening

The history and physical examination—used for all organs.

The first tier of screening for sarcoidosis organ involvement involves eliciting a medical history and performing a physical examination. It is prudent to determine if any symptom that is significantly impacting the patient's quality of life is related to sarcoidosis. As sarcoidosis may affect any organ in the body, any symptom may represent a manifestation of sarcoidosis. Obviously, knowledge of typical and atypical presentations of sarcoidosis is useful to determine if the statistical likelihood of specific sign or symptom is sufficient to warrant further evaluation for sarcoidosis. Descriptions of such presentations are available in the literature [2–5], although they are beyond the scope of this manuscript.

The temporal presentation of symptoms may be useful in determining if they are likely to be related to sarcoidosis. Most granulomatous manifestations of sarcoidosis are usually relatively slow in onset, as it takes time for granulomas to form and reach a sufficient mass to cause symptoms. This is the typical temporal pattern of granulomatous sarcoid skin lesions or pulmonary involvement, and it make take weeks to months for such lesions/symptoms to appreciably develop. On the other hand, if even a minute focus of granulomas develops in a strategically undesirable area, such as the conducting system of the heart or within a vital neural tract in the brain, the onset of symptoms may be sudden and potentially devastating. Many of the non-granulomatous manifestations of sarcoidosis may be very acute in onset, such as the development of erythema nodosum or Lofgren's syndrome [6], with patients not uncommonly claiming that they remember the exact day or hour of onset. In almost all cases, whether sarcoidosis develops acutely or slowly, spontaneous resolution is not immediate; therefore, immediate spontaneous resolution of symptoms suggests that they are unrelated to sarcoidosis.

The medical history and physical examination should encompass all organs as any organ may be involved with sarcoidosis. Particular attention should be paid to symptoms relating to the respiratory system, skin, eyes, peripheral lymph nodes, and liver as these were the five most common organs involved with sarcoidosis in two large series [5,7].

There are some nuances in the approach to screening for specific sarcoidosis organ involvement by means of the history and physical examination. First, skin sarcoidosis has a predilection for tattoos [8] and existing scars [9]. The skin should be carefully examined, with special attention to these sites. Second, despite the presence of parenchymal opacities of chest imaging studies in pulmonary sarcoidosis patients, lung auscultation is usually normal, even when sarcoidosis-related pulmonary fibrosis is present [10]. This absence of physical findings in a patient with diffuse lung disease raises the possibility of sarcoidosis. Third, as previously mentioned, sarcoidosis often involves organs without causing significant symptoms. This may relate to the fact that the granulomatous inflammation of sarcoidosis often maximally located in the interstitial spaces of various tissues [11–16]. However, regardless of reason for sarcoidosis commonly not causing symptoms, the presence of asymptomatic lesions increases the probability that these lesions represent sarcoidosis [17]. Examples clinical characteristics of sarcoidosis that often have no associated symptoms include: stage I chest radiographs [18], cardiac involvement [19–21], anterior uveitis [22], elevated serum liver function tests [23], and bone lesions on imaging [24]. Fourth, sarcoidosis is associated with several "parasarcoidosis syndromes" that frequently cause significant symptoms but do not relate to sarcoid granulomatous involvement of a specific organ (Table 1). Examples of such syndromes include small fiber neuropathy [25,26], fatigue syndromes [27], and various pain syndromes [28]. These syndromes have been postulated to result from systemic release of mediators from the sarcoidosis granuloma [29,30]. It is important for the clinician to identify these parasarcoidosis syndromes for several reasons: a) avoid unnecessary testing for specific sarcoidosis organ involvement; b) reassure that patient that their symptoms have a physiologic basis; and c) treatment of parasarcoidosis syndromes often requires therapy that is not directed at granulomatous inflammation (Table 1) [31–33]. As with specific organ involvement, the diagnosis of these parasarcoidosis syndromes requires exclusion of alternate causes [32,34] and/or diagnostic testing [30].