SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2013; 30; 00-00 © Mattioli 1885

Role of propionibacterium acnes in sarcoidosis: a meta-analysis

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Abstract. *Purpose:* To evaluate the available molecular evidence on the possible role of Propionibacterium acnes (P. acnes) in the development of sarcoidosis, the meta-analysis was performed. *Methods:* Case-control studies from January 1980 to October 2012 on P. acnes associated with sarcoidosis were searched. Overall odds ratios (OR) and 95% confidence intervals (CI) were obtained. *Results:* Nine studies were selected, which included 458 cases and 438 controls. 359 samples from 458 patients were positive with a positive signal rate of 78.4% (33.3% to 92.3%). Significantly elevated sarcoidosis risk was associated with P. acnes (OR = 19.58, 95% CI = 13.06 - 29.36). There was no evidence of publication bias. *Conclusions:* The present data and meta-analysis supports an association between P. acnes and some cases of sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 262-267)*

Key words: Meta-analysis, propionibacterium acnes, sarcoidosis

Introduction

Sarcoidosis is a systemic disease characterized by the presence of noncaseating epitheloid cell granulomas. It can affect the lungs, eyes, lymph nodes and other organs. Although the etiology of sarcoidosis remains unknown, current theory suggests that the disease develops in genetically predisposed hosts who are exposed to certain environmental agents that trigger an exaggerated inflammatory immune response leading to granulomas formation(1). The association of sarcoidosis with genetic factors, especially human leukocyte antigens (HLA) alleles in different populations has been described, but results have varied by cohort, ethnicity, and race, and a consensus about which allele is important in sarcoidosis has not been achieved(2-5). Possible environmental agents include *propionibacterium*, *mycobacterium*, viruses, Borrelia burgdorferi, mycoplasma, etc., and the two strongest contenders are *propionibacterium* and *mycobacterium*. Mycobacterium tuberculosis (MTB) has not been isolated in culture from sarcoidosis lesions. When polymerase chain reaction (PCR) was used to search for mycobacterial DNA in tissue samples from patients with sarcoidosis, some investigators detected mycobacteria(6, 7) and others did not(8, 9). Our previous study showed that MTB is less likely to be a factor in the pathogenesis of sarcoidosis(10).

Propionibacterium acnes (P. acnes) is so far the only bacterium to be isolated in culture from biopsy samples of lymph nodes from patients with sarcoidosis(11). Indeed, *P. acnes* is a strong adjuvant,

Received: 31 March 2013
Accepted after revison: 30 July 2013
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causing granulomas when injected experimentally into sensitised rats(12) and rabbits(13). This bacterium has been regarded as one of the most probable candidate causative organisms. There are some studies about the presence of *P. acnes* in sarcoidosis patients using molecular techniques. Meta-analysis is a useful tool that allows us to synthesize and combine data from various studies in order to improve the statistical power of outcomes. The aim of the current study was to perform a meta-analysis on the role of *P. acnes* in sarcoidosis.

Methods

Search strategy and selection criteria

Electronic databases (PubMed and Embase) were searched for the period from January 1980 to October 2012 using the terms: "Sarcoidosis AND (Propionibacteria OR Propionibacterium)." Additional studies were found in the bibliographies of all the identified publications, including previous review articles and meta-analysis. Studies were included if they met the following criteria: (a) the diagnosis of sarcoidosis was established according to the diagnostic criteria defined by the joint statement of the ATS, ERS and WASOG(1); (b) was a case–control study examining the association between *P. acnes* and sarcoidosis risk; and (c) there was sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI).

Data extraction

Two investigators (Ying Zhou and Yang Hu) carefully extracted the following information from all the eligible case–control studies: author, year of publication, study population, sources of controls, number of cases and controls, details of the molecular technique, and percentage of the samples positive for *P. acnes*. All the data should reached consensus.

Statistical analysis

The Overall odds ratios (OR) and 95% confidence intervals (95%CI) were calculated to assess the strength of association between *P. acnes* and sarcoidosis using Review Manager version 4.2 software (Update Software Ltd., Oxford, UK). Statistical heterogeneity was calculated with Cochran Q statistics. If the result of the heterogeneity test was $P > 0.10$, then the pooled OR estimate of each study was calculated by the fixed-effects model (Mantel & Haenszel 1959). Otherwise, the random-effects model (DerSimonian & Laird 1986) was used. Funnel plots and Egger's linear regression test ($P<0.05$ were considered representative of statistical significance) were carried using Stata11 software (StataCorp LP, Texas, USA) to provide diagnosis of the potential publication bias.

Results

Studies included

In total, we retrieved 62 papers from the electronic databases of PubMed and Embase (Fig. 1). According to the inclusion criteria, 10 case–control studies were identified to investigate the role of *P. acnes* in sarcoidosis. One studies was excluded due to quantitative analysis of propionibacterial DNA in sarcoidosis(14). Therefore, 9 articles were selected for analysis including 458 cases and 438 controls Table 1 (11, 15-22).

Meta-analysis

The main results of this meta-analysis showed that 359 samples from 458 patients were positive with a positive signal rate of 78.4% (ranging from 33.3% to 92.3%) for *P. acnes*. There was significantly elevated sarcoidosis risk associated with *P. acnes* (OR = 19.58, 95% CI = 13.06 - 29.36, $P = 0.15$ for heterogeneity, $P < 0.01$ for overall effect, Fig. 2).

Publication bias

Fig. 3 shows the funnel-plot analysis to detect publication bias of the studies about *P. acnes.* The shape of the funnel plot seemed to be symmetrical, suggesting that there was no publication bias affecting the findings of our meta-analysis. Furthermore, an Egger's test (P values = 0.64) provided statistical evidence for funnel plot symmetry.

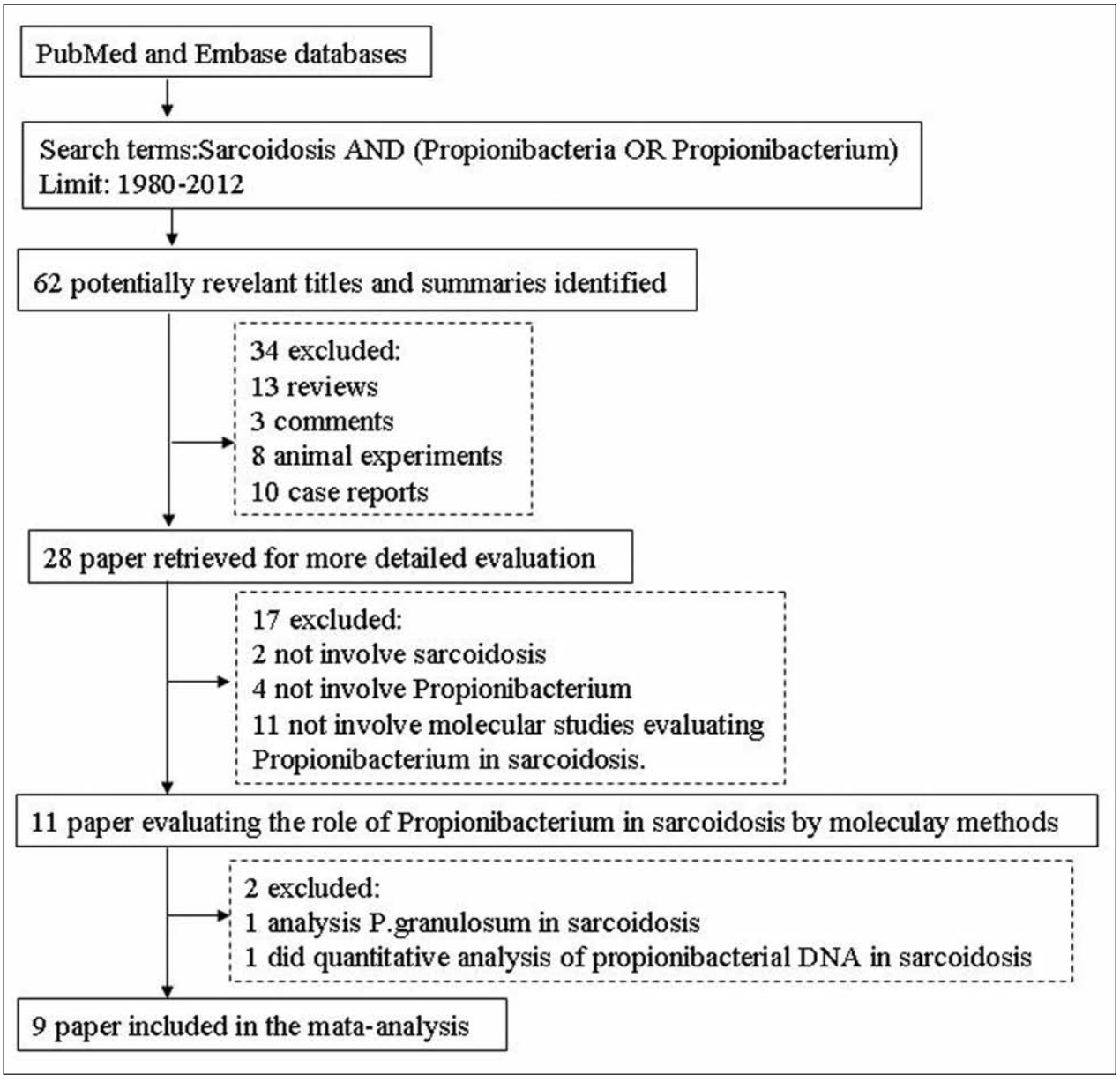

Fig. 1. Flow chart of the included studies.

Discussion

Propionibacterium species are micro-aerophilic, non-sporeforming, pleomorphic, Gram-positive coccobacilli that are ubiquitous. They are constituents of the normal human skin microflora. Major species include *P. acnes* and *propionibacterium granulosum*. *P. acnes* was first isolated from a lesion of acne vulgaris. The pathogenicity of *propionibacterium* is mainly centered around the organism's ability to produce bioactive exocellular products and its interactions with the immune system. Extensive research has shown that *propionibacterium* could modulate the immune system by bacteria or their products(23). As the *P. acnes* antigen tends to polarize macrophages with low intracellular glutathione contents and to induce high IL-12 production resulting in a Th1 shift at that lesion(24), and *P. acnes* cultures can induce

Table 1. Characteristics of case-control studies included in the meta-analysis.

	Sarcoidosis		Controls					
First author	Year	Country	Source of controls	Molecular technique	N	n/N	N	n/N
Mariko Negi	2012	Japan	non-sarcoidosis diseases	Immunohistochemi-cal methods for PAB antibody	196	149/196	79	0/79
Oswald-Richter KA	2012	USA	Cancer, Hodgkin's lymphoma, Normal lymph node	MALDI-IMS for propionibacterial proteins	15	7/15	4	1/4
Yasuhara T	2005	Japan	Rhegmatogenous retinal detachment, epiretinal membranes, tractional retinal detachment with diabetic retino-pathy	PCR for 16S rRNA	6	2/6	6	0/6
Hiramatsu J	2003	Japan	other lung diseases	nested PCR for 16S rRNA	30	21/30	30	7/30
Eishi Y	2002	Japan, Italy, Germany, England.	nonspecific lymphadenitis, lung cancer.	PCR for 16S rRNA	108	93/108	86	25/86
Yamada T	2002	Japan	non-specific lymphadenitis	quantitative real-time PCR for 16S rRNA	9	8/9	9	2/9
Ishige I	1999	Japan	gastric cancer	quantitative PCR for 16S rRNA	15	12/15	15	3/15
Eishi Y	1994	Japan	control lymph nodes	PCR for P. acnes DNA	36	36/39	12	12/29
Abe C	1984	Japan	non-sarcoidosis tissues	isolated in culture	40	31/40	180	38/180

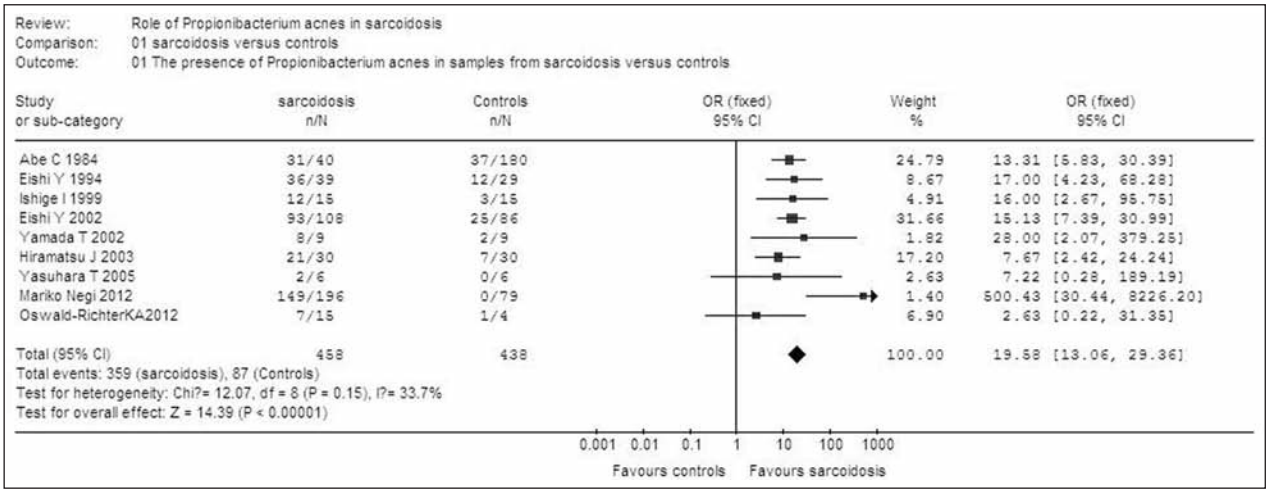

Fig. 2. Forest plot showing the presence of P. acne in sample from Sarcoidosis versus controls.

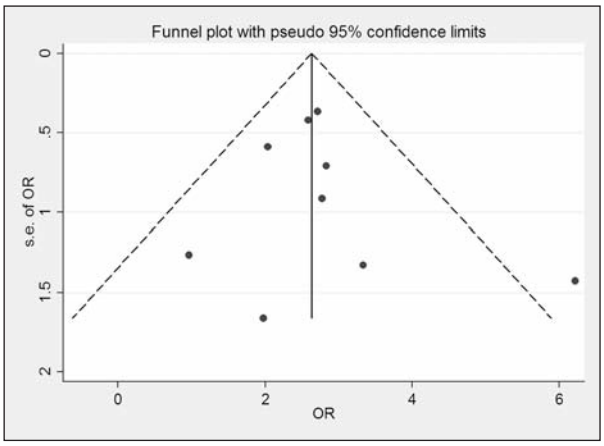

Fig. 3. Funnel-plot analysis to detected publication bias of the studies abut P. acnes.

significant concentrations of cytokines IL-1 beta, TNF-alpha, and IL-8 by enzyme-linked immunosorbent assay(25), it is reasonable to speculate that *P. acnes* antigens induce a delayed hypersensitivity immune response in the sarcoidosis-associated granulomatosis.

In 1984, Abe et al. reported that *P. acnes* was the only bacterium isolated from lymph node biopsy samples taken from 31 out of 40 (77.5%) sarcoid patients(11). Based on the important role of *P. acnes* in sarcoidosis development, a number of studies have reported the association of *P. acnes* with sarcoidosis risk. However, recent findings have shown that *P. acnes* normally resides in peripheral lung tissue and mediastinal lymph nodes and their presence therefore is not specific to sarcoidosis(26). Due to the relative small size of a single study, the results are inconsistent.

As such, meta-analysis is a statistical method of combining the results of a number of different studies in order to provide a larger sample size for evaluation and to produce a stronger conclusion than can be provided by any single study. It provides meaningful or statistically significant results, and may explain heterogeneity between the results of individual studies. It remains an essential tool for summarizing previous studies until such large studies become available. To our knowledge, this is the first meta-analysis about the role of *P. acnes* in sarcoidosis.

We retrieved nine studies, which is a relatively low number, to be included in this analysis, but the total number of patients included for assessment of the major end point was 458 for the *P. acnes* group, and the number of controls was 438. This gives some strength to the findings and provided a more comprehensive analysis on the role of *P. acnes* in sarcoidosis.

The results indicated that 78.4% of patients with sarcoidosis have the presence of *P. acnes* within the lesions and there are significant odds of finding *P. acnes* in samples from sarcoidosis patients (OR 19.58 by the fixed-effects model). These results point to an etiological link between *P. acnes* and sarcoidosis. The absence of publication bias and statistical heterogeneity among studies strengthens our results.

P. acnes are indigenous bacteria found on healthy skin and has been cultured from 21% of 180 tissue samples from patients with diseases other than sarcoidosis(26). Contamination by *P. acnes* from the skin during biopsy has been suspected. But a recent study by quantitative polymerase chain reaction concluded that *P. acnes* DNA is present, and not as a contaminant, in some samples from patients without sarcoidosis, but in much smaller amounts than in patients with sarcoidosis. This may explain the result in this meta-analysis, where 19.9% controls had a presence of *P. acnes*.

In conclusion, our meta-analysis provides reliable results that *P. acnes* is associated with sarcoidosis. Further large and well-designed research is necessary in order to verify and specify the presented associations. Adequately powered studies that employ larger sample sizes, standard case definitions and reproducible methodologies should be adopted for comparative purposes.

Acknowledgments

This study was funded by grants from the Shanghai Municipal Health Bureau Youth Research program (No: 20114Y099), National Natural Science Foundation of China (No: 81200046), and Science and Technology Commission of Shanghai Municipality (No: 114119b2200).

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