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Appendectomy, tonsillectomy, and risk for sarcoidosis – A hospital-based case-control study in Japan

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ABSTRACT

Background: The role of surgery in the onset of sarcoidosis is unclear. We investigated whether surgery is an internal environmental factor for sarcoidosis onset within the Japanese population.

Methods: We enrolled 222 patients diagnosed with sarcoidosis (78 men, 144 women) who were admitted to our department between 1984 and 2012. We also enrolled 529 control subjects (251 men, 278 women), who were matched for sex, age at admission, and year of admission. Surgical history, family history, and smoking status were evaluated.

Results: Multivariate analysis correlated history of appendectomy (OR, 1.55; 95% CI, 1.05–2.29) and tonsillectomy (OR, 2.79; 95% CI, 0.91–8.56) with the occurrence of sarcoidosis; other surgical procedures had no correlation. In women, appendectomy had a stronger association with sarcoidosis (OR, 1.69; 95% CI, 1.05–2.73), as opposed to that in men (OR, 1.39; 95% CI, 0.68–2.85). This association was greater in women aged $\geq$45 years than in those aged $<$45 years. There was a stronger correlation between tonsillectomy and sarcoidosis in women (OR, 3.30; 95% CI, 0.88–12.39), than in men (OR, 1.26; 95% CI, 0.10–16.52). ORs for sarcoidosis were 5.55 (95% CI, 2.02–15.27) and 0.97 (95% CI, 0.52–1.84) in women aged $\geq$45 years with a history of appendectomy at $<$20 years and $\geq$20 years, respectively, with the former being statistically significant.

Conclusions: Appendix and tonsil removal was associated with sarcoidosis onset, suggesting their potential protective role against sarcoidosis development. Further studies are needed to minimize possible confounding factors.

Abbreviations: HLA, human leukocyte antigen; BTNL2, butyrophilin-like 2 gene; IL, interleukin; Th1, T helper type 1; Treg, regulatory T cells; JSSOG, Japanese Society of Sarcoidosis and Other Granulomatous Disorders; OR, odds ratio; CI, confidence interval; SD, standard deviation; IMIDs, immune-mediated inflammatory disorders.

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1. Introduction

Sarcoidosis is a granulomatous disease characterized by systemic, metachronous involvement in multiple organs, of which the lungs are predominantly affected. Presumably, sarcoidosis is an amplified and persistent granulomatous reaction to inhaled antigens that develops when a genetically predisposed individual experiences fluctuations in environmental conditions. A genetic factor that has been a focus of study is the 6p21.3 region on the short arm of chromosome 6, which includes the human leukocyte antigen (HLA) gene class II domain and the butyrophilin-like 2 (BTNL2) gene [1]. Recently, several novel susceptibility loci related to the interleukin (IL)-23/IL-12 signaling pathway were identified [2]. Polymorphisms within these regions are believed to be potential risk factors for sarcoidosis, influencing the ability of T helper type 1 (Th1) and T helper type 17 (Th17) cells to process antigens and regulatory T cells (Tregs) in the regulation of immune responses [3,4].

However, the influence of environmental factors, which can be divided into external factors surrounding an individual and internal factors acting within an individual, remains unclear. Previous epidemiological studies have shown an association between living and working in rural areas and the onset of sarcoidosis [5–7]. Further, there is mounting epidemiological evidence that environmental exposure to multiple microbial organisms increases the risk of sarcoidosis development [6]. Exposure to diverse microbes may contribute to the development of sarcoidosis by not only increasing the number of opportunities for the causative antigen [8] to invade the lungs, but also by modifying an individual's susceptibility to the disease. In our previous single-institution observational study, we showed an upward shift in age at diagnosis of sarcoidosis, with decreasing detection of sarcoidosis in young people over the last four decades [9]. These results probably reflect the recent decrease in rural settings. Smoking has been also suggested to be inversely associated with the development of sarcoidosis [6,10]. With the exception of an epidemiological study showing a possible correlation between sex hormonal factors and the occurrence of sarcoidosis, there is no definitive evidence of influential internal factors [11].

Therefore, we investigated whether or not surgery is an internal environmental factor for the onset of sarcoidosis. We enrolled 222 inpatients with sarcoidosis and 529 matched control subjects who were admitted to the Division of Pulmonary Medicine at Jichi Medical University Hospital over a period of approximately 30 years. Since the Japanese population is relatively genetically homogeneous, this case-control study was expected to elucidate an association between environmental factors and the development of sarcoidosis.

2. Patients and methods

2.1. Patients

Our previous epidemiological study [9] examined 588 consecutive Japanese patients newly diagnosed with sarcoidosis between 1984 and 2012 at Jichi Medical University Hospital, Tochigi Prefecture, Japan. Diagnosis was made based on the 2006 Diagnostic Criteria and Guidelines for Sarcoidosis published by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders (JSSOG) [12]. Among the 488 patients (171 men and 317 women) diagnosed between April 1, 1984, and July 31, 2012, all the patients admitted to the Division of Pulmonary Medicine of this hospital were selected and their medical history prior to hospital admission was obtained. We also obtained family history, smoking history, and an evaluation of their surgical history. The six most commonly identified surgeries, except for gynecological surgeries, in the sarcoidosis group, included appendectomy, tonsillectomy, hemorrhoidectomy, inguinal herniorrhaphy, cholecystectomy, and chronic sinusitis surgery. We excluded patients whose medical records did not contain sufficient information. In total, 222 patients newly diagnosed with sarcoidosis (78 men and 144 women) were enrolled as case subjects (sarcoidosis group).

2.1.1. Controls

Among patients without sarcoidosis who were admitted to the Division of Pulmonary Medicine during the same period, those with definitive tuberculosis or non-tuberculous mycobacteria infection were excluded. All other patients who matched for sex, age at admission (within one year), and calendar year of admission (within one year), were examined. In total, 529 patients (251 men and 278 women) with medical records containing sufficient information were enrolled as control subjects (non-sarcoidosis group).

In the non-sarcoidosis group, 218 patients (41.2%) were primarily admitted for lung cancer, 84 patients (15.9%,) were admitted for infections (including 66 bacterial, nine fungal, and four viral infections), 81 patients (15.3%) were admitted for interstitial pneumonia, 34 patients (6.4%) were admitted for non-lung primary cancer, 28 patients (5.3%) were admitted for bronchial asthma, 13 patients (2.5%) were admitted for comprehensive examinations of a benign tumor, nine patients (1.7%) were admitted for emphysema, and 62 patients (11.7%) were admitted for other conditions.

2.2. Data analysis

In this case-control study, m-to-n matching was used to compare candidate risk factors (family history, smoking history, and surgical history) and sarcoidosis to the control group. To elucidate differences related to sex and age at sarcoidosis onset, stratified samples (men and women, <45 years of age and ≥ 45 years of age) were used for comparison. Moreover, to reveal differences related to age at the time of appendectomy or tonsillectomy, each patient was classified according to the following three conditions: surgery at <20 years old, surgery at ≥ 20 years old, and no history of surgery. From the analysis of appendectomy cases, we specifically excluded the following patients with a history of appendicitis: three women with sarcoidosis and four women and one man in the control group with no information on whether an appendectomy was performed. From the analysis of tonsillectomy cases, we excluded the following patients with a history of tonsillitis: one man and one woman with