Autoimmunity Reviews 12 (2013) 1129–1135

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

The association between silica exposure and development of ANCA-associated vasculitis: Systematic review and meta-analysis

José A. Gómez-Puerta *,[1], Lydia Gedmintas [1], Karen H. Costenbader

Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, United States

ARTICLE INFO

Article history:
Received 13 June 2013
Accepted 20 June 2013
Available online 29 June 2013

Keywords:
Antineutrophil cytoplasmic antibodies
ANCA-associated vasculitides
Silica
Meta-analysis

ABSTRACT

Background: Crystalline silica is among the environmental exposures associated with increased risk of autoimmune diseases, including rheumatoid arthritis, systemic sclerosis and systemic lupus erythematosus. Silica exposure has also been related to the development of ANCA-associated vasculitides (AAV), but past studies appear to conflict as to the presence and magnitude of the associated risks of disease. We aimed to conduct a systematic review of the existing studies and meta-analysis of their results.

Methods: We searched EMBASE, MEDLINE and international scientific conference abstract databases for studies examining the association of silica exposure with AAV. Studies in English, French, or Spanish were included and those examining the association of silica with ANCA-positivity alone were excluded. We assessed study quality using the Newcastle–Ottawa Scale. We meta-analyzed the results using random effects models and tested for heterogeneity. We performed sensitivity and subgroup analyses, examining studies that adjusted for smoking and occupational risk factors as well as studies that analyzed by subtypes of AAV.

Results: We identified 158 potential manuscripts and 3 abstracts related to silica exposure and risk of AAV. 147 were excluded after abstract review and 14 underwent detailed evaluation of full manuscript/abstract. After further application of exclusion criteria, 6 studies (all cases–controls) remained. The studies had moderate heterogeneity in selection of cases and controls, exposure assessment, disease definition and controlling for potential confounders. We found an overall significant summary effect estimate of silica "ever exposure" with development of AAV (summary OR 2.56, 95% CI 1.51–4.36), with moderate heterogeneity ($I^2 = 48.40\%$). ORs were similar for studies examining only MPA (OR 3.95, CI 95% 1.89–8.24), compared to those only studying GPA (OR 3.56, CI 95% 1.85–6.82).

Conclusion: Despite moderate heterogeneity among studies, the totality of the evidence after meta-analysis points to an association between silica exposure and risk for developing AAV.

Contents

* Corresponding author at: Division of Rheumatology, Immunology and Allergy, PBB-B3, Section of Clinical Sciences, 221 Longwood Ave, 3rd floor, Brigham and Women's Hospital, Boston, MA 02115, United States.
E-mail address: JGOMEZPUERTA@PARTNERS.ORG (J.A. Gómez-Puerta).
[1] Both authors contributed equally to this work.

1568-9972/$ – see front matter
http://dx.doi.org/10.1016/j.autrev.2013.06.016

1. Introduction

Vasculitides associated with serum positivity for antineutrophil cytoplasmic antibodies (ANCAs) that affect small to medium-sized vessels are commonly known as ANCA-associated vasculitides (AAV). The most common disease entities that fall in the AAV category include granulomatosis with polyangiitis (GPA) [formerly Wegener granulomatosis], microscopic polyangiitis (MPA), and Churg–Strauss syndrome (CSS), all of which affect the blood vessels systemically, often affecting the kidney and lung. Focal glomerular necrosis, crescent formation, and the absence or paucity of immunoglobulin deposits characterize glomerulonephritis in patients with AAV. Lung involvement ranges from fleeting focal infiltrates or interstitial disease to massive pulmonary hemorrhagic alveolar capillaritis, a life-threatening manifestation of small-vessel vasculitis [1].

Environmental factors are thought to trigger or induce several autoimmune disorders in genetically susceptible subjects [2,3]. While there may be a substantial genetic component to development of AAV, there is also a body of evidence supporting exposure to environmental factors, either directly or indirectly, in the development of AAV [4,5]. These include bacterial infections (i.e. *Staphylococcus aureus*) [6], viral infections (i.e. parvovirus B19) [7], asbestos [8] and silica exposure [2,5]. Exposure to crystalline silica classically takes place in the so-called "dusty trades", mining, sand-blasting, stone-cutting or stone quarry work. High levels of silica exposure also occur in construction work, pottery, agricultural and outdoor workers in areas with silica in the soil [9–11]. During the 1990s, an increased frequency of ANCAs (for instance, anti-myeloperoxidase antibodies) among individuals in mining and construction occupations [12,13] was reported, suggesting that environmental exposure was important for antibody development. In a more recent occupational study [14], 32 different occupations were examined and, although no statistically significant associations were found, a borderline increased risk of AAV was reported for bakers (OR = 1.6, 95% CI 1.0–2.6), paper workers (OR = 1.8, 95% CI, 0.9–3.5), miners (OR = 1.9, 95% CI, 1.0–3.5) and animal keepers (OR = 1.8, 95% CI 0.9–3.5).

Exposure to crystalline silica has been associated with the development of a number of respiratory diseases, including silicosis, progressive pulmonary fibrosis, chronic obstructive pulmonary disease and lung cancer [15]. Has also been reported to be associated with renal insufficiency and rapidly progressive glomerulonephritis [16]. Additionally, silica is known as one of the strongest environmental substances causing overall autoimmunity [17]. Silica is known as a strong T cell adjuvant [17]. Chronic exposure to silica particles activates T responder cells and Treg cells [18]. Silica exposure had been related to the development of several other autoimmune diseases, including rheumatoid arthritis (RA) [19], systemic sclerosis (SSc) [20] and systemic lupus erythematosus (SLE) [21].

Several case–control studies have shown that among patients with AAV, a high percentage (20 to 45%) was previously exposed to silica [22–29]. However, these studies have been difficult to interpret; factors such as small numbers of cases and diverse forms of classification for silica exposure contribute to this difficulty, as do the varying strengths of association between AAV and silica that are reported. Our objective was to perform a meta-analysis of all past studies examining the association of silica exposure and AAV to determine the strength of the association between silica exposure and the development of AAV.

2. Methods

2.1. Data sources

We searched EMBASE and MEDLINE databases from January 1965 until April 2013 for studies examining the association of ANCA vasculitis with silica exposure. The search was performed using the following keywords and Medical Subject Headings: ["silica" or "silic*"] AND ["vasculitis" or "systemic vasculitis" or "primary systemic vasculitis" or "ANCA vasculitis" or "Wegener's" or "Churg Strauss" or "microscopic polyangiitis" or "rapidly progressive glomerulonephritis" or "granulomatosis with polyangiitis"]. We also searched abstracts available online from the following annual meetings: American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), and the International Vasculitis Workshop.

2.2. Study eligibility, selection, and data abstraction

Only studies in English, French, or Spanish were included. We included case–control studies and cohort studies. No randomized controlled trials were found. Case reports, case series, reviews, and letters to the editors were excluded from the study. Attempts were made to contact authors to collect more information from potentially eligible abstracts [30,22]. Eligible studies compared silica exposure among those with AAV to those without AAV, or compared the prevalence of AAV among silica exposed and non-silica exposed populations. Studies examining the association of silica and ANCA-positivity alone were not included in this study, unless the studies also examined the association of silica with the development of clinical vasculitis. Studies examining the association of particular occupations and development of vasculitis were not included unless silica or silicosis was specifically mentioned as an exposure. The two first authors independently reviewed all manuscripts and abstracts to determine study eligibility. Data were then abstracted independently by the two authors. When there was disagreement at either stage, it was resolved by consensus. To facilitate study comparison and meta-analysis, we categorized silica exposure from all studies as ever/never.

2.3. Study quality assessment

The quality of each included paper was reviewed by the first two authors independently using the Newcastle–Ottawa Scale [31] and any disagreement between the scores given by the two reviewers was resolved by consensus. The Newcastle–Ottawa Scale is a commonly used method to assess the quality of non-randomized studies used in a meta-analysis. For case–control studies, the scale assigns points based on: selection of study groups (0–4 points), comparability between study groups (0–2 points), and exposure ascertainment (0–3 points). An a priori decision was made to allocate points to given studies that adjusted for potential confounders.