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Vasculitis as an adverse event following immunization – Systematic literature review☆

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ABSTRACT

Background: Several types of vasculitis have been observed and reported in temporal association with the administration of various vaccines. A systematic review of current evidence is lacking.
Objective: This systematic literature review aimed to assess available evidence and current reporting practice of vasculitides as adverse events following immunization (AEFI).
Methods: We reviewed the literature from 1st January 1994 to 30th June 2014. This review comprises randomized controlled trials, observational studies, case series, case reports, reviews and comments regardless of vaccine and target population.
Results: The initial search resulted in the identification of 6656 articles. Of these, 157 articles were assessed for eligibility and 75 studies were considered for analysis, including 6 retrospective/observational studies, 2 randomized controlled trials, 7 reviews, 11 case series, 46 case reports and 3 comments. Most of the larger, higher quality studies found no casual association between vaccination and subsequent development of vasculitis, including several studies on Kawasaki disease and Henoch-Schönlein purpura (IgA vasculitis). Smaller case series reported a few cases of vasculitis following BCG and vaccines against influenza and hepatitis. Only 24% of the articles reported using a case definition of vasculitis.
Conclusions: Existing literature does not allow establishing a causative link between vaccination and vasculitides. Further investigations were strengthened by the use of standardized case definitions and methods for data collection, analysis and presentation to improve data comparability and interpretation of vasculitis cases following immunization.

☆ The findings, opinions, and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organization (e.g. government, university, or corporation).

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1. Background

1.1. Why this review?

Vasculitides are a group of related disorders characterized by inflammation of blood vessels leading to tissue or end-organ injury [1] with diverse and only partially understood etiology and with a wide spectrum of clinical manifestations and prognosis [2]. The 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides was the most recent attempt to conceptualize vasculitis and the spectrum of clinical manifestations [3]. With a specific focus on the pediatric population, the Paediatric Rheumatology European Society (EULAR/PReS) [4] endorsed consensus criteria for the classification of childhood vasculitides; these were later revised and validated as the Ankara 2008 criteria [5]. Both are among the most valuable contributions to improving a shared understanding and harmonized approach to vasculitis research.

Although vasculitis research is evolving rapidly and new evidence is improving the ability to discern and better describe distinct forms of vasculitis, up-to-date epidemiological data reflecting these developments are limited. Overall, vasculitis in children is rare. The annual incidence of new cases of vasculitis in children is estimated to be 53.3/100,000 subjects [6]. However, incidence rates of vasculitis are age, location and type specific. The most frequent pediatric manifestations are Henoch-Schönlein purpura (HSP) (also called IgA vasculitis according to the new nomenclature) (10–20/100,000) and Kawasaki Disease (KD) (1–19/100,000), but these rates vary by country, with highest KD incidence rates reported in Japan [6,7]. In adults, the most common subtype is cutaneous small vessel vasculitis (or hypersensitivity vasculitis). There are significant geographic and ethnic differences in epidemiology of various types of vasculitis, as illustrated by the common occurrence of microscopic polyangiitis (MPA) in Asian regions, and predominance of granulomatosis with polyangiitis (GPA) in northern Europe and North America [8]. Comparatively, Takayasu's arteritis (TAK) is more common in Japan, and giant cell arteritis (GCA) is more common in Europe and North America. The annual incidence of GCA is up to 66 per 100,000 in a cohort aged 70–79 years, compared to peak incidence of 65 per 1,000,000 for antineutrophil cytoplasmic antibody-associated vasculitis (AAV) in a cohort aged 65–74 years [8]. Additionally, there are also age differences with higher incidence of MPA and GCA after the age of 65 years. Similar geographic and ethnic differences were also reported for systemic diseases associated with vasculitides, including systemic lupus erythematosus (SLE) and sarcoidosis [9]. Epidemiology of vasculitides also depends on environmental triggers, including infections. A successful hepatitis B (HBV) vaccination campaign in France was followed by a drop in incidence of polyarteritis nodosa (PAN) [10]. A broad range of etiologic agents have been linked with vasculitides such as infectious micro-organisms, connective tissue disease, malignancies, different drugs, and toxins, but others remain unknown. Vasculitides may be triggered by an infectious agent or may be a complication of primary autoimmune dysregulation and/or immunosuppressive therapy [11], among other disorders. Various forms of vasculitis have also been observed and reported as adverse events following immunization (AEFI) after various vaccines. KD, HSP and "vasculitis" in general are listed as adverse events in the Summary of Product Characteristics (SPC) of several vaccines [12]. During the 2009 influenza H1N1 pandemic, they were monitored as "adverse events of special interest" by regulatory authorities [13].

The aim of this systematic literature review was to assess the existing evidence of vasculitides as AEFI and to determine the need for standardized case definitions for specific vasculitides as AEFI.

2. Methods

The Brighton Collaboration *Vasculitis Working Group* was created in May 2014. Following the standard Brighton Collaboration Process [14] a systematic literature review was conducted in PubMed, EMBASE, and we also searched in Opengrey.eu and in Web of science (Conference Proceedings Citation Index). The literature search included the following Medical Subject Headings (MESH) terms and free text terms: vaccination, immunization and related truncations (e.g. vaccin*, immun*), vasculitis and its subtypes based on the Chapel Hill Consensus nomenclature and related truncations (e.g. vasculit*, arterit*, kawasaki*). The complete search strategy is available as additional online material (Appendix 1, see Supplementary material). The search included articles between 1st January 1994 and 30th June 2014 in any language and was limited to human studies. Search results were imported into Zotero references manager and de-duplicated. The articles were screened for eligibility based on titles and abstracts (CB). Eligible articles were clinical trials, observational studies, case series, case reports, reviews and comments of vasculitis as AEFI regardless of vaccine, study setting or target population. Full texts of eligible studies were retrieved, and unavailable studies discarded. Uncertainty during the screening process with regard to inclusion/exclusion of studies was resolved by consensus with a second reviewer (CS) or arbitrated by a third (FT). The rationale for study exclusion was recorded as part of the screening process. Data from all publications meeting the inclusion criteria were abstracted into a structured data collection form encompassing the various variables (e.g. type of publication, title, association, type of vasculitis, skin biopsy for histological evaluation/confirmation).

3. Results

An overview of the study flow is presented in Fig. 1. The search in PubMed and EMBASE resulted in the identification of 1572 and 5084 articles, respectively (overall sample 6656). The search in Opengrey.eu and Web of Science did not deliver any additional reference. A total of 5639 records remained after removing duplicates. We then excluded 5240 articles that did not relate to vasculitis or vasculitis following immunization. Full text articles were retrieved for the 399 remaining publications with potentially relevant material for detailed review. An additional 242 articles were excluded as they referred to vasculitis case definitions as such, vasculitis treatment, genetic aspects, pathogenesis or pathophysiology, animal research, surgical procedures, general epidemiology, vaccine effectiveness in patients with vasculitis, reactivation of vaccination injection site reaction, or vasculitis not associated with vaccination. In total, 75 studies were included for analysis, including 6 retrospective/observational studies, 2 randomized controlled trials, 7 reviews, 11 case series, 46 case reports and 3 comments. Details of selected literature are provided as supplementary online material in Table S1.

Over the last decades various vasculitides (Fig. 2) have been reported in association with a variety of vaccines (Fig. 3). Eight clinical studies reported vasculitides following immunization: six retrospective/observational studies [15–20] and two randomized controlled clinical trials [21,22]. Stassen et al. [15] studied 230 consecutive patients with AAV in their retrospective study. They observed no increase in relapses of AAV after vaccination against influenza. The authors considered vaccination against influenza as safe in patients with AAV with respect to increasing the rate of relapses. Goodman et al. [17] estimated the incidence rate of HSP after meningococcal polysaccharide vaccine in a US Vaccine Safety Datalink cohort 16 to 20 years of age. No cases of HSP were seen in the 42 days after 49,027 doses administered. The background

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