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Adjuvant-induced autoimmune syndrome: Systematic analysis of symptoms and management

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ABSTRACT

Introduction: Adjuvant-Induced Autoimmune Syndrome (ASIA) is a complex and controversial condition that arises after exposure to adjuvants present in vaccines, medications, or prostheses. It is characterized by an abnormal immune response in genetically predisposed individuals, leading to the development of various autoimmune symptoms. Although some associations between adjuvants and autoimmune manifestations have been suggested, the scientific evidence is still limited and requires

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further investigation. Materials and Methods: A systematic review of the literature was conducted in the PubMed, Scielo and Scopus databases, using search terms such as "adjuvant-induced autoimmune syndrome", "vaccine adjuvants" and "adverse reactions to adjuvants". Clinical trials, cohort studies, case-control studies, systematic reviews, and case reports published between 2000 and 2024 were included. The selection of studies was made by two independent reviewers, using the GRADE system to assess the methodological quality of the articles. Results: The results indicate that ASIA is associated with a variety of symptoms, such as chronic fatigue, fever, rashes, arthralgias, myalgias, and neurological symptoms. Cases of myocarditis, pericarditis, and interstitial nephritis have also been reported, suggesting possible associations between adjuvants and cardiovascular and renal changes. However, the available evidence is predominantly based on case reports and observational studies, which limits the ability to establish a definitive causal relationship. Conclusion: Although some studies point to a possible association between ASIA and various clinical manifestations, current evidence remains controversial and inconclusive. More research is needed to elucidate the immunological mechanisms involved and develop more effective diagnostic and therapeutic strategies. The continuous dissemination of reliable information to healthcare professionals is critical for informed clinical decision-making and the promotion of safe care.

Keywords: Adjuvant-Induced Autoimmune Syndrome, Vaccine Adjuvants, Autoimmunity.

INTRODUCTION

Adjuvant-Induced Autoimmune/Inflammatory Syndrome (ASIA) was first described by Shoenfeld and Agmon-Levin in 2011, to highlight a growing group of disorders characterized by dysregulation of the innate and adaptive immune system following exposure to adjuvants (Shoenfeld et al., 2018). Adjuvants are substances that, when introduced into the body, stimulate immune reactions, and are often used in vaccines to intensify the immune response against antigens (Perricone et al., 2018). In addition to vaccine adjuvants, other substances, such as liquid paraffin, silicone gel, acrylamides, hyaluronic acid, aluminum hydroxide, squalene, silica, polypropylene screens, and methacrylate compounds, also have adjuvant properties and can trigger autoimmune responses (Cohen Tervaert et al., 2023).

Several clinical case reports and series of heterogeneous autoimmune conditions, such as systemic sclerosis, systemic lupus erythematosus, and rheumatoid arthritis, have been associated with the use of different adjuvants (Jara et al., 2017). Specifically, cases of Hashimoto's thyroiditis and subacute thyroiditis have been observed after exposure to vaccines and silicone implants, suggesting a potential role of adjuvants in inducing autoimmune disorders (Watad et al., 2017). A systematic review conducted by Jara et al. (2017) identified 305 cases of severe ASIA among 4,479 cases analyzed, with the majority of these cases related to HPV and influenza vaccines, silicone implants, and mineral oil injections.

Although the efficacy and safety of vaccines are widely recognized, adjuvants such as aluminum hydroxide, used to enhance the immune response, can induce autoimmune and inflammatory manifestations in genetically predisposed or susceptible individuals (Gherardi et al., 2001; Watad et al., 2019). Given the potential clinical impact of ASIA, it is essential to better understand its symptoms, triggers, and management strategies.

The objective is to conduct a systematic analysis of the symptoms associated with Adjuvant-Induced Autoimmune Syndrome (ASIA) and to review the management and treatment approaches available to improve the care of patients affected by this condition.

MATERIALS AND METHODS

The present study was carried out in the form of a literature review. Scientific articles were searched in the PubMed, Scielo and Scopus databases. Search terms such as "adjuvant-induced autoimmune syndrome", "vaccine adjuvants", "adverse reactions to adjuvants", "autoimmune diseases" and "autoimmune inflammatory responses" were used. Studies published between 2000 and 2024 were selected, including clinical trials, cohort studies, case-control studies, systematic reviews, and case reports that discussed clinical manifestations, immunological mechanisms, risk

factors, or management strategies for Adjuvant-Induced Autoimmune/Inflammatory Syndrome (ASIA).

The screening of the articles was conducted by two independent reviewers to ensure the quality and relevance of the information. They assessed the methodological quality of the studies using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, categorizing the strength of the evidence from high to very low. Information on the types of adjuvants involved, the associated clinical manifestations, the diagnostic methods, and the therapeutic approaches employed were extracted and analyzed.

The data collected included the prevalence and incidence of symptoms associated with ASIA, predisposing factors, types of adjuvants, and treatment outcomes. Qualitative synthesis was performed to identify common patterns and trends among the studies, considering the methodological variability and limitations of each article. In addition, a sensitivity analysis was performed to verify the robustness of the results, excluding studies with high heterogeneity or low methodological quality.

RESULTS AND DISCUSSION

Adjuvant-Induced Autoimmune Syndrome (ASIA) remains a controversial and poorly understood topic that is widely debated in the medical community. Considered a form of autoimmune disease, ASIA occurs when the immune system mistakenly attacks healthy tissues in the body after exposure to adjuvants, which are substances introduced to stimulate the immune response. The ASIA hypothesis suggests that adjuvants present in vaccines, drugs, or prostheses may trigger an abnormal immune response in genetically predisposed individuals, leading to the development of autoimmunity (Shoenfeld et al., 2018; Watad et al., 2017).

The adjuvants most frequently implicated in ASIA include aluminum salts, such as aluminum hydroxide, which are widely used in vaccines, as well as others such as squalene, silicon, mineral oil, and pristane. However, the causal relationship between these adjuvants and the development of the syndrome is still the subject of debate (Petrik et al., 2008; Gherardi et al., 2001). For example, studies in animal models and some clinical reports suggest an association between exposure to adjuvants, such as aluminum present in certain vaccines, and the development of autoimmune diseases (Petrik et al., 2008). On the other hand, research has also shown inconsistent results, not being able to establish a direct causal relationship between exposure to adjuvants and the emergence of autoimmunity in humans (Gherardi et al., 2001; Watad et al., 2019).

The most common symptoms reported in ASIA are chronic fatigue, fever, rashes, arthralgias, myalgias, pyrexia, cognitive impairment, and neurological symptoms, as well as sleep disturbances, such as difficulties falling asleep or maintaining sleep, often not restorative, and malaise after

physical exertion (Cohen Tervaert et al., 2023). Regarding cardiovascular alterations, cases of myocarditis, pericarditis, and vasculitis have also been reported. For example, one case study documented the development of myocarditis in a patient after influenza vaccination, suggesting a possible association with ASIA (Kounis et al., 2016).

In addition to cardiovascular manifestations, some studies indicate a possible relationship between ASIA and renal alterations. A case of interstitial nephritis, observed in a patient after hepatitis B vaccination, suggests a possible association between the vaccine and the development of the syndrome (Peleg et al., 2015). As for endocrine changes, the literature is even more limited, but there are reports of thyroid dysfunctions, such as hypothyroidism and autoimmune thyroiditis, in patients with ASIA (Watad et al., 2016).

Therefore, while some studies reinforce the hypothesis of an association between adjuvants and the induction of autoimmunity, others fail to establish a definitive causal relationship. This reflects the need for more robust research to clarify the mechanisms underlying ASIA and determine what factors may predispose certain individuals to developing this condition.

SYMPTOMS

ASIA is characterized by a wide variety of symptoms that reflect immune dysregulation triggered by exposure to adjuvants. The most common symptoms include chronic fatigue, fever, skin rashes, arthralgia (joint pain), myalgias (muscle pain), pyrexia (persistent fever), cognitive impairment, and neurological symptoms such as difficulty concentrating and remembering. Sleep disorders, such as insomnia or non-restorative sleep, are also frequent, often accompanied by malaise after physical exertion (Cohen Tervaert et al., 2023). In more severe cases, cardiovascular manifestations, such as myocarditis and pericarditis, as well as renal and endocrine symptoms, such as interstitial nephritis and autoimmune thyroiditis, may occur (Kounis et al., 2016; Peleg et al., 2015; Watad et al., 2016).

DIAGNOSIS

The diagnosis of ASIA is complex and involves the exclusion of other autoimmune diseases. There are no specific biomarkers for ASIA, which makes diagnosis dependent on detailed clinical analysis of the patient's history and the identification of a possible temporal relationship between exposure to adjuvants and symptom onset. Shoenfeld et al. (2018) proposed diagnostic criteria that include the presence of compatible clinical manifestations (such as chronic fatigue, myalgias, and neurological disorders), a history of exposure to adjuvants, a latency time of up to two years between exposure and the development of symptoms, and the exclusion of other known causes. Further

testing, such as laboratory tests for inflammatory markers, autoantibodies, and imaging studies, may be helpful in confirming the presence of inflammation or tissue damage.

HANDLING

The management of ASIA is focused on controlling symptoms and reducing exposure to the suspected adjuvant. Removal of silicone implants or other foreign materials has shown symptomatic relief in some cases (Kushida-Contreras et al., 2024). The use of immunosuppressive or anti-inflammatory drugs, such as corticosteroids, may be indicated to reduce autoimmune activity in patients with severe symptoms. In addition, supportive therapies, such as pain management analgesics, can be utilized as needed (Brodell et al., 2024; Cohen Tervaert et al., 2023).

Patients should be monitored regularly to assess symptom progression and adjust treatment as needed. The approach should be individualized, considering the severity of symptoms, response to treatment, and the presence of comorbidities. Preventive management strategies, such as identifying genetically predisposed individuals prior to exposure to adjuvants, may be important to minimize the risk of developing ASIA in vulnerable populations.

CONCLUSION

In summary, although there are reports and studies that suggest a possible association between ASIA and various clinical manifestations, including cardiovascular, renal, and endocrine symptoms, scientific evidence is still limited and often controversial. The exact pathogenesis of ASIA is not fully elucidated, and most of the current knowledge is based on case reports and observational studies, which have significant methodological limitations.

It is essential that future research focuses on clarifying the underlying immunological mechanisms and identifying specific biomarkers for the diagnosis and management of ASIA. The continuous dissemination of accurate and up-to-date information to healthcare professionals and the general public is crucial to ensure informed clinical decisions and promote a safe and effective approach to medical practice.

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