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Review

Revisiting adverse reactions to vaccines: A critical appraisal of Autoimmune Syndrome Induced by Adjuvants (ASIA)

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ABSTRACT

In 2011 Shoenfeld and Agmon-Levin proposed a new syndrome as a way of grouping together a range of emerging autoimmune diseases with possible adjuvant-associated causes, Autoimmune/Auto-inflammatory Syndrome Induced by Adjuvants (ASIA). At present, there is no evidence to suggest that ASIA syndrome is a viable explanation for unusual autoimmune diseases. Since the initial paper, over 80 publications have discussed ASIA. This systematic review examines the research that has been done to investigate whether ASIA is a broad umbrella term with little clinical significance, or whether there is some underlying mechanism which could be utilised to reduce the occurrence of adjuvant mediated disease. Twenty-seven animal, epidemiological and case studies were reviewed. Unfortunately, a robust animal model of ASIA using biologically relevant doses of adjuvants has yet to be defined. It is also apparent that the broadness of the current ASIA criteria lack stringency and, as a result, very few cases of autoimmune disease could be excluded from a diagnosis of ASIA. The current studies involving human cases are so diverse, in both external stimuli and in resulting conditions, that there is currently a lack of reproducible evidence for any consistent relationship between adjuvant and autoimmune condition. The addition of a mandatory criterion requiring temporal association and clinically relevant adjuvant dose would allow better definition of what constitutes a diagnosis of ASIA.

1. Introduction

Autoimmune/Auto-inflammatory Syndrome Induced by Adjuvants (ASIA) was first proposed four years ago by Yehuda Shoenfeld and Nancy Agmon-Levin [1] in this journal. Since this initial proposition there have been over 80 papers specifically dealing with ASIA published in the literature.

What makes ASIA noteworthy is that it is a syndrome without a clearly defined causative agent or resulting symptoms. It is a loose grouping of possible causative agents that may be correlated with autoimmune conditions. The authors themselves conclude that exposure to an adjuvant alone is unlikely to lead to ASIA, with other factors such as genetics, or exposure to either a deleterious environmental agent or another adjuvant required. Additionally, if a patient is diagnosed with ASIA, it is unlikely to result in a change in treatment protocol.

By comparison, Acquired Immune Deficiency Syndrome (AIDS) is a condition for which the causative agent is clearly defined – the human immunodeficiency virus (HIV) – and which cannot occur without this causative agent. If a patient suffering from a variety of symptoms is diagnosed with HIV then the treatment will change from addressing the symptoms to targeting the causative agent; in this case the patient will likely be treated with antiretroviral medications, something that would not occur in a patient with the same symptoms but with a negative HIV diagnosis.

While there have been more than 80 papers discussing ASIA, from a wide range of authors, the majority have been reviews, editorials or opinion pieces.

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2. Method

This is a systematic review of the literature surrounding ASIA. Two reviewers carried out a comprehensive literature search independently. Electronic searches were carried out on PubMed and Scopus. Articles published between 2011 and 2015 were included. Only articles written in or translated into English were included.

2.1. The following search terms were used

ASIA Syndrome OR Shoenfeld Syndrome OR Autoimmune/Inflammatory syndrome induced by adjuvants OR Autoimmune Syndrome Induced by Adjuvants.

Duplicate titles were removed. Although there was a wider range of literature exploring associations between a specific adjuvant/vaccine and a specific diagnosis, we excluded any publications that did not specifically mention ASIA, as this review is only examining papers where ASIA is the primary focus.

This review focuses on the studies which have specifically examined ASIA syndrome, with a particular focus on understanding causation rather than simply correlation.

3. Defining ASIA

Table 1 outlines the four major and four minor criteria for a diagnosis of ASIA described by Shoenfeld and Agmon-Levin [1]. Throughout the literature there appears to be a consensus that having either two major criteria, or one major and two minor criteria, is sufficient for a diagnosis of ASIA. However, problems arise when the criteria are examined.

3.1. Major criteria

The first major criterion is “Exposure to an external stimuli (infection, vaccine, silicone, adjuvant)”. This criterion is extremely broad, especially in light of its use within the published literature; some papers describe this criterion as being satisfied despite up to fifteen years elapsing between a patient's exposure to a discrete stimulus (such as vaccination) and the onset of symptoms [2].

The wide temporal association within the literature means that use of the first major criterion as part of an ASIA diagnosis is problematic. Some vaccinations, such as those against influenza, are recommended annually. Others such as DTaP are currently recommended every 5–8 years. Additionally, the first major criterion includes infection as an example of an external stimulus. Very few people would be likely to go a single year without any form of infection, let alone 15 years. As this criterion currently stands, very few people, if any, would not satisfy this broad definition of being exposed to these external stimuli.

The second major criterion describes the appearance of “typical” clinical manifestations. Many of the symptoms described are general in nature including fever, dry mouth, muscle soreness, and unrefreshing sleep and could be associated with a variety of conditions. Even if these symptoms were chronic and pathological, any person with an autoimmune condition would fulfil this criterion, thus they can in no way be classified as identifying symptoms.

The first two major criteria, either individually or together, were utilised by most human studies we examined in presenting a diagnosis of ASIA. As outlined above, there are very few cases that could be excluded from an ASIA diagnosis based on these first two criteria. There is no clearly defined temporal component of association with an external stimulus. In the original article, Shoenfeld and Agmon-Levin [1] refer to two analyses of seasonal influenza vaccines associated with an increased risk of Guillain-Barré syndrome. Both studies [3,4] highlight that differences in the frequency in Guillain-Barré syndrome occurred within six weeks of vaccination. In the absence of a defined biochemical mechanism a strong temporal association between a stimulus and condition is necessary, both for robust diagnosis and for identifying the true susceptible population, in order to develop possible biological markers associated with ASIA.

Additionally, the external stimuli themselves need to be more clearly defined. Which infections are related to which autoimmune conditions? What dose constitutes an adjuvant? Can the hundreds of grams of silicone found in silicone breast implants (SBI) reasonably be considered an adjuvant or would conditions associated with SBI leakage be due to silicone toxicity, and as such no longer be classed as ASIA?

Major criterion three is more specific as it states that removal of the inciting agent results in clinical improvement. While there may still be issues with causation versus correlation, a diagnosis by elimination appears to be a more reliable diagnostic tool.

Major criterion four states “typical biopsy of involved organs”. It is unclear what “typical” refers to. If we are assuming that a patient presents with an autoimmune condition that fulfils criterion two then it is entirely probable that they would also fulfil criterion four and hence be diagnosed with ASIA without any requirement for an adjuvant based causational agent.

3.2. Minor criteria

While the minor criteria (Table 1) involve a more quantitative approach, they all address autoimmune disease without requiring the contribution of an external stimulus as defined in major criterion one. The exception is the later portion of the first minor criterion which states “appearance of … antibodies directed at the suspected adjuvant”. If there were a temporal association between a discrete external stimulus and the appearance of antibodies against that stimulus it would provide good evidence for a causal association. However the link between the appearance of these antibodies and a disease state would still need to be made and none of the criteria address this point.

The criteria outlined by Shoenfeld and Agmon-Levin [1] are numerous, with up to 20 combinations of major/minor criteria that would allow for a diagnosis of ASIA. It is possible to use these criteria to examine the role of an adjuvant in causing an autoimmune condition, but other factors such as a plausible biological mechanism and a temporal association between the treatment and

Table 1
Criteria for the diagnosis of ASIA, according to Shoenfeld and Agmon-Levon.

Suggested criteria for the diagnosis of ‘ASIA’.
Major criteria:
• Exposure to an external stimuli (Infection, vaccine, silicone, adjuvant) prior to clinical manifestations.
• The appearance of ’typical’ clinical manifestations:
– Myalgia, myositis or muscle weakness
– Arthralgia and/or arthritis
– Chronic fatigue, un-refreshing sleep or sleep disturbances
– Neurological manifestations (especially associated with demyelination)
– Cognitive impairment, memory loss
– Pyrexia, dry mouth
• Removal of inciting agent induces improvement
• Typical biopsy of involved organs
Minor criteria:
• The appearance of autoantibodies or antibodies directed at the suspected adjuvant
• Other clinical manifestations (i.e. irritable bowel syn.)
• Specific HLA (i.e. HLA DRB1, HLA DQB1)
• Evolvement of an autoimmune disease (i.e. MS, SSc)