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EDITORIAL

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and vaccines: Navigating the nexus

Bedanta Roy[1*], Sellaiah S. Pillay[2]

Corresponding author:

[1]Dr. Bedanta Roy, Ph.D., Associate Professor, Department of Physiology [ORCID]
Email: bedanta.roy@gmail.com

[2]Prof. Dato' Dr. Sellaiah S. Pillay, AMP; DPMP
MBBS; M.MED Radiology; FAMM
Dean & Consultant Radiologist [ORCID]

[1,2]Faculty of Medicine, Quest International University, No. 227, Plaza Teh Teng Seng (Level 2), Jalan Raja Permaisuri Bainun, 30250 Ipoh, Perak Darul Ridzuan, Malaysia

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Quest International University (QIU), No.227, Plaza Teh Teng Seng (Level 2), Jalan Raja Permaisuri Bainun, 30250 Ipoh, Perak Darul Ridzuan, Malaysia

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ASIA stands for autoimmune/inflammatory syndrome induced by adjuvants (ASIA), was first introduced by Shoenfeld *et al*. in 2011. [1] The clinical manifestations of ASIA include persistent fatigue, joint pain, muscle pain, fever, sicca symptoms, cognitive dysfunction, and neurological complications. Adjuvants are compounds that stimulate innate and adaptive immune response in several ways, including modifying the host's immune system, influencing cellular immunity, B cells activation, immunoregulatory cells, stimulating antibody production in response to viral infection, and hastening molecular mimicry. [2] Prominent examples of adjuvants include aluminum salts (mostly aluminum phosphate or hydroxide), squalene, silica, and several pathogenic agents. Adjuvants enter the body through the vaccines, mineral oils, silicone implants, heavy metals like mercury, and titanium and a wide range of other products. [1, 3]

Adjuvants are commonly used in the field of medicine, particularly in manufacturing vaccines. Aluminium hydroxide is used as an adjuvant in immunisations, along with the viral antigens. Aluminum's capacity to boost the immune response allows for using lesser quantities of antigens. Adjuvants enhance and amplify the immune response to a specific antigen, creating a large number of antibodies against a specific pathogen. [4] They also play crucial roles in complement activation, innate immune system stimulation and T-helper cells (TH)1 and TH2 activation. [5]

Although adjuvants are considered as safe, unfortunately in susceptible and predisposed individuals it may induce an autoimmune reaction. The increased immunogenicity generated by the adjuvants might result in heightened reactogenicity, which is not always benign, involving pathological stimulation. [6] The correlation between exposure to adjuvants and autoimmunity is evident in five autoimmune conditions that exhibit similar manifestations of autoimmunity which includes postvaccination phenomena, macrophagic myofasciitis syndrome, Gulf war syndrome, siliconosis, and sick building syndrome. Jara *et al*. reported in a systematic review that a total of 4479 cases of ASIA had been discovered to date, where 305 cases were classified as serious, and mostly developed symptoms after receiving vaccines of human papillomavirus, hepatitis B virus, and seasonal influenza. [7]

Aluminium, which is used in vaccines of hepatitis, tetanus, influenza, pneumococcus may lead to multiple

sclerosis, chronic fatigue syndrome, polymyalgia rheumatica and chronic fatigue syndrome. [8] Aluminum-based vaccine adjuvants have been linked to post-vaccination complications and symptoms related to ASIA. [9] Upon injection, the vaccine containing aluminium does not dissolve immediately in the area outside the cells, but instead gathers at the injection site, creating agglomerate of aluminium. The prolonged dissolving time enables the injected aluminium particles to be promptly grasped by immune cells and transported to various organs, such as the brain, where an inflammatory reaction triggers and induce persistent neurotoxicity. [10] A study on genetically susceptible mice exhibited increased seroconversion and antibody levels for systemic lupus erythematosus (SLE) after receiving HBV vaccination. [11] During a 6-year period of administering the quadrivalent HPV vaccine, case-control research found that there was a higher reported incidence of arthritis, vasculitis, systemic lupus erythematosus (SLE), and neurological diseases within 1 to 7 weeks following immunisation. [12] Several additional connections have been established between vaccination and autoimmune reactions. Few of the most prominent were the outbreak of Guillain-Barre syndrome following H1N1 and HBV vaccination, the occurrence of idiopathic thrombocytopenic purpura (ITP) after receiving Measles-mumps-rubella (MMR) and varicella zoster vaccines, the development of arthritis following diphtheria tetanus-pertussis (DTP) and MMR vaccinations, [13] and the occurrence of Hashimoto's thyroiditis after receiving the influenza vaccine. [14]

There are three major mechanisms identified for autoimmune association with ASIA. Firstly, the molecular mimicry, evident for genetically predisposition for autoimmunity, occurs in demyelinating disease induced by the HBV. Secondly the structural similarity between viral antigen (or other component of the vaccine) and a self-antigen. Thirdly the enhanced immune complexes which leads to vasculitis and aggravation of a preexisting autoimmune condition. [15]

There is no doubt that the development of safe and effective vaccines against illnesses that cause significant death or serious illness has been one of the most remarkable scientific achievements of the 21st century. But at the same time, it is equally important to be aware of the development of autoimmunity and to identify specific high-risk individuals in order to prevent such adverse responses.

Regards,

Dr. Bedanta Roy, Ph.D. Associate Professor, Department of Physiology, Faculty of Medicine, QIU
Editor-in-Chief, Quest International Journal of Medical and Health Sciences

Prof. Dato' Dr. Sellaiah S. Pillay, AMP; DPMP
MBBS; M.MED RADIOLOGY; FAMM
Dean & Consultant Radiologist, Faculty of Medicine, QIU
Co-Editor-in-Chief, Quest International Journal of Medical and Health Sciences

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