AUTO-IMMUNITY and VACCINATION - Abstracts

J Prev Med Hyg. 2018 Sep 28;59(3):E194-E199. PMID:30397675 **Free PMC Article**

HPV vaccine and autoimmune diseases: systematic review and meta-analysis of the literature.

Genovese C[1], LA Fauci V[1], Squeri A[1], Trimarchi G[2], Squeri R[1].
1 Department of Biomedical Sciences and Morphological and Functional Images, University of Messina, Postgraduate Medical School in Hygiene and Preventive Medicine, Messina, Italy.
2 Department of Economics, University of Messina, Italy.

Abstract

BACKGROUND: In the literature conflicting opinions are detectable on the onset of adverse events as autoimmune disease post HPV vaccine and often case reports describes the onset of one of these events, but don't emerge a clear relationship and we don't have data to support it.
METHODS: We carried out a systematic review to identify all scientific publications dealing with the correlation between vaccine anti-papillomavirus and new onset of autoimmune diseases. We searched the main scientific databases (PubMed, Sciverse Scopus, Web of knowledge and Cochrane Central Register of Controlled Clinical Trials) for the following search terms: "vaccine"; "anti-papillomavirus"; "autoimmune"; "disease"; "disorder". To evaluate the safety of HPV vaccines, the dichotomous data on the number of subjects experiencing an autoimmune disorder in the study vaccine group and the placebo group were extracted from each study with subsequent determination of the risk ratios and their 95% confidence intervals. We combined data statistically using a random effects model.
RESULTS: We conduct a meta-analysis on six studies on bivalent and quadrivalent HPV vaccine. The total number of subjects included in the meta-analysis comprised 243,289 in the vaccine group and 248,820 in control groups. Four of the six trials had a Jadad score of 3 or 4 indicating an adequate trial quality. The most frequent autoimmune disease observed across the six studies were musculoskeletal,CNS conditions and endocrinological conditions . The results of the meta-analysis demonstrated no correlation between autoimmune disorders and HPV vaccines (pooled OR 1.038, 95% CI 0.689-1.562).
CONCLUSIONS: No correlation was identified for bivalent and quadrivalent HPV vaccines. It's therefore essential to correctly inform the general population in order to try to increase both Italian and international vaccination coverage.
Critical comment. *The placebo groups contained no never-vaccinated subjects. Rather, HPV-vaccinated subjects were compared to other vaccinated subjects. Hence this meta-analysis compared the incidence of autoimmune diseases in 2 vaccinated groups, one of which received the HPV vaccination, and the other which received other vaccines but not the HPV vaccine. Both vaccinated groups - HPV-vaccinated and non-HPV-vaccinated induced autoimmune outcomes at equivalent results according to this metaanalysis.*

J Allergy Clin Immunol Pract. 2018 Mar - Apr;6(2):707. PMID:29525002

ASIA, chronic fatigue syndrome and selective low dose neurotoxicity of aluminium adjuvants. *[NO ABSTRACT]*

Crépeaux G[1], Gherardi RK[2], Authier FJ[2].
1 Inserm U955 E10, Université Paris Est Créteil (UPEC), Créteil, France; Ecole Nationale Vétérinaire d'Alfort, Maisons-Alfort, France. Electronic address: Guillemette.crepeaux@vet-alfort.fr.
2 Inserm U955 E10, Université Paris Est Créteil (UPEC), Créteil, France; Reference Center for Neuromuscular Disorders, H. Mondor Hospital, Assistance Publique-Hôpitaux de Paris, Créteil, France.

EPMA J. 2017 Jul 20;8(3):295-311. PMID:29021840 **Free PMC Article**

Vaccination and autoimmune diseases: is prevention of adverse health effects on the horizon?

Vadalà M[1,2], Poddighe D[3], Laurino C[1,2], Palmieri B[1,2].
1 Department of General Surgery and Surgical Specialties, Medical School, Surgical Clinic, University of Modena and Reggio Emilia, Modena, Italy.
2 Network of the Second Opinion, Modena, MO Italy.
3 Department of Pediatrics, ASST Melegnano e Martesana, Milano, Italy.

Abstract

Autoimmune diseases, including multiple sclerosis and type 1 diabetes mellitus, affect about 5% of the worldwide population. In the last decade, reports have accumulated on various autoimmune disorders, such as idiopathic thrombocytopenia purpura, myopericarditis, primary ovarian failure, and systemic lupus erythematosus (SLE), following vaccination. In this review, we discuss the possible underlying mechanisms of autoimmune reactions following vaccinations and review cases of autoimmune diseases that have been correlated with vaccination. Molecular mimicry and bystander activation are reported as possible mechanisms by which vaccines can cause autoimmune reactions. The individuals who might be susceptible to develop these reactions could be especially not only those with previous post-vaccination phenomena and those with allergies but also in individuals who are prone to develop autoimmune diseases, such as those with a family history of autoimmunity or with known autoantibodies, and the genetic predisposed individuals. Further research is encouraged into the direct associations between vaccines and autoimmune conditions, and the biological mechanisms behind them.

Immunol Res. 2017 Feb;65(1):46-54. PMID:27406735 **Free PMC Article**

Quadrivalent human papillomavirus vaccine and autoimmune adverse events: a case-control assessment of the vaccine adverse event reporting system (VAERS) database.

Geier DA[1], Geier MR[2].

1 Institute of Chronic Illnesses, Inc, 14 Redgate Ct, Silver Spring, MD, 20905, USA.

2 Institute of Chronic Illnesses, Inc, 14 Redgate Ct, Silver Spring, MD, 20905, USA. mgeier@comcast.net.

Abstract Gardasil is a quadrivalent human papillomavirus (HPV4) vaccine that was approved for use by the US Food and Drug Administration in June 2006. HPV4 vaccine is routinely recommended for administration to women in the USA who are 11-12 years old by the Advisory Committee on Immunization Practices. Previous studies suggest HPV4 vaccine administration was associated with autoimmune diseases. As a consequence, an epidemiological assessment of the vaccine adverse event reporting system database was undertaken for adverse event reports associated with vaccines administered from 2006 to 2014 to 6-39 year-old recipients with a listed US residence and a specified female gender. Cases with the serious autoimmune adverse event (SAAE) outcomes of gastroenteritis (odds ratio (OR) 4.627, 95 % confidence interval (CI) 1.892-12.389), rheumatoid arthritis (OR 5.629, 95 % CI 2.809-12.039), thrombocytopenia (OR 2.178, 95 % CI 1.222-3.885), systemic lupus erythematosus (OR 7.626, 95 % CI 3.385-19.366), vasculitis (OR 3.420, 95 % CI 1.211-10.408), alopecia (OR 8.894, 95 % CI 6.255-12.914), CNS demyelinating conditions (OR 1.585, 95 % CI 1.129-2.213), ovarian damage (OR 14.961, 95 % CI 6.728-39.199), or irritable bowel syndrome (OR 10.021, 95 % CI 3.725-33.749) were significantly more likely than controls to have received HPV4 vaccine (median onset of initial symptoms ranged from 3 to 37 days post-HPV4 vaccination). Cases with the outcome of Guillain-Barre syndrome (OR 0.839, 95 % CI 0.601-1.145) were no more likely than controls to have received HPV4 vaccine. In addition, cases with the known HPV4-related outcome of syncope were significantly more likely than controls to have received HPV4 vaccine (OR 5.342, 95 % CI 4.942-5.777). Cases with the general health outcomes of infection (OR 0.765, 95 % CI 0.428-1.312), conjunctivitis (OR 1.010, 95 % CI 0.480-2.016), diarrhea (OR 0.927, 95 % CI 0.809-1.059), or pneumonia (OR 0.785, 95 % CI 0.481-1.246) were no more likely than controls to have received HPV4 vaccine. Confirmatory epidemiological studies in other databases should be undertaken and long-term clinical consequences of HPV-linked SAAEs should be examined.

Immunol Res. 2016 Jul 13 PMID: 27412294

Severe manifestations of autoimmune syndrome induced by adjuvants (Shoenfeld's syndrome).

Jara LJ[1,2], García-Collinot G[3], Medina G[4,5], Cruz-Dominguez MD[3,5], Vera-Lastra O[6,5], Carranza-Muleiro RA[3], Saavedra MA[7,5].

[1]Direction of Education and Research, Hospital de Especialidades Centro Médico Nacional La Raza, IMSS, Seris/Zaachila S/N, Colonia La Raza, Mexico City, Mexico. luis_jara_quezada@hotmail.com.

[2]Universidad Nacional Autónoma de México, Mexico City, Mexico. luis_jara_quezada@hotmail.com.

[3]Research Division, Hospital de Especialidades Centro Médico Nacional La Raza, IMSS, Seris/Zaachila S/N, Colonia La Raza, Mexico City, Mexico.

[4]Clinical Research Unit, Hospital de Especialidades Centro Médico Nacional La Raza, IMSS, Seris/Zaachila S/N, Colonia La Raza, Mexico City, Mexico.

[5]Universidad Nacional Autónoma de México, Mexico City, Mexico.

[6]Internal Medicine Department, Hospital de Especialidades Centro Médico Nacional La Raza, IMSS, Seris/Zaachila S/N, Colonia La Raza, Mexico City, Mexico.

[7]Rheumatology Department, Hospital de Especialidades Centro Médico Nacional La Raza, IMSS, Seris/Zaachila S/N, Colonia La Raza, Mexico City, Mexico.

Abstract Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) encompassing conditions linked to

previous exposure to an adjuvant substance. The clinical picture is very heterogeneous, from mild to severe manifestations, including death. However, the systematic analysis of severe ASIA cases has not been performed. The aim of this study was to systematically review the literature on severe ASIA cases. A systematic review of the literature was performed investigating severe ASIA cases. All publications were identified through PubMed, EMBASE, MEDLINE and Cochrane. Articles published from 2011 to 2016 were included. Severe ASIA was arbitrarily defined as follows: major organ involvement, life-threatening conditions, intensive treatment, disability, hospitalization and outcome (survival and death). Cases described before 2011 were excluded. From 2011 to 2016, we identified 4479 ASIA cases, of them 305 fulfilled arbitrary criteria of severe ASIA including our case presentation and 11 deaths. The majority of severe ASIA cases were related to HPV vaccine, silicone, influenza vaccine and mineral oil injections. The interval from exposition to severe manifestation was from 2 days to 23 years. (1) This is the first study that analyzes all cases published on ASIA with severe manifestations. (2) The current HPV vaccine is both effective and generally safe. However, it should be noted that severe autoimmune side effects have been reported in several studies. Severe ASIA may be observed after influenza vaccines, and other vaccines. (3) Efforts should be made to discover the connection between adjuvants, autoimmunity and autoimmune diseases, because there is an increase in cases severe and life-threatening of ASIA.

Immunol Res. 2016 Jul 13. PMID: 27406735

Quadrivalent human papillomavirus vaccine and autoimmune adverse events: a case-control assessment of the vaccine adverse event reporting system (VAERS) database.

Geier DA[1], Geier MR[2].

[1]Institute of Chronic Illnesses, Inc, 14 Redgate Ct, Silver Spring, MD, 20905, USA.
[2]Institute of Chronic Illnesses, Inc, 14 Redgate Ct, Silver Spring, MD, 20905, USA.
mgeier@comcast.net.

Abstract

Gardasil is a quadrivalent human papillomavirus (HPV4) vaccine that was approved for use by the US Food and Drug Administration in June 2006. HPV4 vaccine is routinely recommended for administration to women in the USA who are 11-12 years old by the Advisory Committee on Immunization Practices. Previous studies suggest HPV4 vaccine administration was associated with autoimmune diseases. As a consequence, an epidemiological assessment of the vaccine adverse event reporting system database was undertaken for adverse event reports associated with vaccines administered from 2006 to 2014 to 6-39 year-old recipients with a listed US residence and a specified female gender. Cases with the serious autoimmune adverse event (SAAE) outcomes of **gastroenteritis** (odds ratio (OR) 4.627, 95 % confidence interval (CI) 1.892-12.389), **rheumatoid arthritis** (OR 5.629, 95 % CI 2.809-12.039), **thrombocytopenia** (OR 2.178, 95 % CI 1.222-3.885), **systemic lupus erythematosus** (OR 7.626, 95 % CI 3.385-19.366), **vasculitis** (OR 3.420, 95 % CI 1.211-10.408), **alopecia** (OR 8.894, 95 % CI 6.255-12.914), **CNS demyelinating conditions** (OR 1.585, 95 % CI 1.129-2.213), **ovarian damage** (OR 14.961, 95 % CI 6.728-39.199), or **irritable bowel syndrome** (OR 10.021, 95 % CI 3.725-33.749) were significantly more likely than controls to have received HPV4 vaccine (median onset of initial symptoms ranged from 3 to 37 days post-HPV4 vaccination). Cases with the outcome of Guillain-Barre syndrome (OR 0.839, 95 % CI 0.601-1.145) were no more likely than controls to have received HPV4 vaccine. In addition, cases with the known HPV4-related outcome of **syncope** were significantly more likely than controls to have received HPV4 vaccine (OR 5.342, 95 % CI 4.942-5.777). Cases with the general health outcomes of infection (OR 0.765, 95 % CI 0.428-1.312), conjunctivitis (OR 1.010, 95 % CI 0.480-2.016), diarrhea (OR 0.927, 95 % CI 0.809-1.059), or pneumonia (OR 0.785, 95 % CI 0.481-1.246) were no more likely than controls to have received HPV4 vaccine. Confirmatory epidemiological studies in other databases should be undertaken and long-term clinical consequences of HPV-linked SAAEs should be examined.

Curr Opin Neurol. 2016 Jun;29(3):362-71. PMID: 27023738

Vaccine-associated inflammatory diseases of the central nervous system: from signals to causation.

Nguyen XH[1], Saoudi A, Liblau RS.

[1a]INSERM, U1043 bCNRS, U5282 cCentre de Physiopathologie Toulouse-Purpan (CPTP), Université de Toulouse dDépartement d'Immunologie, Hôpital Purpan, CHU Toulouse, Toulouse, France.

Abstract

PURPOSE OF REVIEW: As the most cost-effective intervention in preventive medicine and as a crucial element of any public health program, vaccination is used extensively with over 90% coverage in many countries. As approximately 5-8% of the population in developed countries suffer from an autoimmune disorder, people with an autoimmune disease are most likely to be exposed to some vaccines before or after the disease onset. In fact, a number of inflammatory disorders of the central nervous system have been associated with the administration of various vaccines. These adverse events, be they spurious associations or genuine reactions to the vaccine, may lead to difficulties in obtaining public trust in mass vaccination

programs. There is, thus, an urgent need to understand whether vaccination triggers or enhances autoimmune responses.
RECENT FINDINGS: By reviewing vaccine-associated inflammatory diseases of the central nervous system, this study describes the current knowledge on whether the safety signal was coincidental, as in the case of multiple sclerosis with several vaccines, or truly reflected a causal link, as in narcolepsy with cataplexy following pandemic H1N1 influenza virus vaccination.
SUMMARY: The lessons learnt emphasize a central role of thorough, ideally prospective, epidemiological studies followed, if the signal is deemed plausible or real, by immunological investigations.

Isr Med Assoc J. 2016 Mar-Apr;18(3-4):150-3. PMID: 27228631**Free full text**

Autoimmune/Inflammatory Syndrome Induced by Adjuvants and Sjögren's Syndrome.

Colafrancesco S, Perricone C, Shoenfeld Y.

Abstract
Sjögren's syndrome (SS), a chronic systemic autoimmune inflammatory condition involving the exocrine glands, has been suggested to be part of the spectrum of the Autoimmune/ inflammatory Syndrome Induced by Adjuvants (ASIA). ASIA incorporates an umbrella of clinical conditions including siliconosis, macrophage myofasciitis syndrome, and post-vaccination phenomena that occur after the exposure to a substance, namely the adjuvant. Interestingly, SS and ASIA share several common features. Firstly, a shared pathogenic mechanism involving a disruption of the immune system balance, with B cell proliferation, cytokine production and tissue infiltration, has been proposed. Patients with ASIA often present clinical features resembling those of SS; dry mouth and dry eyes have also been included in the proposed classification criteria for ASIA. Finally, several case reports have suggested that both vaccines and silicone may trigger the development of SS. Unveiling these common pathways will contribute considerably to our understanding and management of both conditions.

Nihon Rinsho Meneki Gakkai Kaishi. 2016;39(2):145-9. PMID: 27212601

A case of systemic lupus erythematosus (SLE) following Human papillomavirus (HPV) vaccination.

Ito H[1], Noda K, Hirai K, Ukichi T, Furuya K, Kurosaka D.
[1]*Division of Rheumatology, Department of Internal Medicine, The Jikei University School of Medicine.*

Abstract A 15-year-old young woman received the Human papillomavirus (HPV) vaccines. Following the second HPV vaccination, intermittent fever, myalgia, arthritis and malar rash developed, and she was admitted to our hospital. Laboratory studies showed positive results for antinuclear antibody, anti-dsDNA antibody and anti-Sm antibody. Systemic lupus erythematosus (SLE) was diagnosed according to the Systemic Lupus International Collaborative Clinics 2012. Magnetic resonance imaging showed abnormal hyperintense areas in the fascia, and en bloc biopsy showed fasciitis. Treatment with prednisolone resulted in an amelioration of the symptoms. Reportedly, SLE developed after HPV vaccinations in some patients. Most such patients have a past or family history of autoimmune disease and presented SLE symptoms after the second vaccination. We describe herein a patient in whom SLE developed in association with HPV vaccination.

Allergy Asthma Clin Immunol. 2016 Feb 11;12:6. PMID: 26877725

Post-vaccination myositis and myocarditis in a previously healthy male.

Cheng MP[1], Kozoriz MG[2], Ahmadi AA[3], Kelsall J[4], Paquette K[5], Onrot JM[6].
[1]*Division of Infectious Diseases and Department of Medical Microbiology, Glen site, McGill University Health Centre, 1001 Boulevard Décarie, Room E05. 1811.2, Montreal, QC H4A 3J1 Canada.*
[2]*Department of Radiology, University of British Columbia, Vancouver, BC Canada.*
[3]*Department of Cardiology, University of British Columbia, Vancouver, BC Canada.*
[4]*Division of Rheumatology, University of British Columbia, Vancouver, BC Canada ; Division of Internal Medicine, University of British Columbia, Vancouver, BC Canada.*
[5]*Department of Pediatrics, University of British Columbia, Vancouver, BC Canada.*
[6]*Division of Internal Medicine, University of British Columbia, Vancouver, BC Canada.*

Abstract
BACKGROUND: The immunological literature has been redefining clinical phenomena as hypotheses emerge regarding causal links between triggers, immunologic manifestations, and their specific inflammatory cascades. Of late, autoimmune manifestations that appear to be caused by an external adjuvant have been grouped into a complex syndrome referred to as autoimmune/inflammatory syndrome induced by adjuvants (ASIA). This syndrome may present with diverse clinical problems, which may include neurocognitive impairment, inflammatory musculoskeletal changes, and constitutional symptoms. There is evidence in the

literature linking vaccines to different auto-immune manifestations. Vaccines have not traditionally been reported to trigger ASIA, although reports are emerging linking the human papilloma virus and hepatitis B vaccines to it.
CASE PRESENTATION: We report the first suspected case of ASIA in a previously healthy patient who received the Fluad seasonal influenza vaccine, which contains the MF59 adjuvant. He presented to hospital with profound weakness and was diagnosed with severe rhabdomyolysis. He also had elevated troponin-I and extensive cardiac investigations enabled the diagnosis of myocarditis. His infectious and rheumatologic work-ups were negative. He responded well to conservative management and did not require immune suppressive therapy.
CONCLUSION: Given the benefits of the influenza vaccine, and the low incidence of clinically significant complications, we encourage ongoing seasonal influenza immunization. However, ongoing surveillance is required to evaluate the occurrence of rare adverse events, including ASIA.

Autoimmun Rev. 2015 Oct;14(10):880-8. PMID:26031899

On vaccine's adjuvants and autoimmunity: Current evidence and future perspectives.

Pellegrino P[1], Clementi E[2], Radice S[1].
1 Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences, University Hospital "Luigi Sacco", Università di Milano, 20157 Milan, Italy.
2 Scientific Institute IRCCS E. Medea, 23842 Bosisio Parini, Lecco, Italy; Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences, Consiglio Nazionale delle Ricerche Institute of Neuroscience, University Hospital "Luigi Sacco", Università di Milano, 20157 Milan, Italy. Electronic address: emilio.clementi@unimi.it.
Abstract Adjuvants are compounds incorporated into vaccines to enhance immunogenicity and the development of these molecules has become an expanding field of research in the last decades. Adding an adjuvant to a vaccine antigen leads to several advantages, including dose sparing and the induction of a more rapid, broader and strong immune response. Several of these molecules have been approved, including aluminium salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes and AS04. Adjuvants have recently been implicated in the new syndrome named "ASIA-Autoimmune/inflammatory Syndrome Induced by Adjuvants", which describes an umbrella of clinical conditions including post-vaccination adverse reactions. Recent studies implicate a web of mechanisms in the development of vaccine adjuvant-induced autoimmune diseases, in particular, in those associated with aluminium-based compounds. Fewer and unsystematised data are instead available about other adjuvants, despite recent evidence indicating that vaccines with different adjuvants may also cause specific autoimmune adverse reactions possible towards different pathogenic mechanisms. This topic is of importance as the specific mechanism of action of each single adjuvant may have different effects on the course of different diseases. Herein, we review the current evidence about the mechanism of action of currently employed adjuvants and discuss the mechanisms by which such components may trigger autoimmunity.

Pharmacol Res. 2015 Aug 12;100:190-209. PMID: 26275795

Vaccines, adjuvants and autoimmunity.

Guimarães LE[1], Baker B[1], Perricone C[2], Shoenfeld Y[3].
[1]The Zabludowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center, Tel-Hashomer, Israel.
[2]Reumatologia, Dipartimento di Medicina Interna e Specialità Mediche, Sapienza Università di Roma, Italy.
[3]The Zabludowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center, Tel-Hashomer, Israel; Incumbent of the Laura Schwarz-kipp chair for research of autoimmune diseases, Sackler Faculty of Medicine, Tel-Aviv University, Israel. Electronic address: shoenfel@post.tau.ac.il.
Abstract Vaccines and autoimmunity are linked fields. Vaccine efficacy is based on whether host immune response against an antigen can elicit a memory T-cell response over time. Although the described side effects thus far have been mostly transient and acute, vaccines are able to elicit the immune system towards an autoimmune reaction. The diagnosis of a definite autoimmune disease and the occurrence of fatal outcome post-vaccination have been less frequently reported. Since vaccines are given to previously healthy hosts, who may have never developed the disease had they not been immunized, adverse events should be carefully accessed and evaluated even if they represent a limited number of occurrences. In this review of the literature, there is evidence of vaccine-induced autoimmunity and adjuvant-induced autoimmunity in both experimental models as well as human patients. Adjuvants and infectious agents may exert their immune-enhancing effects through various functional activities, encompassed by the adjuvant effect. These mechanisms are shared by different conditions triggered by adjuvants leading to the autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome). In conclusion, there are several case reports of autoimmune diseases following vaccines, however, due to the limited number of cases, the different classifications of symptoms and the long latency period of the diseases, every attempt for an epidemiological study has so far failed to deliver a connection. Despite this, efforts

to unveil the connection between the triggering of the immune system by adjuvants and the development of autoimmune conditions should be undertaken. Vaccinomics is a field that may bring to light novel customized, personalized treatment approaches in the future.

Autoimmun Rev. 2015 May 29. pii: S1568-9972(15)00122-6. PMID: 26031899

On vaccine's adjuvants and autoimmunity: Current evidence and future perspectives.

Pellegrino P[1], Clementi E[2], Radice S[1].

[1]Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences, University Hospital "Luigi Sacco", Università di Milano, 20157 Milan, Italy.

[2]Scientific Institute IRCCS E. Medea, 23842 Bosisio Parini, Lecco, Italy; Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences, Consiglio Nazionale delle Ricerche Institute of Neuroscience, University Hospital "Luigi Sacco", Università di Milano, 20157 Milan, Italy. Electronic address: emilio.clementi@unimi.it.

Abstract Adjuvants are compounds incorporated into vaccines to enhance immunogenicity and the development of these molecules has become an expanding field of research in the last decades. Adding an adjuvant to a vaccine antigen leads to several advantages, including dose sparing and the induction of a more rapid, broader and strong immune response. Several of these molecules have been approved, including aluminium salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes and AS04. Adjuvants have recently been implicated in the new syndrome named "ASIA-Autoimmune/inflammatory Syndrome Induced by Adjuvants", which describes an umbrella of clinical conditions including post-vaccination adverse reactions. Recent studies implicate a web of mechanisms in the development of vaccine adjuvant-induced autoimmune diseases, in particular, in those associated with aluminium-based compounds. Fewer and unsystematised data are instead available about other adjuvants, despite recent evidence indicating that vaccines with different adjuvants may also cause specific autoimmune adverse reactions possible towards different pathogenic mechanisms. This topic is of importance as the specific mechanism of action of each single adjuvant may have different effects on the course of different diseases. Herein, we review the current evidence about the mechanism of action of currently employed adjuvants and discuss the mechanisms by which such components may trigger autoimmunity.

J Autoimmun. 2015 May;59:77-84. PMID: 25794485

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

Hawkes D[1], Benhamu J[2], Sidwell T[3], Miles R[4], Dunlop RA[5].

[1]Department of Pharmacology and Therapeutics, The University of Melbourne, Victoria, Australia; Friends of Science in Medicine, Melbourne, Victoria, Australia. Electronic address: dhawkes@unimelb.edu.au.

[2] Friends of Science in Medicine, Melbourne, Victoria, Australia.

[3] Department of Molecular Immunology, The Walter and Eliza Hall Institute of Medical Research, Victoria, Australia.

[4] Greenslopes Clinical School of Medicine, University of Queensland, Greenslopes, Queensland, Australia; Department of Renal Medicine, Greenslopes Private Hospital, Greenslopes, Queensland, Australia.

[5] Australian School of Advanced Medicine, Macquarie Park, NSW, Australia.

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.

Inflamm Allergy Drug Targets. 2015;14(2):94-8. PMID: 26728772

Vaccination and Induction of Autoimmune Diseases.

Toussirot É[1], Bereau M.

[1]Clinical Investigation Center in Biotherapy, INSERM CIC-1431, University Hospital, Place St Jacques, 25000 Besancon, France. etoussirot@chu-besancon.fr.

Abstract Vaccines have been suspected of playing a role in inducing autoimmune disease (AID) for a long time. However, apart from certain specific vaccine strains and complications (such as the swine flu vaccine and Guillain-Barré syndrome in 1976, thrombocytopenia and the Measles-Mumps-Rubella vaccine), this role has not been established. In spite of this, many isolated cases or series of cases of arthritis, vasculitis, and central or peripheral nervous system symptoms following vaccination have been reported. These cases tend to be very infrequent and

usually only the short-term outcomes are described. This paper will examine the arguments for and against the relationship between vaccines and AID, bearing in mind that no association between the two has been clearly identified up to now. The role of adjuvants in vaccines has been described by other teams and in a more general syndrome (Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants). Thus, cases of AID triggered by vaccines are highly rare and raise questions about the interaction between vaccines and/or their adjuvants and the genetic context of autoimmune disease. These observations should therefore not undermine the benefits of vaccination.

Pharmacol Res. 2015 Feb;92:18-22. PMID:25277820

Predicting post-vaccination autoimmunity: who might be at risk?

Soriano A[1], Nesher G[2], Shoenfeld Y[3].

1 Department of Clinical Medicine and Rheumatology, Campus Bio-Medico University, Rome, Italy.

2 Department of Internal Medicine A, Shaare Zedek Medical Center, and the Hebrew University Medical School, Jerusalem, Israel. Electronic address: nesherg@szmc.org.il.

3 The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Sackler Faculty of Medicine, Incumbent of the Laura Schwarz-Kip Chair for Research of Autoimmune Diseases, Tel-Aviv University, Israel.

Abstract Vaccinations have been used as an essential tool in the fight against infectious diseases, and succeeded in improving public health. However, adverse effects, including autoimmune conditions may occur following vaccinations (autoimmune/inflammatory syndrome induced by adjuvants--ASIA syndrome). It has been postulated that autoimmunity could be triggered or enhanced by the vaccine immunogen contents, as well as by adjuvants, which are used to increase the immune reaction to the immunogen. Fortunately, vaccination-related ASIA is uncommon. Yet, by defining individuals at risk we may further limit the number of individuals developing post-vaccination ASIA. In this perspective we defined four groups of individuals who might be susceptible to develop vaccination-induced ASIA: patients with prior post-vaccination autoimmune phenomena, patients with a medical history of autoimmunity, patients with a history of allergic reactions, and individuals who are prone to develop autoimmunity (having a family history of autoimmune diseases; asymptomatic carriers of autoantibodies; carrying certain genetic profiles, etc.).

Immunol Res. 2014 Dec;60(2-3):376-83. PMID: 25427994

Chronic fatigue syndrome and fibromyalgia following immunization with the hepatitis B vaccine: another angle of the 'autoimmune (auto-inflammatory) syndrome induced by adjuvants' (ASIA).

Agmon-Levin N1, Zafrir Y, Kivity S, Balofsky A, Amital H, Shoenfeld Y.

1The Zabludowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center, 52621, Tel-Hashomer, Israel.

Abstract

The objectives of this study were to gather information regarding demographic and clinical characteristics of patients diagnosed with either fibromyalgia (FM) or chronic fatigue (CFS) following hepatitis B vaccination (HBVv) and furthermore to apply the recently suggested criteria of autoimmune (auto-inflammatory) syndromes induced by adjuvants (ASIA), in the aim of identifying common characteristics that may suggest an association between fibromyalgia, chronic fatigue and HBV vaccination. Medical records of 19 patients with CFS and/or fibromyalgia following HBVv immunization were analyzed. All of which were immunized during 1990-2008 in different centers in the USA. All medical records were evaluated for demographics, medical history, the number of vaccine doses, as well as immediate and long term post-immunization adverse events and clinical manifestations. In addition, available blood tests, imaging results, treatments and outcomes were analyzed. ASIA criteria were applied to all patients. The mean age of patients was 28.6 ± 11 years, of which 68.4 % were females. 21.05 % had either personal or familial background of autoimmune disease. The mean latency period from the last dose of HBVv to onset of symptoms was 38.6 ± 79.4 days, ranging from days to a year. Eight (42.1 %) patients continued with the immunization program despite experiencing adverse events. Manifestations that were commonly reported included neurological manifestations (84.2 %), musculoskeletal (78.9 %), psychiatric (63.1 %), fatigue (63.1 %), gastrointestinal complains (58 %) and mucocutaneous manifestations (36.8 %). Autoantibodies were detected in 71 % of patients tested. All patients fulfilled the ASIA criteria. This study suggests that in some cases CFS and FM can be temporally related to immunization, as part of ASIA syndrome. The appearance of adverse event during immunization, the presence of autoimmune susceptibility and higher titers of autoantibodies all can be suggested as risk factors. ASIA criteria were fulfilled in all patients eluding the plausible link between ASIA and CFS/FM.

Immunol Res. 2014 Dec;60(2-3):226-35. PMID: 25427992

Immune thrombocytopenic purpura (ITP) associated with vaccinations: a review of reported cases.

Perricone C1, Ceccarelli F, Nesher G, Borella E, Odeh Q, Conti F, Shoenfeld Y, Valesini G.

1Reumatologia, Dipartimento di Medicina Interna e Specialità Mediche, Sapienza Università di Roma, Rome, Italy.

Abstract
Immune thrombocytopenic purpura (ITP) is an autoimmune condition characterized by low platelet count with mucocutaneous and other bleedings. Clinical manifestations may range from spontaneous formation of purpura and petechiae, especially on the extremities, to epistaxis, bleeding at the gums or menorrhagia, any of which occur usually if the platelet count is below 20,000 per µl. A very low count may result in the spontaneous formation of hematomas in the mouth or on other mucous membranes. Fatal complications, including subarachnoid or intracerebral, lower gastrointestinal or other internal bleeding can arise due to an extremely low count. Vaccines may induce ITP by several mechanisms. Vaccine-associated autoimmunity may stem not only from the antigen-mediated responses but also from other constituents of the vaccine, such as yeast proteins, adjuvants, and preservatives diluents. The most likely is through virally induced molecular mimicry. The binding of pathogenic autoantibodies to platelet and megakaryocytes may cause thrombocytopenia by different mechanisms, such as opsonization, direct activation of complement, or apoptotic pathways. The autoantibodies hypothesis is not sufficient to explain all ITP cases: In the anti-platelet antibody-negative cases, a complementary mechanism based on T cell immune-mediated mechanism has been suggested. In particular, T cell subsets seem dysregulated with an increased production of pro-inflammatory cytokines, as IFN-γ and TNF, and chemokines, as CXCL10. Vaccines are one of the most striking discoveries in human history that changed dramatically life expectancy. Nonetheless, the occurrence of adverse events and autoimmune phenomena has been described following vaccination, and ITP may represent one of this.

JAMA Neurol. 2014 Dec;71(12):1506-13. PMID: 25329096

Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases.

Langer-Gould A[1], Qian L[2], Tartof SY[2], Brara SM[3], Jacobsen SJ[2], Beaber BE[3], Sy LS[2], Chao C[2], Hechter R[2], Tseng HF[2].

[1]Department of Research and Evaluation, Kaiser Permanente, Southern California, Pasadena[2]Department of Neurology, Los Angeles Medical Center, Southern California Permanente Medical Group, Los Angeles.
[2]Department of Research and Evaluation, Kaiser Permanente, Southern California, Pasadena.
[3]Department of Neurology, Los Angeles Medical Center, Southern California Permanente Medical Group, Los Angeles.

Abstract
IMPORTANCE: Because vaccinations are common, even a small increased risk of multiple sclerosis (MS) or other acquired central nervous system demyelinating syndromes (CNS ADS) could have a significant effect on public health.
OBJECTIVE: To determine whether vaccines, particularly those for hepatitis B (HepB) and human papillomavirus (HPV), increase the risk of MS or other CNS ADS.
DESIGN, SETTING, AND PARTICIPANTS: A nested case-control study was conducted using data obtained from the complete electronic health records of Kaiser Permanente Southern California (KPSC) members. Cases were identified through the KPSC CNS ADS cohort between 2008 and 2011, which included extensive review of medical records by an MS specialist. Five controls per case were matched on age, sex, and zip code.
EXPOSURES: Vaccination of any type (particularly HepB and HPV) identified through the electronic vaccination records system.
MAIN OUTCOMES AND MEASURES: All forms of CNS ADS were analyzed using conditional logistic regression adjusted for race/ethnicity, health care utilization, comorbid diseases, and infectious illnesses before symptom onset.
RESULTS: We identified 780 incident cases of CNS ADS and 3885 controls; 92 cases and 459 controls were females aged 9 to 26 years, which is the indicated age range for HPV vaccination. There were no associations between HepB vaccination (odds ratio [OR], 1.12; 95% CI, 0.72-1.73), HPV vaccination (OR, 1.05; 95% CI, 0.62-1.78), or any vaccination (OR, 1.03; 95% CI, 0.86-1.22) and the risk of CNS ADS up to 3 years later. **Vaccination of any type was associated with an increased risk of CNS ADS onset within the first 30 days after vaccination in younger (<50 years) individuals (OR, 2.32; 95% CI, 1.18-4.57).**
CONCLUSIONS AND RELEVANCE:
We found no longer-term association of vaccines with MS or any other CNS ADS, which argues against a causal association. **The short-term increase in risk suggests that vaccines may accelerate the transition from subclinical to overt autoimmunity in patients with existing disease. Our findings support clinical anecdotes of CNS ADS symptom onset shortly after vaccination** but do not suggest a need for a change in vaccine policy. !!??!!

Acta Neurol Taiwan. 2014 Sep;23(3):95-101. PMID: 26077181

Churg-Strauss Syndrome Following Vaccination Against 2010 Influenza A (H1N1): A Case Report.

Fu MH[1], Tsai WC[1], Lan J[2], Lu CH[1], Lee LH[3], Huang CC[1].

[1]Department of Neurology, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan.
[2]Department of Pathology, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan.
[3]Department of Neurology, E-Da Hospital, Kaohsiung, Taiwan.

Abstract
PURPOSE AND BACKGROUND: Churg-Strauss syndrome (CSS) is a systemic inflammatory disorder characterized by asthma, transient pulmonary infiltration, hyper-eosinophilia, and systemic vasculitis. Reported triggering factors include infections, drugs, allergic desensitization, and vaccinations, although cases involving the latter two are extremely rare. Herein,

we describe a patient who developed CSS after receiving an H1N1 vaccination.
CASE REPORT: A 55-year-old woman presented with fever, skin eruptions, and sensory impairment of her feet within one week after an H1N1 vaccine injection. A chest X-ray showed pulmonary infiltrations in both lower lung fields. Eosinophilia was noted in a hematological test, and an electrophysiological study revealed a pattern of mononeuritis multiplex. A skin biopsy was performed which revealed palisading necrotizing granuloma around a degenerated dermis and eosinophilic infiltration of the blood vessel walls. These findings combined with the hematological and electrophysiological findings met the criteria of CSS according to the American College of Rheumatology. The patient recovered well after steroid treatment.
CONCLUSION: This case highlights the possibility that the H1N1 vaccination can trigger CSS. Due to the rarity of reported autoimmune events after vaccine administration and the obscure causal association between autoimmunity and a vaccine, further post-marketing surveillance and research are necessary to clarify the relationship and identify risk factors.

Immunotherapy. 2014;6(10):1055-71. PMID: 25428645

Are there negative CNS impacts of aluminum adjuvants used in vaccines and immunotherapy?

Shaw CA[1], Li D, Tomljenovic L.

[1]Neural Dynamics Research Group, 828 W. 10th Ave, Vancouver, BC, V5Z 1L8, Canada.

Abstract

In spite of a common view that aluminum (Al) salts are inert and therefore harmless as vaccine adjuvants or in immunotherapy, the reality is quite different. In the following article we briefly review the literature on Al neurotoxicity and the use of Al salts as vaccine adjuvants and consider not only direct toxic actions on the nervous system, but also the potential impact for triggering autoimmunity. Autoimmune and inflammatory responses affecting the CNS appear to underlie some forms of neurological disease, including developmental disorders. Al has been demonstrated to impact the CNS at every level, including by changing gene expression. These outcomes should raise concerns about the increasing use of Al salts as vaccine adjuvants and for the application as more general immune stimulants.

J Autoimmun. 2014 Jun;51:10-6. PMID: 24774584

Sjögren's syndrome: another facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA).

Colafrancesco S[1], Perricone C[1], Priori R[2], Valesini G[2], Shoenfeld Y[3].

[1]Department of Internal Medicine and Medical Specialities, Rheumatology Unit, Sapienza University of Rome, Italy; The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel.

[2]Department of Internal Medicine and Medical Specialities, Rheumatology Unit, Sapienza University of Rome, Italy.

[3]The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel; Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Sackler Faculty of Medicine, Tel Aviv University, Israel. Electronic address: shoenfel@post.tau.ac.il.

Abstract

Recently, a new syndrome, namely the "Autoimmune/inflammatory syndrome induced by adjuvants" (ASIA) has been defined. In this syndrome different conditions characterized by common signs and symptoms and induced by the presence of an adjuvant are included. The adjuvant is a substance capable of boosting the immune response and of acting as a trigger in the development of autoimmune diseases. Post-vaccination autoimmune phenomena represent a major issue of ASIA. Indeed, despite vaccines represent a mainstay in the improvement of human health, several of these have been implicated as a potential trigger for autoimmune diseases. Sjogren's Syndrome (SjS) is a systemic chronic autoimmune inflammatory disease characterized by the presence of an inflammatory involvement of exocrine glands accompanied by systemic manifestations. Own to the straight association between infectious agents exposure (mainly viruses) and sicca syndrome development, the possible link between vaccine and SjS is not surprising. Indeed, a few cases of SjS following vaccine delivery have been reported. At the same extent, the induction of SjS following silicone exposure has been described too. Thus, the aim of this review was to focus on SjS and its possible development following vaccine or silicone exposure in order to define another possible facet of the ASIA syndrome.

J Autoimmun. 2014 May;50:1-11. PMID: 24559657 **Free full text**

Narcolepsy, 2009 A(H1N1) pandemic influenza, and pandemic influenza vaccinations: what is known and unknown about the neurological disorder, the role for autoimmunity, and vaccine adjuvants.

Ahmed SS[1], Schur PH[2], MacDonald NE[3], Steinman L[4].

[1]Global Clinical Sciences, Vaccines Research, Novartis Vaccines Srl, via, Fiorentina 1, Siena 53100, Italy. Electronic address: sohail.ahmed@novartis.com.

[2]Harvard Medical School, Division of Rheumatology, Brigham and Women's, Hospital, 45 Francis Street, Boston, MA 02115, USA. Electronic address: pschur@partners.org.

[3]Dalhousie University, Division Pediatric Infectious Diseases, IWK Health Center, 5850/5980 University Avenue, PO Box 9700, Halifax, Nova Scotia B3K 6R8, Canada. Electronic address: noni.macdonald@dal.ca.

[4]Beckman Center for Molecular Medicine, B002, 279 Campus Drive, Stanford University, Stanford, CA 94305, USA. Electronic address: steinman@stanford.edu.

Abstract

The vaccine safety surveillance system effectively detected a very rare adverse event, narcolepsy, in subjects

receiving AS03-adjuvanted A(H1N1) pandemic vaccine made using the European inactivation/purification protocol. The reports of increased cases of narcolepsy in non-vaccinated subjects infected with wild A(H1N1) pandemic influenza virus suggest a role for the viral antigen(s) in disease development. However, additional investigations are needed to better understand what factor(s) in wild influenza infection trigger(s) narcolepsy in susceptible hosts. An estimated 31 million doses of European AS03-adjuvanted A(H1N1) pandemic vaccine were used in more than 47 countries. The Canadian AS03-adjuvanted A(H1N1) pandemic vaccine was used with high coverage in Canada where an estimated 12 million doses were administered. As no similar narcolepsy association has been reported to date with the AS03-adjuvanted A(H1N1) pandemic vaccine made using the Canadian inactivation/purification protocol, this suggests that the AS03 adjuvant alone may not be responsible for the narcolepsy association. To date, no narcolepsy association has been reported with the MF59®-adjuvanted A(H1N1) pandemic vaccine. This review article provides a brief background on narcolepsy, outlines the different types of vaccine preparations including the ones for influenza, reviews the accumulated evidence for the safety of adjuvants, and explores the association between autoimmune diseases and natural infections. It concludes by assimilating the historical observations and recent clinical studies to formulate a feasible hypothesis on why vaccine-associated narcolepsy may not be solely linked to the AS03 adjuvant but more likely be linked to how the specific influenza antigen component of the European AS03-adjuvanted pandemic vaccine was prepared. Careful and long-term epidemiological studies of subjects who developed narcolepsy in association with AS03-adjuvanted A(H1N1) pandemic vaccine prepared with the European inactivation/purification protocol are needed.

Autoimmun Rev. 2014 Mar;13(3):215-24. PMID: 24514081

The spectrum of post-vaccination inflammatory CNS demyelinating syndromes.

Karussis D, Petrou P.

Abstract A wide variety of inflammatory diseases temporally associated with the administration of various vaccines, has been reported in the literature. A PubMed search from 1979 to 2013 revealed seventy one (71) documented cases. The most commonly reported vaccinations that were associated with CNS demyelinating diseases included influenza (21 cases), human papilloma virus (HPV) (9 cases), hepatitis A or B (8 cases), rabies (5 cases), measles (5 cases), rubella (5 cases), yellow fever (3 cases), anthrax (2 cases),meningococcus (2 cases) and tetanus (2 cases). The vast majority of post-vaccination CNS demyelinating syndromes, are related to influenza vaccination and this could be attributed to the high percentage of the population that received the vaccine during the HI1N1 epidemia from 2009 to 2012. Usually the symptoms of the CNS demyelinating syndrome appear few days following the immunization (mean: 14.2 days) but there are cases where the clinical presentation was delayed (more than 3 weeks or even up to 5 months post-vaccination) (approximately a third of all the reported cases). In terms of the clinical presentation and the affected CNS areas, there is a great diversity among the reported cases of post-vaccination acute demyelinating syndromes. Optic neuritis was the prominent clinical presentation in 38 cases, multifocal disseminated demyelination in 30, myelitis in 24 and encephalitis in 17. Interestingly in a rather high proportion of the patients (and especially following influenza and human papiloma virus vaccination-HPV) the dominant localizations of demyelination were the optic nerves and the myelon, presenting as optic neuritis and myelitis (with or without additional manifestations of ADEM), reminiscent to neuromyelitic optica (or, more generally, the NMO-spectrum of diseases). Seven patients suffered an NMO-like disease following HPV and we had two similar cases in our Center. One patient with post-vaccination ADEM, subsequently developed NMO. Overall, the risk of a demyelinating CNS disease following vaccination, although non-negligible, is relatively low. The risk of onset or relapse of CNS demyelination following infections against which the vaccines are aimed to protect, is substantially higher and the benefits of vaccinations surpass the potential risks of CNS inflammation. This does not in any way exempt us from “learning the lessons” taught by the reported cases and searching new and safer ways to improve vaccination techniques and increase their safety profile.

J Autoimmun. 2013 Dec;47:1-16. PMID: 24238833

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the pathogenic, clinical and diagnostic aspects.

Perricone C[1], Colafrancesco S, Mazor RD, Soriano A, Agmon-Levin N, Shoenfeld Y.

[1]The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel; Reumatologia, Dipartimento di Medicina Interna e Specialità Mediche, Sapienza Università di Roma, Rome, Italy.

Abstract

In 2011 a new syndrome termed 'ASIA Autoimmune/Inflammatory Syndrome Induced by Adjuvants' was defined pointing to summarize for the first time the spectrum of immune-mediated diseases triggered by an adjuvant stimulus such as chronic exposure to silicone, tetramethylpentadecane, pristane, aluminum and other adjuvants, as well as infectious components, that also may have an adjuvant effect. All these environmental factors have been found to induce autoimmunity by themselves both in animal models and in humans: for instance, silicone was associated with siliconosis, aluminum hydroxide with post-vaccination phenomena and macrophagic myofasciitis syndrome. Several mechanisms have been hypothesized to be involved in the onset of adjuvant-

induced autoimmunity; a genetic favorable background plays a key role in the appearance on such vaccine-related diseases and also justifies the rarity of these phenomena. This paper will focus on protean facets which are part of ASIA, focusing on the roles and mechanisms of action of different adjuvants which lead to the autoimmune/inflammatory response. The data herein illustrate the critical role of environmental factors in the induction of autoimmunity. Indeed, it is the interplay of genetic susceptibility and environment that is the major player for the initiation of breach of tolerance.

Am J Reprod Immunol. 2013 Oct;70(4):309-16. PMID: 23902317

Human papilloma virus vaccine and primary ovarian failure: another facet of the autoimmune/inflammatory syndrome induced by adjuvants.

Colafrancesco S[1], Perricone C, Tomljenovic L, Shoenfeld Y.

[1]Zabludowicz Center for Autoimmune Diseases Sheba Medical Center, Tel-Hashomer, Israel; Rheumatology Unit, Department of Internal Medicine and Medical Specialities, Sapienza University of Rome, Rome, Italy.

Abstract

PROBLEM: Post-vaccination autoimmune phenomena are a major facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and different vaccines, including HPV, have been identified as possible causes.

METHOD OF STUDY: The medical history of three young women who presented with secondary amenorrhea following HPV vaccination was collected. Data regarding type of vaccine, number of vaccination, personal, clinical and serological features, as well as response to treatments were analyzed.

RESULTS: All three patients developed secondary amenorrhea following HPV vaccinations, which did not resolve upon treatment with hormone replacement therapies. In all three cases sexual development was normal and genetic screen revealed no pertinent abnormalities (i.e., Turner's syndrome, Fragile X test were all negative). Serological evaluations showed low levels of estradiol and increased FSH and LH and in two cases, specific auto-antibodies were detected (antiovarian and anti thyroid), suggesting that the HPV vaccine triggered an autoimmune response. Pelvic ultrasound did not reveal any abnormalities in any of the three cases. All three patients experienced a range of common non-specific post-vaccine symptoms including nausea, headache, sleep disturbances, arthralgia and a range of cognitive and psychiatric disturbances. According to these clinical features, a diagnosis of primary ovarian failure (POF) was determined which also fulfilled the required criteria for the ASIA syndrome.

CONCLUSION: We documented here the evidence of the potential of the HPV vaccine to trigger a life-disabling autoimmune condition. The increasing number of similar reports of post HPV vaccine-linked autoimmunity and the uncertainty of long-term clinical benefits of HPV vaccination are a matter of public health that warrants further rigorous inquiry.

Immunol Res. 2013 Jul;56(2-3):299-303. PMID: 23576057

Adverse events following immunization with vaccines containing adjuvants.

Cerpa-Cruz S[1], Paredes-Casillas P, Landeros Navarro E, Bernard-Medina AG, Martínez-Bonilla G, Gutiérrez-Ureña S.

[1]Rheumatology and Immunology Department, Hospital Civil de Guadalajara Fray Antonio Alcalde, Hospital 278, SH, Colonia El Retiro, 44280, Guadalajara, Jalisco, Mexico. sacer04@prodigy.net.mx

Abstract

A traditional infectious disease vaccine is a preparation of live attenuated, inactivated or killed pathogen that stimulates immunity. Vaccine immunologic adjuvants are compounds incorporated into vaccines to enhance immunogenicity. Adjuvants have recently been implicated in the new syndrome named ASIA autoimmune/inflammatory syndrome induced by adjuvants. The objective describes the frequencies of post-vaccination clinical syndrome induced by adjuvants. We performed a cross-sectional study; adverse event following immunization was defined as any untoward medical occurrence that follows immunization 54 days prior to the event. Data on vaccinations and other risk factors were obtained from daily epidemiologic surveillance. Descriptive statistics were done using means and standard deviation, and odds ratio adjusted for potential confounding variables was calculated with SPSS 17 software. Forty-three out of 120 patients with moderate or severe manifestations following immunization were hospitalized from 2008 to 2011. All patients fulfilled at least 2 major and 1 minor criteria suggested by Shoenfeld and Agmon-Levin for ASIA diagnosis. The most frequent clinical findings were pyrexia 68%, arthralgias 47%, cutaneous disorders 33%, muscle weakness 16% and myalgias 14%. Three patients had diagnosis of Guillain-Barre syndrome, one patient had Adult-Still's disease 3 days after vaccination. A total of 76% of the events occurred in the first 3 days post-vaccination. Two patients with previous autoimmune disease showed severe adverse reactions with the reactivation of their illness. Minor local reactions were present in 49% of patients. Vaccines containing adjuvants may be associated with an increased risk of autoimmune/inflammatory adverse events following immunization.

Immunol Res. 2013 Jul;56(2-3):304-16. PMID: 23609067

Aluminium in the central nervous system (CNS): toxicity in humans and animals, vaccine adjuvants, and autoimmunity. Shaw CA[1], Tomljenovic L.

[1]*Neural Dynamics Research Group, Department of Ophthalmology and Visual Sciences, University of British Columbia (UBC), 828 W. 10th Ave., Vancouver, BC, V5Z 1L8, Canada. cashawlab@gmail.com*

Abstract

We have examined the neurotoxicity of aluminum in humans and animals under various conditions, following different routes of administration, and provide an overview of the various associated disease states. The literature demonstrates clearly negative impacts of aluminum on the nervous system across the age span. In adults, aluminum exposure can lead to apparently age-related neurological deficits resembling Alzheimer's and has been linked to this disease and to the Guamanian variant, ALS-PDC. Similar outcomes have been found in animal models. In addition, injection of aluminum adjuvants in an attempt to model Gulf War syndrome and associated neurological deficits leads to an ALS phenotype in young male mice. In young children, a highly significant correlation exists between the number of pediatric aluminum-adjuvanted vaccines administered and the rate of autism spectrum disorders. Many of the features of aluminum-induced neurotoxicity may arise, in part, from autoimmune reactions, as part of the ASIA syndrome.

Expert Rev Clin Immunol. 2013 Apr;9(4):361-73. PMID: 23557271

Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome): clinical and immunological spectrum.

Vera-Lastra O[1], Medina G, Cruz-Dominguez Mdel P, Jara LJ, Shoenfeld Y.

[1]*Hospital de Especialidades Centro Médico La Raza, Instituto Mexicano del Seguro Social, Mexico City, Mexico.*

Abstract

An adjuvant is a substance that enhances the antigen-specific immune response, induces the release of inflammatory cytokines, and interacts with Toll-like receptors and the NALP3 inflammasome. The immunological consequence of these actions is to stimulate the innate and adaptive immune response. The activation of the immune system by adjuvants, a desirable effect, could trigger manifestations of autoimmunity or autoimmune disease. Recently, a new syndrome was introduced, autoimmune/inflammatory syndrome induced by adjuvants (ASIA), that includes postvaccination phenomena, macrophagic myofasciitis, Gulf War syndrome and siliconosis. This syndrome is characterized by nonspecific and specific manifestations of autoimmune disease. The main substances associated with ASIA are squalene (Gulf War syndrome), aluminum hydroxide (postvaccination phenomena, macrophagic myofasciitis) and silicone with siliconosis. Mineral oil, guaiacol and iodine gadital are also associated with ASIA. The following review describes the wide clinical spectrum and pathogenesis of ASIA including defined autoimmune diseases and nonspecific autoimmune manifestations, as well as the outlook of future research in this field.

BMC Med. 2013 Apr 4;11:101. PMID: 23557479 **Free PMC Article**

Novel pebbles in the mosaic of autoimmunity. Perricone C, Agmon-Levin N, Shoenfeld Y.

Abstract

Almost 25 years ago, the concept of the 'mosaic of autoimmunity' was introduced to the scientific community, and since then this concept has continuously evolved, with new pebbles being added regularly. We are now looking at an era in which the players of autoimmunity have changed names and roles. In this issue of BMC Medicine, several aspects of autoimmunity have been addressed, suggesting that we are now at the forefront of autoimmunity science. Within the environmental factors generating autoimmunity are now included unsuspected molecules such as vitamin D and aluminum. Some adjuvants such as aluminum are recognized as causal factors in the development of the autoimmune response. An entirely new syndrome, the autoimmune/inflammatory syndrome induced by adjuvants (ASIA), has been recently described. This is the new wind blowing within the branches of autoimmunity, adding knowledge to physicians for helping patients with autoimmune disease.

J R Soc Interface. 2013 Feb;10(79):20120536. PMID: 23173193 **Free PMC Article**

Applications of polymeric adjuvants in studying autoimmune responses and vaccination against infectious diseases.

Shakya AK[1], Nandakumar KS.

[1]*Medical Inflammation Research, Department of Medical Biochemistry and Biophysics, Karolinska Institute, , Stockholm, Sweden.*

Abstract

Polymers as an adjuvant are capable of enhancing the vaccine potential against various infectious diseases and also are being used to study the actual autoimmune responses using self-antigen(s) without involving any major immune deviation. Several natural polysaccharides and their derivatives originating from microbes and plants have been tested for their adjuvant potential. Similarly, numerous synthetic polymers including polyelectrolytes, polyesters, polyanhydrides, non-ionic block copolymers and external stimuli responsive polymers have

demonstrated adjuvant capacity using different antigens. Adjuvant potential of these polymers mainly depends on their solubility, molecular weight, degree of branching and the conformation of polymeric backbone. These polymers have the ability not only to activate humoral but also cellular immune responses in the host. The depot effect, which involves slow release of antigen over a long duration of time, using different forms (particulate, solution and gel) of polymers, and enhances the co-stimulatory signals for optimal immune activation, is the underlying principle of their adjuvant properties. Possibly, polymers may also interact and activate various toll-like receptors and inflammasomes, thus involving several innate immune system players in the ensuing immune response. Biocompatibility, biodegradability, easy production and purification, and non-toxic properties of most of the polymers make them attractive candidates for substituting conventional adjuvants that have undesirable effects in the host.

Tomljenovic L, Shoenfeld Y. Association between vaccination and Guillain-Barré syndrome (Comment). The Lancet _____ online 2013.

Shoenfeld Y, Agmon-Levin N. Autoimmune or auto-inflammatory syndromes induced by adjuvants. Harefuah 151: 9-11, 2012.

Bijl M, Agmon-Levin N, Dayer JM, Israeli E, Gatto M, Shoenfeld Y. Vaccination of patients with auto-immune inflammatory rheumatic diseases requires careful benefit-risk assessment. Autoimmun Rev. 2012; 11: 572-6.

Shoenfeld Y. Letter to the Editor: HPV vaccines and autoimmune diseases. J Intern Med 2012; Jul;272(1):98;

Israeli E, Agmon-Levin N, Blank M, Chapman J, Shoenfeld Y. Guillain-barre Syndrome – a classical autoimmune disease triggered by infection on vaccination. Clin Rev Allergy Immunol 42: 121-130, 2012.

Lupus. 2012 Feb;21(2):118-20. PMID: 22235040

The spectrum of ASIA: 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants'. *[No abstract]*

Agmon-Levin N, Hughes GR, Shoenfeld Y.

Summary: "It seems that the role of adjuvants [aluminum in vaccines] in the pathogenesis of immune-mediated diseases can no longer be ignored, and the medical community must look towards producing safer adjuvants. Another cornerstone of ASIA is the complex interaction between autoimmunity and adjuvanted vaccines. On the one hand vaccines are beneficial for the vast majority of subjects including those who suffer from autoimmune-rheumatic diseases as delineated in this issue by van Assen and Bijl.16 On the other hand in a small minority of individuals vaccine can trigger the appearance of autoantibodies as documented by Vista et al.17 and Perdan-Pirkmajer et al.18 Moreover, a link between immunization and defined autoimmune diseases has been reported elsewhere and herein."

Lupus. 2012 Feb;21(2):146-52. PMID: 22235045

Autoimmunity following hepatitis B vaccine as part of the spectrum of 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants' (ASIA): analysis of 93 cases.

Zafrir Y[1], Agmon-Levin N, Paz Z, Shilton T, Shoenfeld Y.

[1]*The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel.*

Abstract

OBJECTIVES: In this study we analyzed the clinical and demographic manifestations among patients diagnosed with immune/autoimmune-mediated diseases post-hepatitis B vaccination. We aimed to find common denominators for all patients, regardless of different diagnosed diseases, as well as the correlation to the criteria of Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants (ASIA).

PATIENTS AND METHODS: We have retrospectively analyzed the medical records of 114 patients, from different centers in the USA, diagnosed with immune-mediated diseases following immunization with hepatitis-B vaccine (HBVv). All patients in this cohort sought legal consultation. Of these, 93/114 patients diagnosed with disease

before applying for legal consultation were included in the study. All medical records were evaluated for demographics, medical history, number of vaccine doses, peri-immunization adverse events and clinical manifestations of diseases. In addition, available blood tests, imaging results, treatments and outcomes were recorded. Signs and symptoms of the different immune-mediated diseases were grouped according to the organ or system involved. ASIA criteria were applied to all patients.
RESULTS: The mean age of 93 patients was 26.5 ± 15 years; 69.2% were female and 21% were considered autoimmune susceptible. The mean latency period from the last dose of HBVv and onset of symptoms was 43.2 days. Of note, 47% of patients continued with the immunization program despite experiencing adverse events. Manifestations that were commonly reported included neuro-psychiatric (70%), fatigue (42%) mucocutaneous (30%), musculoskeletal (59%) and gastrointestinal (50%) complaints. Elevated titers of autoantibodies were documented in 80% of sera tested. In this cohort 80/93 patients (86%), comprising 57/59 (96%) adults and 23/34 (68%) children, fulfilled the required criteria for ASIA.
CONCLUSIONS: Common clinical characteristics were observed among 93 patients diagnosed with immune-mediated conditions post-HBVv, suggesting a common denominator in these diseases. In addition, risk factors such as history of autoimmune diseases and the appearance of adverse event(s) during immunization may serve to predict the risk of post-immunization diseases. The ASIA criteria were found to be very useful among adults with post-vaccination events. The application of the ASIA criteria to pediatric populations requires further study.

Lupus. 2012 Feb;21(2):223-30. PMID: 22235057

Mechanisms of aluminum adjuvant toxicity and autoimmunity in pediatric populations.

Tomljenovic L[1], Shaw CA.

[1]Neural Dynamics Research Group, Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, BC, Canada. lucijat77@gmail.com

Abstract

Immune challenges during early development, including those vaccine-induced, can lead to permanent detrimental alterations of the brain and immune function. Experimental evidence also shows that simultaneous administration of as little as two to three immune adjuvants can overcome genetic resistance to autoimmunity. In some developed countries, by the time children are 4 to 6 years old, they will have received a total of 126 antigenic compounds along with high amounts of aluminum (Al) adjuvants through routine vaccinations. According to the US Food and Drug Administration, safety assessments for vaccines have often not included appropriate toxicity studies because vaccines have not been viewed as inherently toxic. Taken together, these observations raise plausible concerns about the overall safety of current childhood vaccination programs. When assessing adjuvant toxicity in children, several key points ought to be considered: (i) infants and children should not be viewed as "small adults" with regard to toxicological risk as their unique physiology makes them much more vulnerable to toxic insults; (ii) in adult humans Al vaccine adjuvants have been linked to a variety of serious autoimmune and inflammatory conditions (i.e., "ASIA"), yet children are regularly exposed to much higher amounts of Al from vaccines than adults; (iii) it is often assumed that peripheral immune responses do not affect brain function. However, it is now clearly established that there is a bidirectional neuro-immune cross-talk that plays crucial roles in immunoregulation as well as brain function. In turn, perturbations of the neuro-immune axis have been demonstrated in many autoimmune diseases encompassed in "ASIA" and are thought to be driven by a hyperactive immune response; and (iv) the same components of the neuro-immune axis that play key roles in brain development and immune function are heavily targeted by Al adjuvants. In summary, research evidence shows that increasing concerns about current vaccination practices may indeed be warranted. Because children may be most at risk of vaccine-induced complications, a rigorous evaluation of the vaccine-related adverse health impacts in the pediatric population is urgently needed.

Lupus. 2012 Feb;21(2):146-52. PMID: 22235045

Autoimmunity following hepatitis B vaccine as part of the spectrum of 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants' (ASIA): analysis of 93 cases.

Zafrir Y[1], Agmon-Levin N, Paz Z, Shilton T, Shoenfeld Y.

[1]The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel.

Abstract

OBJECTIVES: In this study we analyzed the clinical and demographic manifestations among patients diagnosed with immune/autoimmune-mediated diseases post-hepatitis B vaccination. We aimed to find common denominators for all patients, regardless of different diagnosed diseases, as well as the correlation to the criteria of Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants (ASIA).
PATIENTS AND METHODS: We have retrospectively analyzed the medical records of 114 patients, from different centers in the USA, diagnosed with immune-mediated diseases following immunization with hepatitis-B vaccine (HBVv). All patients in this cohort sought legal consultation. Of these, 93/114 patients diagnosed with disease before applying for legal consultation were included in the study. All medical records were evaluated for demographics, medical history, number of vaccine doses, peri-immunization adverse events and clinical

manifestations of diseases. In addition, available blood tests, imaging results, treatments and outcomes were recorded. Signs and symptoms of the different immune-mediated diseases were grouped according to the organ or system involved. ASIA criteria were applied to all patients.
RESULTS: The mean age of 93 patients was 26.5 ± 15 years; 69.2% were female and 21% were considered autoimmune susceptible. The mean latency period from the last dose of HBVv and onset of symptoms was 43.2 days. Of note, 47% of patients continued with the immunization program despite experiencing adverse events. Manifestations that were commonly reported included neuro-psychiatric (70%), fatigue (42%) mucocutaneous (30%), musculoskeletal (59%) and gastrointestinal (50%) complaints. Elevated titers of autoantibodies were documented in 80% of sera tested. In this cohort 80/93 patients (86%), comprising 57/59 (96%) adults and 23/34 (68%) children, fulfilled the required criteria for ASIA.
CONCLUSIONS: Common clinical characteristics were observed among 93 patients diagnosed with immune-mediated conditions post-HBVv, suggesting a common denominator in these diseases. In addition, risk factors such as history of autoimmune diseases and the appearance of adverse event(s) during immunization may serve to predict the risk of post-immunization diseases. The ASIA criteria were found to be very useful among adults with post-vaccination events. The application of the ASIA criteria to pediatric populations requires further study.

Lupus. 2012 Feb;21(2):146-52. PMID: 22235045

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Abstract

OBJECTIVES: In this study we analyzed the clinical and demographic manifestations among patients diagnosed with immune/autoimmune-mediated diseases post-hepatitis B vaccination. We aimed to find common denominators for all patients, regardless of different diagnosed diseases, as well as the correlation to the criteria of Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants (ASIA).
PATIENTS AND METHODS: We have retrospectively analyzed the medical records of 114 patients, from different centers in the USA, diagnosed with immune-mediated diseases following immunization with hepatitis-B vaccine (HBVv). All patients in this cohort sought legal consultation. Of these, 93/114 patients diagnosed with disease before applying for legal consultation were included in the study. All medical records were evaluated for demographics, medical history, number of vaccine doses, peri-immunization adverse events and clinical manifestations of diseases. In addition, available blood tests, imaging results, treatments and outcomes were recorded. Signs and symptoms of the different immune-mediated diseases were grouped according to the organ or system involved. ASIA criteria were applied to all patients.
RESULTS: The mean age of 93 patients was 26.5 ± 15 years; 69.2% were female and 21% were considered autoimmune susceptible. The mean latency period from the last dose of HBVv and onset of symptoms was 43.2 days. Of note, 47% of patients continued with the immunization program despite experiencing adverse events. Manifestations that were commonly reported included neuro-psychiatric (70%), fatigue (42%) mucocutaneous (30%), musculoskeletal (59%) and gastrointestinal (50%) complaints. Elevated titers of autoantibodies were documented in 80% of sera tested. In this cohort 80/93 patients (86%), comprising 57/59 (96%) adults and 23/34 (68%) children, fulfilled the required criteria for ASIA.
CONCLUSIONS: Common clinical characteristics were observed among 93 patients diagnosed with immune-mediated conditions post-HBVv, suggesting a common denominator in these diseases. In addition, risk factors such as history of autoimmune diseases and the appearance of adverse event(s) during immunization may serve to predict the risk of post-immunization diseases. The ASIA criteria were found to be very useful among adults with post-vaccination events. The application of the ASIA criteria to pediatric populations requires further study.

Lupus. 2012 Feb;21(2):175-83. PMID: 22235050

Autoimmune response following influenza vaccination in patients with autoimmune inflammatory rheumatic disease.

Perdan-Pirkmajer K[1], Thallinger GG, Snoj N, Čučnik S, Žigon P, Kveder T, Logar D, Praprotnik S, Tomšič M, Sodin-Semrl S, Ambrožič A.

[1]University Medical Centre Ljubljana, Department of Rheumatology, Ljubljana, Slovenia.

Abstract

Vaccines have undoubtedly brought overwhelming benefits to mankind and are considered safe and effective. Nevertheless, they can occasionally stimulate autoantibody production or even a recently defined syndrome known as autoimmune/inflammatory syndrome induced by adjuvants (ASIA). There is scarce data regarding autoimmune response after seasonal/influenza A (H1N1) vaccine in patients with autoimmune inflammatory rheumatic disease (AIRD). The objective of our study was therefore to determine autoimmune response in a large group of AIRD patients vaccinated against seasonal and/or H1N1 influenza. We conducted a prospective cohort

study with a 6-month follow-up. Two-hundred and eighteen patients with AIRD (50 vaccinated against seasonal influenza, six against H1N1, 104 against both, 58 non-vaccinated controls) and 41 apparently healthy controls (nine vaccinated against seasonal influenza, three against H1N1, 18 against both, 11 non-vaccinated controls) were included. Blood samples were taken and screened for autoantibodies [antinuclear antibody (ANA), anti-extractable nuclear antigen (anti-ENA), anticardiolipin (aCL) IgG/IgM antibodies, anti-beta 2-glycoprotein I (anti-β2GPI)] at inclusion in the study, before each vaccination, 1 month after the last vaccination and 6 months after inclusion. For non-vaccinated participants (patients and healthy controls) blood samples were taken at the time of inclusion in the study and 6 months later. We report that after the administration of seasonal/H1N1 vaccine there were mostly transient changes in autoantibody production in AIRD patients and in healthy participants. However, a small subset of patients, especially ANA-positive patients, had a tendency towards anti-ENA development. Although no convincing differences between the seasonal and H1N1 vaccines were observed, our results imply that there might be a slight tendency of the H1N1 vaccine towards aCL induction. Although seasonal and H1N1 vaccines are safe and effective, they also have the potential to induce autoantibodies in selected AIRD patients and healthy adults. Follow-up of such individuals is proposed and further research is needed.

Diabet Med. 2012 Jan;29(1):88-9. PMID: 21781156

Development of fulminant Type 1 diabetes with thrombocytopenia after influenza vaccination: a case report.

Yasuda H[1], Nagata M, Moriyama H, Kobayashi H, Akisaki T, Ueda H, Hara K, Yokono K.

[1]Department of Internal and Geriatric Medicine, Kobe University Graduate School of Medicine, Kobe, Japan. yasuda@med.kobe-u.ac.jp

Abstract

BACKGROUND: Fulminant Type 1 diabetes was originally reported as idiopathic Type 1 diabetes. Involvement of viral infections in the pathogenesis of fulminant T1D has been suggested, but the development of fulminant Type 1 diabetes after influenza vaccination has not been reported.

CASE REPORT: We report a case of fulminant Type 1 diabetes with thrombocytopenia following influenza vaccination. A 54-year-old man was admitted to hospital with hyperglycaemia and diabetic ketosis. Seven days before admission, he received a seasonal influenza vaccine for the prevention of influenza infection. On admission, blood glucose was 29 mmol/L and HbA1c 40 mmol/mol (5.9%). Fasting and 2-h C-peptide immunoreactivity were <0.0333 nmol/L and 0.0999 nmol/L, respectively. Anti-GAD and anti-IA-2 antibodies were negative, so no autoimmunity seemed to participate in the etiology. ELISPOT assay also showed no association with T cell-mediated autoimmunity. HLA genotypes were consistent with susceptibility to fulminant Type 1 diabetes. After the abrupt onset of diabetes, he showed mild thrombocytopenia, which has been observed for approximately 5 years after diabetes development.

CONCLUSION: This is the first description of fulminant Type 1 diabetes after influenza vaccination. Our observation raises the possibility that influenza vaccination might trigger this condition via the TLR7 pathway.

J Inorg Biochem. 2011 Nov;105(11):1489-99. PMID: 22099159

Do aluminum vaccine adjuvants contribute to the rising prevalence of autism?

Tomljenovic L[1], Shaw CA.

[1]Neural Dynamics Research Group, Department of Ophthalmology and Visual Sciences, University of British Columbia, 828 W. 10th Ave, Vancouver, BC, Canada V5Z 1L8. lucijat77@gmail.com

Abstract Autism spectrum disorders (ASD) are serious multisystem developmental disorders and an urgent global public health concern. Dysfunctional immunity and impaired brain function are core deficits in ASD. Aluminum (Al), the most commonly used vaccine adjuvant, is a demonstrated neurotoxin and a strong immune stimulator. Hence, adjuvant Al has the potential to induce neuroimmune disorders. When assessing adjuvant toxicity in children, two key points ought to be considered: (i) children should not be viewed as "small adults" as their unique physiology makes them much more vulnerable to toxic insults; and (ii) if exposure to Al from only few vaccines can lead to cognitive impairment and autoimmunity in adults, is it unreasonable to question whether the current pediatric schedules, often containing 18 Al adjuvanted vaccines, are safe for children? By applying Hill's criteria for establishing causality between exposure and outcome we investigated whether exposure to Al from vaccines could be contributing to the rise in ASD prevalence in the Western world. Our results show that: (i) children from countries with the highest ASD prevalence appear to have the highest exposure to Al from vaccines; (ii) the increase in exposure to Al adjuvants significantly correlates with the increase in ASD prevalence in the United States observed over the last two decades (Pearson r=0.92, p<0.0001); and (iii) a significant correlation exists between the amounts of Al administered to preschool children and the current prevalence of ASD in seven Western countries, particularly at 3-4 months of age (Pearson r=0.89-0.94, p=0.0018-0.0248). The application of the Hill's criteria to these data indicates that the correlation between Al in vaccines and ASD may be causal. Because children

represent a fraction of the population most at risk for complications following exposure to Al, a more rigorous evaluation of Al adjuvant safety seems warranted.

BMJ. 2011 Oct 12;343:d5956. PMID: 21994316 **Free PMC Article**

Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden.

Bardage C[1], Persson I, Ortqvist A, Bergman U, Ludvigsson JF, Granath F.

[1]Medical Products Agency, PO Box 26, SE-751 03 Uppsala, Sweden.

Abstract

OBJECTIVE: To examine the risk of neurological and autoimmune disorders of special interest in people vaccinated against pandemic influenza A (H1N1) with Pandemrix (GlaxoSmithKline, Middlesex, UK) compared with unvaccinated people over 8-10 months.

DESIGN: Retrospective cohort study linking individualised data on pandemic vaccinations to an inpatient and specialist database on healthcare utilisation in Stockholm county for follow-up during and after the pandemic period.

SETTING: Stockholm county, Sweden. Population All people registered in Stockholm county on 1 October 2009 and who had lived in this region since 1 January 1998; 1,024,019 were vaccinated against H1N1 and 921,005 remained unvaccinated.

MAIN OUTCOME MEASURES: Neurological and autoimmune diagnoses according to the European Medicines Agency strategy for monitoring of adverse events of special interest defined using ICD-10 codes for Guillain-Barré syndrome, Bell's palsy, multiple sclerosis, polyneuropathy, anaesthesia or hypoaesthesia, paraesthesia, narcolepsy (added), and autoimmune conditions such as rheumatoid arthritis, inflammatory bowel disease, and type 1 diabetes; and short term mortality according to vaccination status.

RESULTS: Excess risks among vaccinated compared with unvaccinated people were of low magnitude for Bell's palsy (hazard ratio 1.25, 95% confidence interval 1.06 to 1.48) and paraesthesia (1.11, 1.00 to 1.23) after adjustment for age, sex, socioeconomic status, and healthcare utilisation. Risks for Guillain-Barré syndrome, multiple sclerosis, type 1 diabetes, and rheumatoid arthritis remained unchanged. The risks of paraesthesia and inflammatory bowel disease among those vaccinated in the early phase (within 45 days from 1 October 2009) of the vaccination campaign were significantly increased; the risk being increased within the first six weeks after vaccination. Those vaccinated in the early phase were at a slightly reduced risk of death than those who were unvaccinated (0.94, 0.91 to 0.98), whereas those vaccinated in the late phase had an overall reduced mortality (0.68, 0.64 to 0.71). These associations could be real or explained, partly or entirely, by residual confounding.

CONCLUSIONS: Results for the safety of Pandemrix over 8-10 months of follow-up were reassuring -notably, no change in the risk for Guillain-Barré syndrome, multiple sclerosis, type 1 diabetes, or rheumatoid arthritis. Relative risks were significantly increased for Bell's palsy, paraesthesia, and inflammatory bowel disease after vaccination, predominantly in the early phase of the vaccination campaign. Small numbers of children and adolescents with narcolepsy precluded any meaningful conclusions.

Shoenfeld Y - Autoimmune (autoinflammatory) syndrome induced by adjuvants provides a diagnostic framework for enigmatic conditions. The Rheumatologist 6 No. 6: 26-32, 2011.

Shoenfeld Y, Agmon-Levin N. 'ASIA' – autoimmune / inflammatory syndrome induced by adjuvants. J of Autoimmun 36: 4-8, 2011.

Bol Asoc Med P R. 2011 Apr-Jun;103(2):48-52. PMID: 22111471

Subacute thyroiditis and dyserythropoesis after influenza vaccination suggesting immune dysregulation.

Hernán Martinez J[1], Corder E, Uzcategui M, Garcia M, Sostre S, Garcia A.

[1]Microbiology and Immunology Department, San Juan Bautista School of Medicine, San Juan Bautista Medical Center, Caguas, Puerto Rico. jhernan.martinez@gmail.com

Abstract Subacute thyroiditis (SAT) is an extremely rare complication of influenza vaccination. Several infectious agents have been related with SAT. It is also well known the association between HLA-B35 and the development of SAT. We describe a case of subacute thyroiditis and dyserythropoesis occurring shortly after administration of an influenza vaccine in a 55-year-old man with history of diabetes and psoriasis, family history of autoimmunity without clinical evidence of acute viral infection prior to the onset of symptoms. We propose that, the events occurring in the patient may be explained as result of complex interactions between the individual genetic background and environmental exposure to infectious agents that generated a pro-inflammatory status, where the vaccine was the trigger for the subsequent alterations in thyroid and bone marrow. These findings highlight the importance of immunogenetic factors involved in response to vaccination that is the central theme in the growing

field of 'vaccinomics'.

J Investig Allergol Clin Immunol. 2011;21(5):389-93. PMID: 21905502 **Free full text**

Autoimmunity and hepatitis A vaccine in children.

Karali Z[1], Basaranoglu ST, Karali Y, Oral B, Kilic SS.

[1]Department of Pediatrics, Division of Pediatric Immunology, Uludag University Medical Faculty, Bursa, Turkey.

Abstract

BACKGROUND: Universal vaccination remains the most effective way of preventing the spread of many infectious diseases. Although most adverse effects attributed to vaccines are mild, rare reactions such as autoimmunity do occur.

OBJECTIVES: We aimed to evaluate the possible role played by hepatitis A vaccine (HAV) in inducing the synthesis of autoantibodies. The study included 40 healthy children vaccinated with 2 doses of HAV at a 6-month interval. The children were investigated for autoantibodies including anti-nuclear antibodies (ANAs), anti-smooth muscle antibodies, anti-nDNA, anti-microsomal antibodies, anti-cardiolipin (aCL) immunoglobulin (Ig) M/IgG, anti-ds DNA, ANA profile, and anti-neutrophil cytoplasmic antibody profile.

RESULTS: One month after the first dose, ANAs at a titer of 1:100 and aCL IgG at 23.7 IgM phospholipid units were detected in 4 children and 1 child, respectively. Of the ANA-positive children, 1 also had ASMA positivity, and another had perinuclear and cytoplasmic ANCA positivity. After the second dose, 3 of the children had aCL IgM. In addition, 2 distinct children had positive anti-thyroid microsomal antibodies and ANA after the second dose. The presence of these autoantibodies following vaccination was statistically significant (P = .002). At month 12 of the study, only 2 children continued to be ANA-positive at the same titer as after the first vaccine dose.

CONCLUSIONS: Although HAV can induce the production of autoantibodies, none of the children developed autoimmune disorders. Long-term follow up is necessary to check whether autoimmune disorders develop in children who still have ANA. Genetic, immunological, environmental, and hormonal factors are also important in the development of vaccine-induced autoimmunity.

Presse Med. 2011 Mar;40(3):248-52. PMID: 21232908

[Flu vaccine and auto-immune and/or inflammatory diseases]. *[Article in French]*

Duchet-Niedziolka P[1], Hanslik T, Mouthon L, Guillevin L, Launay O.

[1]Université Paris Descartes, Assistance publique-Hôpitaux de Paris (AP-HP), hôpital Cochin, centre d'investigation clinique de vaccinologie Cochin Pasteur, Inserm, CIC BT505, Paris, France.

Abstract Patients with systemic inflammatory and/or autoimmune diseases have an increased risk of infections particularly severe influenza infections. Annually vaccination can prevent these infections. Available data about the influenza vaccine in these patients show that, it remains well tolerated and effective even if the antibody response is lower compared to healthy controls. These data encourage to vaccine every year patients with systemic inflammatory and/or autoimmune diseases with influenza vaccine, particularly patients taking immunosuppressant drugs or having respiratory, cardiac or renal chronic diseases according to guidelines. More data are needed about the severity of influenza infection and the efficacy of influenza vaccination in patients with systemic inflammatory and/or autoimmune diseases to improve their vaccine coverage.

J Autoimmun. 2011 Feb;36(1):4-8. PMID: 20708902

'ASIA' - autoimmune/inflammatory syndrome induced by adjuvants.

Shoenfeld Y[1], Agmon-Levin N.

[1]The Zabludowicz Center for Autoimmune Diseases, Department of Medicine B' Sheba Medical Center, Tel-Hashomer, Israel. shoenfel@post.tau.ac.il

Abstract The role of various environmental factors in the pathogenesis of immune mediated diseases is well established. Of which, factors entailing an immune adjuvant activity such as infectious agents, silicone, aluminium salts and others were associated with defined and non-defined immune mediated diseases both in animal models and in humans. In recent years, four conditions: siliconosis, the Gulf war syndrome (GWS), the macrophagic myofasciitis syndrome (MMF) and post-vaccination phenomena were linked with previous exposure to an adjuvant. Furthermore, these four diseases share a similar complex of signs and symptoms which further support a common denominator.Thus, we review herein the current data regarding the role of adjuvants in the pathogenesis of immune mediated diseases as well as the amassed data regarding each of these four conditions. Relating to the current knowledge we would like to suggest to include these comparable conditions under a common syndrome entitled ASIA, "Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants".

J Endocrinol Invest. 2010 Jul-Aug;33(7):506. PMID: 20671410

Subacute thyroiditis following the H1N1 vaccine. [No abstract]

Girgis CM, Russo RR, Benson K.

Int Rev Immunol. 2010 Jun;29(3):247-69. PMID: 20521925

Could autoimmunity be induced by vaccination?

Salemi S[1], D'Amelio R.

[1]Azienda Ospedaliera S. Andrea, Rome, Italy.

Abstract Autoimmune reactions to vaccinations may rarely be induced in predisposed individuals by molecular mimicry or bystander activation mechanisms. Autoimmune reactions reliably considered vaccine-associated, include Guillain-Barré syndrome after 1976 swine influenza vaccine, immune thrombocytopenic purpura after measles/mumps/rubella vaccine, and myopericarditis after smallpox vaccination, whereas the suspected association between hepatitis B vaccine and multiple sclerosis has not been further confirmed, even though it has been recently reconsidered, and the one between childhood immunization and type 1 diabetes seems by now to be definitively gone down. Larger epidemiological studies are needed to obtain more reliable data in most suggested associations.

J Neurol Sci. 2010 May 15;292(1-2):1-4. PMID: 20207367

Neuromuscular disorders associated with Hepatitis B vaccination.

Stübgen JP[1].

[1]Department of Neurology and Neuroscience, Weill Cornell Medical College/New York Presbyterian Hospital, 525 East 68th Street, New York, NY 10065-4885, USA. pstuebge@med.cornell.edu

Abstract The hepatitis B virus (HBV) is an important infectious cause of acute and chronic liver disease throughout the world. Recombinant hepatitis B vaccines have been developed to combat morbidity and mortality associated with HBV infection. These vaccines have been associated with autoimmune diseases mostly among adult vaccine recipients. Epidemiological surveys have not established unequivocal causality between the hepatitis B vaccine and the development of various autoimmune neuromuscular disorders. However, case histories and series hint at a temporal association between hepatitis B vaccines and the development of various neuropathy syndromes, polyarteritis nodosa complicated by vasculitic neuropathy, myasthenia gravis and dermatomyositis. Conceivably, the hepatitis B vaccines have a potential to occasionally trigger the onset of immune diseases in individuals with an underlying genetic or immunological susceptibility.

Transplantation. 2010 Apr 15;89(7):838-44. PMID: 20179666 **Free PMC Article**

Effects of influenza immunization on humoral and cellular alloreactivity in humans.

Danziger-Isakov L[1], Cherkassky L, Siegel H, McManamon M, Kramer K, Budev M, Sawinski D, Augustine JJ, Hricik DE, Fairchild R, Heeger PS, Poggio ED.

[1]Department of Pediatrics, Cleveland Clinic, Cleveland, OH, USA.

Abstract

BACKGROUND: Alloreactive T cells and anti-human leukocyte antigen antibodies mediate transplant injury. Environmental exposures, including vaccinations, may activate the alloimmune repertoire leading to accelerated allograft injury. To test whether vaccination impacts human alloimmunity, we analyzed humoral and cellular immune reactivity in subjects undergoing influenza vaccination.

METHODS: We serially obtained blood samples from 30 healthy subjects and 8 kidney and 9 lung transplant recipients who received influenza vaccination, and from 20 healthy unvaccinated controls. We measured cellular and humoral anti-influenza responses, anti-human leukocyte antigen antibodies, and alloreactive T-cell immunity (interferon-gamma ELISPOT) at 0, 2, 4, and 12 weeks after vaccination.

RESULTS: Vaccination induced influenza-reactive humoral and cellular responses in control subjects and in transplant recipients. Only two of 30 vaccinated volunteers developed new alloantibodies, but none of the transplant patients. Vaccination also specifically and significantly augmented cellular alloimmunity based on reactivity to a panel of stimulators in both healthy subjects and in transplant recipients within 4 weeks of vaccination. The enhanced cellular alloresponse waned toward prevaccine levels by week 12.

CONCLUSION: Our findings newly demonstrate that influenza vaccination can have a significant impact on the potency of the alloimmune repertoire. Because the strength of the alloresponse influences long-term graft function, our results suggest that further investigation of alloimmune monitoring after vaccination is needed.

Discov Med. 2010 Feb;9(45):90-7. PMID: 20193633 **Free full text**

Vaccines and autoimmune diseases of the adult.

Orbach H[1], Agmon-Levin N, Zandman-Goddard G.

[1]Department of Medicine B, Wolfson Medical Center, Holon, Israel.

Abstract Infectious agents contribute to the environmental factors involved in the development of autoimmune diseases possibly through molecular mimicry mechanisms. Hence, it is feasible that vaccinations may also contribute to the mosaic of autoimmunity. Evidence for the association of vaccinations and the development of these diseases is presented in this review. Infrequently reported post-vaccination autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis, inflammatory myopathies, multiple sclerosis, Guillain-Barré syndrome, and vasculitis. In addition, we will discuss macrophagic myofasciitis, aluminum containing vaccines, and the recent evidence for autoimmunity following the use of human papillomavirus vaccine.

PLoS One. 2009 Dec 31;4(12):e8382. PMID:20046868 **Free PMC Article**

Self-organized criticality theory of autoimmunity.

Tsumiyama K[1], Miyazaki Y, Shiozawa S.
1 Department of Biophysics, Kobe University Graduate School of Health Science, Kobe, Japan.

Abstract

BACKGROUND: The cause of autoimmunity, which is unknown, is investigated from a different angle, i.e., the defect in immune 'system', to explain the cause of autoimmunity.

METHODOLOGY/PRINCIPAL FINDINGS: Repeated immunization with antigen causes systemic autoimmunity in mice otherwise not prone to spontaneous autoimmune diseases. Overstimulation of CD4(+) T cells led to the development of autoantibody-inducing CD4(+) T (aiCD4(+) T) cell which had undergone T cell receptor (TCR) revision and was capable of inducing autoantibodies. The aiCD4(+) T cell was induced by de novo TCR revision but not by cross-reaction, and subsequently overstimulated CD8(+) T cells, driving them to become antigen-specific cytotoxic T lymphocytes (CTL). These CTLs could be further matured by antigen cross-presentation, after which they caused autoimmune tissue injury akin to systemic lupus erythematosus (SLE).

CONCLUSIONS/SIGNIFICANCE: Systemic autoimmunity appears to be the inevitable consequence of over-stimulating the host's immune 'system' by repeated immunization with antigen, to the levels that surpass system's self-organized criticality.

Lupus. 2009 Nov;18(13):1198-204. PMID: 19880568

Transverse myelitis and vaccines: a multi-analysis.

Agmon-Levin N[1], Kivity S, Szyper-Kravitz M, Shoenfeld Y.
[1]Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel.

Abstract Transverse myelitis is a rare clinical syndrome in which an immune-mediated process causes neural injury to the spinal cord. The pathogenesis of transverse myelitis is mostly of an autoimmune nature, triggered by various environmental factors, including vaccination. Our aim here was to search for and analyze reported cases of transverse myelitis following vaccination. A systematic review of PubMed, EMBASE and DynaMed for all English-language journals published between 1970 and 2009 was preformed, utilizing the key words transverse myelitis, myelitis, vaccines, post-vaccination, vaccination and autoimmunity. We have disclosed 37 reported cases of transverse myelitis associated with different vaccines including those against hepatitis B virus, measles-mumps-rubella, diphtheria-tetanus-pertussis and others, given to infants, children and adults. In most of these reported cases the temporal association was between several days and 3 months, although a longer time frame of up to several years was also suggested. Although vaccines harbor a major contribution to public health in the modern era, in rare cases they may be associated with autoimmune phenomena such as transverse myelitis. The associations of different vaccines with a single autoimmune phenomenon allude to the idea that a common denominator of these vaccines, such as an adjuvant, might trigger this syndrome.

Lupus. 2009 Nov;18(13):1186-91. PMID: 19880566

Vaccination of healthy subjects and autoantibodies: from mice through dogs to humans.

Toplak N[1], Avcin T.
[1]Department of Allergology, Rheumatology and Clinical Immunology, University Children's Hospital, University Medical Centre Ljubljana, Slovenia. natasa.toplak@kclj.si

Abstract Vaccination against pathogenic microorganisms is one of the major achievements of modern medicine, but due to an increasing number of reports of adverse reactions the vaccination procedure has induced also considerable debate. It is well known that certain infections are involved in triggering the production of autoantibodies, which could lead to autoimmune adverse reactions in genetically predisposed subjects. Based on these findings it was assumed that vaccinations might induce similar autoimmune reactions. At present there is no clear-cut evidence that vaccinations are associated with overt autoimmune diseases but it has been demonstrated that in genetically predisposed persons vaccination can trigger the production of autoantibodies and autoimmune adverse reactions. The first studies investigating the production of autoantibodies following vaccination were done in dogs and mice. Several studies investigated the production of autoantibodies following vaccination in patients with autoimmune diseases, but there are only limited data on the autoimmune responses after vaccinations in apparently healthy humans. This review summarizes current evidence on the vaccination-induced autoantibodies in apparently healthy subjects including studies in animals and humans.

Nat Rev Rheumatol. 2009 Nov;5(11):648-52. PMID: 19865091

Vaccines and autoimmunity.

Agmon-Levin N[1], Paz Z, Israeli E, Shoenfeld Y.
[1]Center for Autoimmune Diseases and Department of Medicine B, Sheba Medical Center, Sheba Medical Center, Tel-Hashomer 52621, Israel.

Abstract Vaccines have been used for over 200 years and are the most effective way of preventing the morbidity and mortality associated with infections. Like other drugs, vaccines can cause adverse events, but unlike conventional medicines, which are prescribed to people who are ill, vaccines are administered to healthy individuals, thus increasing the concern over adverse reactions. Most side effects attributed to vaccines are mild, acute and transient; however, rare reactions such as hypersensitivity, induction of infection, and autoimmunity do occur and can be severe and even fatal. The rarity and subacute presentation of post-vaccination autoimmune phenomena means that ascertaining causality between these events can be difficult. Moreover, the latency period between vaccination and autoimmunity ranges from days to years. In this article, on the basis of published evidence and our own experience, we discuss the various aspects of the causal and temporal interactions between vaccines and autoimmune phenomena, as well as the possible mechanisms by which different components of vaccines might induce autoimmunity.

Ann N Y Acad Sci. 2009 Sep;1173:619-26. PMID: 19758207

Influenza and autoimmunity.

Toplak N[1], Avcin T.

[1]Department of Allergology, Rheumatology and Clinical Immunology, University Children's Hospital, University Medical Centre, Ljubljana, Slovenia. natasa.toplak@kclj.si

Abstract Influenza infection can cause mild to severe illness and can even lead to death. The best way to prevent infection is vaccination against influenza. Complications of influenza infection are not only a consequence of acute infection but can also present as late autoimmune response. Influenza is not frequently implicated as a trigger for autoimmune diseases, but case reports of autoimmune adverse events have been published even following influenza vaccination. In this article we review published data on autoimmune diseases following influenza infection and vaccination. We also discuss immunity of influenza infection in connection to pathogenesis of autoimmune response and autoimmune disease.

Autoimmun Rev. 2008 Dec;8(2):134-8. PMID: 18700173

Autoimmune response following annual influenza vaccination in 92 apparently healthy adults.

Toplak N[1], Kveder T, Trampus-Bakija A, Subelj V, Cucnik S, Avcin T.

[1]Department of Allergology, Rheumatology and Clinical Immunology, University Children's Hospital, University Medical Centre Ljubljana, Slovenia. natasa.toplak@kclj.si

Abstract

OBJECTIVE: To evaluate the possibility of autoimmune responses following annual influenza vaccination in a large cohort of apparently healthy adults.

METHODS: Autoantibodies including antinuclear antibodies (ANA), anticardiolipin antibodies (aCL), anti-beta(2)-glycoprotein I antibodies (anti-beta(2)-GPI), lupus anticoagulant (LA) and anti-extractable nuclear antigen antibodies (anti-ENA) were determined in 92 healthy adult subjects, staff at the University Children's Hospital Ljubljana. Blood samples were taken from each participant before the vaccination, 1 month and 6 months after the annual influenza vaccination.

RESULTS: Before the influenza vaccination, 26% of participants were positive for ANA, 16% for aCL, 7% for anti-beta(2)-GPI, 2% for LA and 1% for anti-ENA. There were no statistically significant differences in the percentage of positive ANA, aCL, anti-beta(2)-GPI, LA and anti-ENA before, 1 month and 6 months after the vaccination. One month after the vaccination 24% of participants demonstrated changes in the levels of autoantibodies including 15% of participants with increased level of autoantibodies or appearance of new autoantibodies. Six months after the vaccination 26% of participants demonstrated changes in the levels of autoantibodies including 13% of participants with increased level of autoantibodies or appearance of new autoantibodies. Persistently elevated levels of autoantibodies were observed in 7 (8%) participants and 2 showed progressively increased levels of IgM aCL or IgA anti-beta(2)-GPI, respectively. Eleven participants had a transient increase in autoantibodies.

DISCUSSION: Influenza vaccination in general did not alter the percentage of healthy adults with positive autoantibodies. Transiently or persistently increased levels of autoantibodies or appearance of new autoantibodies was demonstrated in up to 15% of apparently healthy adults after the influenza vaccination.

Lupus. 2009 Nov;18(13):1192-7. PMID:19880567

Ten cases of systemic lupus erythematosus related to hepatitis B vaccine.

Agmon-Levin N[1], Zafrir Y, Paz Z, Shilton T, Zandman-Goddard G, Shoenfeld Y.

1 Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel.

Abstract The objective of this article is to identify common and atypical features of systemic lupus erythematosus diagnosed following hepatitis B vaccination. We analyzed retrospectively the medical records of 10 systemic lupus erythematosus patients from different centers, who developed the disease following hepatitis B vaccination and determined the prevalence of different manifestations and the time association to vaccination. In this case series, 80% of the patients were female, mean age 35 +/- 9 years, of which 20% received one inoculation, 20% received two doses and 60% received all three inoculations. The mean

latency period from the first hepatitis B virus immunization and onset of autoimmune symptoms was 56.3 days. All patients were diagnosed with systemic lupus erythematosus, according to the American College of Rheumatology revised criteria within 1 year. The prevalence of some systemic lupus erythematosus manifestations was typical and included involvement of the joints (100%), skin (80%), muscles (60%) and photosensitivity (30%). Other symptoms differed in this unique group of systemic lupus erythematosus patients such as low rate of kidney and hematologic involvement, and a relatively high rate of hepatitis (20%). Neurological (80%) and pulmonary (70%) symptoms were also common in this group. Data from this case-series, and previously documented cases in the literature could only show a temporal relation between hepatitis B vaccination and the appearance of systemic lupus erythematosus. Systemic lupus erythematosus related to vaccine may differ from idiopathic systemic lupus erythematosus in its clinical presentation and may resemble drug-induced systemic lupus erythematosus. Thus, physicians should be alerted to this potential association, its possible long latency period and unique presentations, and be encouraged to report and analyze these cases.

Kaohsiung J Med Sci. 2006 Jun;22(6):297-300. PMID: 16793568

Subacute thyroiditis following influenza vaccine (Vaxigrip) in a young female.

Hsiao JY[1], Hsin SC, Hsieh MC, Hsia PJ, Shin SJ.

[1]Department of Endocrinology and Metabolism, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan.

Abstract Subacute thyroiditis (SAT), also called de Quervain thyroiditis or granulomatous thyroiditis, is a self-limiting, possibly viral, and inflammatory thyroid disorder that is usually associated with thyroid pain and systemic symptoms. This report details a case of SAT possibly associated with influenza vaccine (Vaxigrip) in a young female. The diagnosis, therapeutic management and outcome are discussed.

Transplantation. 2005 Aug 15;80(3):297-302. PMID: 16082322

Heterogeneous alterations in human alloimmunity associated with Hepatitis B immunization.

Roddy M[1], Clemente M, Poggio ED, Bukowski R, Thakkar S, Waxenecker G, Loibner H, Himmler G, Hricik DE, Heeger PS.

[1]Department of Immunology, The Cleveland Clinic Foundation, Cleveland, OH 44195, USA.

Abstract

BACKGROUND: The presence of alloantibodies and/or alloreactive T cells in a patient prior to a transplant can impact graft outcome. Environmental factors, including therapeutic vaccinations, may influence the strength and/or specificity of alloimmunity.

METHODS: To address this issue, we prospectively evaluated the effects of two different immunization protocols in human subjects on cellular alloimmunity using an IFNgamma ELISPOT assay and on alloantibody reactivity by flow cytometric analysis of HLA-coated beads. All the normal healthy subjects received hepatitis B vaccination.

RESULTS: Vaccination/immunization was associated with augmentation of cellular and/or humoral alloimmune reactivity in >50% of the test subjects. The effects were heterogeneous in that some detected increases were transient, peaking 30-60 days postimmunization, whereas others persisted for the length of the study. Antibodies reactive to the immunizing agent did not cross react with the detected alloantibodies, suggesting that the augmentation of alloimmune reactivity was most likely due to a nonspecific adjuvant effect from the vaccine.

CONCLUSIONS: Therapeutic vaccinations can alter the strength of cellular and humoral alloimmunity in humans. The results suggest that serial immune monitoring of alloreactivity might be beneficial when immunizations are administered to potential transplant recipients.

Autoimmunity. 2005 May;38(3):235-45. PMID: 16126512

Infection, vaccines and other environmental triggers of autoimmunity.

Molina V[1], Shoenfeld Y.

[1]Department of Medicine B and The Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel.

Abstract The etiology of autoimmune diseases is still not clear but genetic, immunological, hormonal and environmental factors are considered to be important triggers. Most often autoimmunity is not followed by clinical symptoms unless an additional event such as an environmental factor favors an overt expression. Many environmental factors are known to affect the immune system and may play a role as triggers of the autoimmune mosaic. Infections: bacterial, viral and parasitic infections are known to induce and exacerbate autoimmune diseases, mainly by the mechanism of molecular mimicry. This was studied for some syndromes as for the association between SLE and EBV infection, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection and more. Vaccines, in several reports were found to be temporally followed by a new onset of autoimmune diseases. The same mechanisms that act in infectious invasion of the host, apply equally to the host response to vaccination. It has been accepted for diphtheria and tetanus toxoid, polio and measles vaccines and GBS. Also, this theory has been accepted for MMR vaccination and development of autoimmune

thrombocytopenia, MS has been associated with HBV vaccination. Occupational and other chemical exposures are considered as triggers for autoimmunity. A debate still exists about the role of silicone implants in induction of scleroderma like disease. Not only foreign chemicals and agents have been associated with induction of autoimmunity, but also an intrinsic hormonal exposure, such as estrogens. This might explain the sexual dimorphism in autoimmunity. Better understanding of these environmental risk factors will likely lead to explanation of the mechanisms of onset and progression of autoimmune diseases and may lead to effective preventive involvement in specific high-risk groups. So by diagnosing a new patient with autoimmune disease a wide anamnesis work should be done.

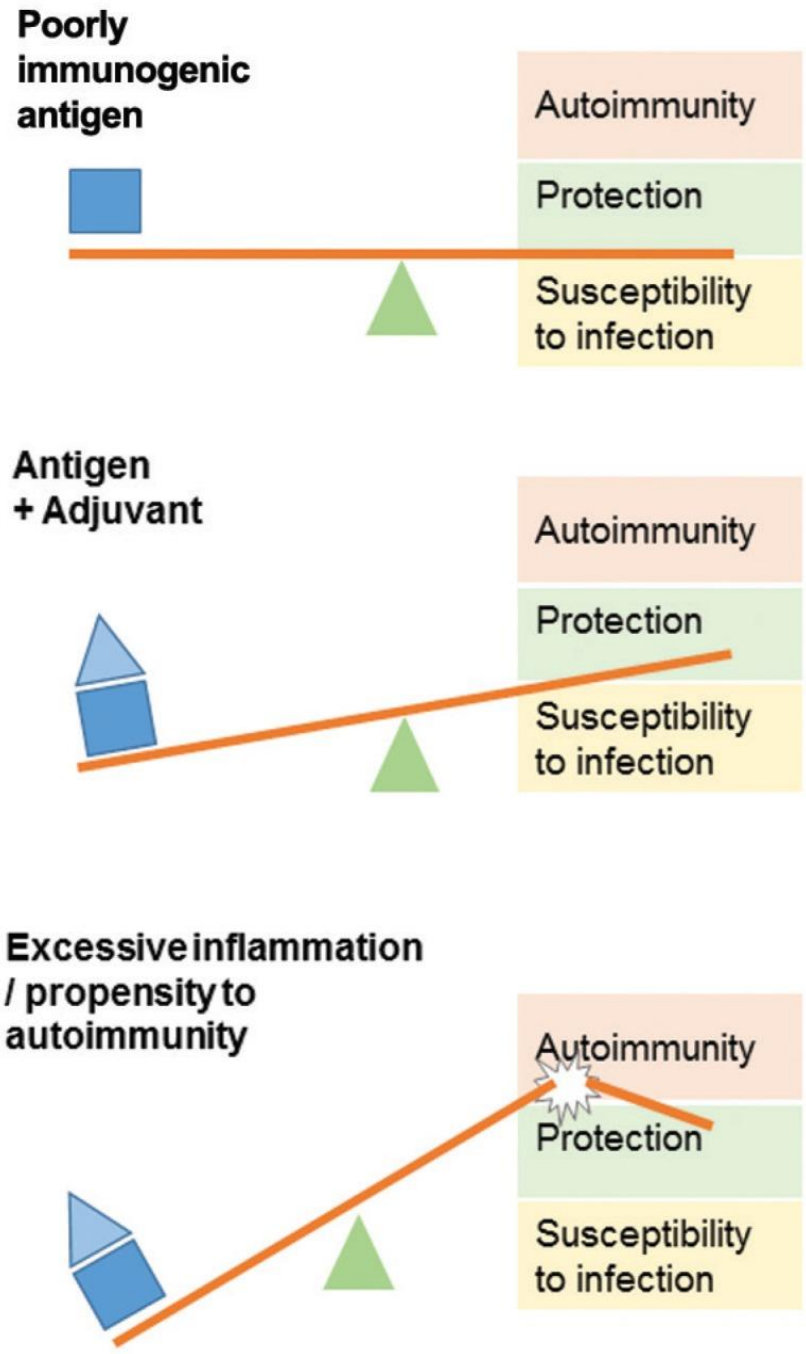

Fig. 2
differences in the response to adjuvants. To overcome the obstacle of low immunogenicity of an antigen, protein-based vaccines often use adjuvants to obtain adequate levels of protection. In individuals with a certain predisposition to the development of autoimmunity, the excessive immune response can trigger autoimmune phenomena.

Discrepancies in the evaluation of the safety of the human papillomavirus vaccine
Mem Inst Oswaldo Cruz. 2018;113(8):e180063.

Adv Vet Med. 1999;41:733-47. PMID:9890057

Vaccine-induced autoimmunity in the dog.

Hogenesch H[1], Azcona-Olivera J, Scott-Moncrieff C, Snyder PW, Glickman LT.
1 Department of Veterinary Pathobiology, Purdue University, West Lafayette, Indiana 47907, USA.

"the most likely sources of cross-reactive epitopes are bovine serum and cell culture components. These are present in almost all vaccines as residual components of the cell culture necessary to generate vaccine viruses and may purposely be added to the vaccine as a stabilizer. In the presence of an adjuvant, these bovine products stimulate a strong immune response and induce antibodies that cross-react with conserved canine antigens."

Comment:

Vinu Arumugham: 27 October 2019

For 20 years, the medical community has known that bovine proteins in adjuvanted vaccines sicken dogs with autoimmunity.

Yet, they sickened millions of humans and continue to sicken millions more with the same animal protein (bovine, chick, porcine) containing adjuvanted vaccines.