

REAZIONI AVVERSE da VACCINO: HPV

[Autoimmun Rev.](#) 2019 Apr;18(4):415-425. doi: 10.1016/j.autrev.2018.12.005. Epub 2019 Feb 14.

Immunoglobuline letali: autoanticorpi e morte cardiaca improvvisa

[Ryabkova VA](#), [Shubik YV](#), [Erman MV](#), [Churilov LP](#), [Kanduc D](#), [Shoenfeld Y](#)

Abstract

La morte cardiaca improvvisa (SCD) è una morte inaspettata a causa di cause cardiache che si verificano in un breve periodo di tempo (generalmente entro 1 ora dall'esordio dei sintomi) in una persona con malattia cardiaca nota o sconosciuta. I pazienti con cardiomiopatie, miocardite, cardiopatia ischemica e canalopatie cardiache sono a rischio di SCD. Tuttavia, una certa percentuale di casi di autopsia-negativi di SCD nei giovani (<35 anni) rimangono inspiegabili anche dopo un test genetico post-mortem. Gli autoanticorpi contro le proteine cardiache possono essere potenzialmente coinvolti nella patogenesi di diverse malattie cardiache e nell'insorgenza di SCD inspiegabile. In questa recensione analizziamo studi clinici e animali che chiariscono la prevalenza di questi autoanticorpi in pazienti con diverse patologie cardiache e la loro rilevanza patofisiologica. Proponiamo una classificazione degli autoanticorpi associati alle malattie cardiache e ci concentriamo sui loro effetti molecolari e cellulari. Gli anticorpi anti-beta del recettore adrenergico e gli anticorpi anti-muscarinici del recettore dell'acetilcolina influenzano le proprietà elettrofisiologiche del miocardio e sono stati segnalati come i predittori indipendenti di SCD in pazienti con diverse patologie cardiache. Il meccanismo autoimmune è proposto per le reazioni avverse correlate al cuore in seguito alla vaccinazione del papillomavirus umano (HPV). La condivisione di pentapeptidi tra antigeni di HPV, recettori adrenergici e recettori muscarinici di acetilcolina supporta questa ipotesi. Gli effetti disregolanti degli autoanticorpi contro i canali ionici di calcio e potassio possono essere la base per le fenocope autoimmuni delle canalopatie genetiche cardiache, che sono anche associate a SCD.

[Drug Saf.](#) 2017 Dec;40(12):1219-1229. doi: 10.1007/s40264-017-0574-6.

Sospetti effetti avversi dopo la vaccinazione contro il papillomavirus umano: una relazione temporale tra la somministrazione di vaccino e l'aspetto dei sintomi in Giappone

[Ozawa K](#), [Hineno A](#), [Kinoshita T](#), [Ishihara S](#), [Ikeda SI](#).

Abstract

INTRODUZIONE: In Giappone, dopo aver ricevuto la vaccinazione contro il papillomavirus umano, un numero significativo di adolescenti ha accusato vari sintomi, la maggior parte dei quali è stata ascritta alla sindrome da dolore cronico regionale, intolleranza ortostatica e / o disfunzione cognitiva. Tuttavia, non è stato stabilito un nesso causale tra la vaccinazione contro il papillomavirus umano e lo sviluppo di questi sintomi.

OBIETTIVO: Lo scopo di questo studio era di chiarire la relazione temporale tra la vaccinazione del papillomavirus umano e la comparsa dei sintomi post-vaccinazione.

METODI: Tra giugno 2013 e dicembre 2016, abbiamo esaminato i sintomi e i risultati obiettivi in 163 pazienti di sesso femminile che avevano ricevuto la vaccinazione contro il papillomavirus umano. Abbiamo utilizzato criteri diagnostici appena definiti per l'inclusione accurata dei pazienti che hanno manifestato sintomi avversi dopo la vaccinazione contro il papillomavirus umano; questi criteri diagnostici sono stati creati per questo studio e quindi la loro validità e affidabilità non sono state stabilite.

RISULTATI: Complessivamente sono state escluse 43 donne. Tra i rimanenti 120 pazienti, 30 sono stati diagnosticati con sintomi definiti correlati al vaccino e 42 sono stati diagnosticati come

probabili. Tra questi 72 pazienti, l'età alla vaccinazione iniziale variava da 11 a 19 anni (in media $13,6 \pm 1,6$ anni) e l'età alla comparsa dei sintomi variava da 12 a 20 anni (in media $14,4 \pm 1,7$ anni). I pazienti hanno ricevuto l'iniezione iniziale di vaccino da papillomavirus umano tra maggio 2010 e aprile 2013. La prima ragazza affetta ha sviluppato sintomi nell'ottobre 2010 e le ultime due ragazze affette hanno sviluppato sintomi nell'ottobre 2015. Il tempo di insorgenza dopo il primo vaccinedosio variava da 1 a 1532 giorni (media $319,7 \pm 349,3$ giorni).

CONCLUSIONI: Il periodo di vaccinazione contro il papillomavirus umano si è notevolmente sovrapposto a quello dello sviluppo di sintomi unici dopo la vaccinazione. Sulla base di questi eventi sequenziali, si suggerisce che la vaccinazione del papillomavirus umano sia correlata alla prevalenza transitoriamente elevata dei sintomi precedentemente menzionati, tra cui la sindrome del dolore cronico regionale e le disfunzioni neurologiche e cognitive nei pazienti vaccinati.

[Indian J Med Ethics](#). 2017 Apr-Jun;2(2):82-88.

Lezioni apprese in Giappone dalle reazioni avverse al vaccino HPV: una prospettiva di etica medica

[Beppu H](#), [Minaguchi M](#), [Uchide K](#), [Kumamoto K](#), [Sekiguchi M](#), [Yaju Y](#)

Abstract

Il vaccino contro il papillomavirus umano (HPV) è stato associato a una serie di reazioni avverse gravi. La gamma dei sintomi è diversificata e si sviluppano in modo multistrato per un lungo periodo di tempo. L'argomentazione per la sicurezza e l'efficacia del vaccino contro l'HPV presenta i seguenti difetti: (i) non viene presa in considerazione la base genetica delle malattie autoimmuni e gli argomenti che non tengono conto di ciò non possono assicurare la sicurezza del vaccino; (ii) i meccanismi di evasione immunitaria dell'HPV, che richiedono che il vaccino HPV mantenga un livello anticorpale straordinariamente alto per un lungo periodo di tempo affinché sia efficace, non sono presi in considerazione; e (iii) i limiti di efficacia del vaccino. Discutiamo anche di varie questioni emerse nel corso dello sviluppo, della promozione e della distribuzione del vaccino, nonché delle insidie riscontrate nel monitoraggio degli eventi avversi e nella verifica epidemiologica.

[Autoimmun Rev](#). 2016 Nov;15(11):1054-1061. doi: 10.1016/j.autrev.2016.07.030. Epub 2016 Aug 1.

Dall'HBV all'HPV: progettazione di vaccini per vaste e intensive campagne di vaccinazione in tutto il mondo

[Kanduc D](#), [Shoenfeld Y](#)

Abstract

Proteine HBsAg e HPV L1 - gli antigeni HBV e HPV utilizzati negli attuali vaccini - condividono sequenze amminoacidiche con proteine umane come la proteina 5 associata a cardiomiopatia, titinica, proteina-arginina deiminasi, proteina ubiquitina-ligasi E3 RNF19A, fagotto, proteina G recettore accoppiato per acidi grassi, isoforma dell'insulina 2 e chinasi della chinasi della chinasi proteica mitogenata 10, tra l'altro. Molti peptidi condivisi fanno anche parte di epitopi immunopositivi. I dati 1) supportano la possibilità di reazioni crociate tra i due antigeni virali e le proteine umane che, quando alterate, possono associarsi a malattie neuropsichiatriche, cardiovascolari e metaboliche quali sclerosi multipla, sclerosi laterale amiotrofica, diabete e morte improvvisa; 2) confermare il concetto che solo i vaccini basati su sequenze uniche per i patogeni potrebbero annullare potenziali rischi di crossreattività nei protocolli di vaccinazione.

[Immunol Res](#). 2017 Feb;65(1):106-116. doi: 10.1007/s12026-016-8820-z.

Sindrome somatoforme grave e sindromi disautonomiche dopo vaccinazione HPV: serie di casi e revisione della letteratura

[Palmieri B](#), [Poddighe D](#), [Vadalà M](#), [Laurino C](#), [Carnovale C](#), [Clementi E](#)

Erratum in

[Erratum to: Severe somatoform and dysautonomic syndromes after HPV vaccination: case series and review of literature.](#) [Immunol Res. 2017]

Abstract

Il virus del papilloma umano (HPV) è riconosciuto come una delle principali cause di cancro cervicale tra le donne di tutto il mondo. Attualmente sono disponibili due vaccini HPV: Gardasil® e Cervarix®. Entrambi i vaccini racchiudono le proteine antigeniche virali, ma differiscono per quanto riguarda i sistemi biologici di coltura e le componenti adiuvanti. Recentemente, una serie di sintomi, che indicano la disfunzione del sistema nervoso, è stata descritta dopo la vaccinazione contro l'HPV. Abbiamo retrospettivamente descritto una serie di casi di cui 18 ragazze (di età compresa tra 12 e 24 anni) riferite alla nostra "Second Opinion Medical Network" per la valutazione di "neuropatia con disfunzione autonoma" dopo la vaccinazione HPV. Tutte le ragazze si sono lamentate di sintomi somatoformi di lunga durata e invalidanti (inclusi astenia, cefalea, disfunzioni cognitive, mialgia, tachicardia sinusale ed eruzioni cutanee) che si sono sviluppati da 1 a 5 giorni (n = 11), 5-15 giorni (n = 5) e 15-20 giorni (n = 2) dopo la vaccinazione. Questi casi possono essere inclusi nella disfunzione immunitaria descritta di recente denominata sindrome autoimmune / infiammatoria indotta da adiuvanti (ASIA). Il vaccino HPV, attraverso il suo componente adiuvante, è ipotizzato per indurre un'attivazione anormale del sistema immunitario, coinvolgendo anche le cellule glia nel sistema nervoso. Ulteriori ricerche dovrebbero mirare a definire gli aspetti patologici e clinici di queste malattie post-vaccinazione e identificare un background genetico che predisponga a queste reazioni avverse.

[Hum Vaccin Immunother.](#) 2016 Oct 2;12(10):2662-2665. doi: 10.1080/21645515.2016.1192737. Epub 2016 Jun 13.

Adverse events following HPV immunization in Australia: Establishment of a clinical network.

[Crawford NW](#), [Hodgson K](#), [Gold M](#), [Buttery J](#), [Wood N](#); [AEFI-CAN network](#).

Abstract

OBJECTIVE: To formalise a collaborative national Adverse Events Following Immunisation Clinical Assessment Network (AEFI-CAN) following the expansion of the Australian Human Papillomavirus (HPV) immunisation program to boys in 2013.

METHODS: AEFI-CAN linked state-based vaccine safety clinics and the Department of Health including the Therapeutic Goods Administration (TGA). Monthly teleconferences held to discuss HPV related cases. AEFI conditions of interest recorded in a centralised database.

RESULTS: Between 1st January 2013 - 31st October 2014, 118 HPV AEFI were documented, 56% in males. The median age was 13 y (range 12-16 years). The majority of AEFI reports were after dose 1 (59%). 76 of 118 (64%) AEFI were seen in a vaccine safety clinic: 62% in Victoria, NSW (16%), South Australia (9%) and Western Australia (8%). Eight TeleHealth consultations were undertaken. AEFI were categorised as: rash 24% of reports (n = 28), urticaria/angioedema 23% (n = 27), anaphylaxis 3% (n = 4). Syncope was also reported (n = 12, 10%) and other neurological events (n = 22, 19%).

CONCLUSIONS: We demonstrated the advantages of a national network, providing a collaborative approach to AEFI review and management. The vaccine safety network has applicability to any vaccination program, and has potential to collaborate more broadly with regional pharmacovigilance partners such as New Zealand.

[Clin Rheumatol](#). 2015 Jul;34(7):1165-9. doi: 10.1007/s10067-015-2969-z. Epub 2015 May 20.

Hypothesis: Human papillomavirus vaccination syndrome--small fiber neuropathy and dysautonomia could be its underlying pathogenesis.

[Martínez-Lavín M](#)

Abstract

Vaccination has been one of the most effective public health measures in the history of medicine. However, seemingly inexplicit adverse reactions have been described after the injection of the newer vaccines vs. human papillomavirus (HPV). The symptoms more often reported are chronic pain with paresthesias, headaches, fatigue, and orthostatic intolerance. Adverse reactions appear to be more frequent after HPV vaccination when compared to other type of immunizations. Different isolated cases and small series have described the development of complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), and fibromyalgia after HPV vaccination. These are illnesses often difficult to diagnose that have overlapping clinical features. Sympathetic nervous system dysfunction seems to play a major role in the pathogenesis of these syndromes. Also, small fiber neuropathy has been recently recognized in CRPS, POTS, and fibromyalgia. This article forwards the hypothesis that small fiber neuropathy and dysautonomia could be the common underlying pathogenesis to the group of rare, but severe reactions that follow HPV vaccination. Clinicians should be aware of the possible association between HPV vaccination and the development of these difficult to diagnose painful dysautonomic

[Pediatr Dermatol](#). 2015 Mar-Apr;32(2):e48-9. doi: 10.1111/pde.12516. Epub 2015 Feb 18.

Eruzione di droga lichenoidale dopo vaccinazione con papillomavirus umano

[Laschinger ME](#)¹, [Schleichert RA](#), [Green B](#).

Abstract

Le reazioni ai farmaci lichenoidali sono state collegate a un lungo e crescente elenco di farmaci, la maggior parte dei quali sono utilizzati principalmente negli adulti, rendendo queste reazioni estremamente rare nei bambini. Per quanto a nostra conoscenza, questo case report è il primo di una eruzione di un farmaco lichenoidale in un bambino dopo la vaccinazione contro il papillomavirus umano.

[Curr Drug Saf](#). 2014 Mar;9(1):65-8.

Human papilloma virus vaccine associated uveitis.

[Holt HD](#), [Hinkle DM](#), [Falk NS](#), [Fraunfelder FT](#), [Fraunfelder FW](#)

Abstract

PURPOSE: To report a possible association between human papilloma virus (HPV) vaccination and uveitis.

METHODS: Spontaneous reports from the National Registry of Drug-Induced Ocular Side effects, World Health Organization and Food and Drug Administration were collected on uveitis associated with human papilloma virus vaccination. A MEDLINE search was performed using keywords "uveitis," "iritis," "iridocyclitis," "human papilloma virus," "Cervarix", and "Gardasil."

MAIN OUTCOME MEASURES: Data garnered from spontaneous reports included the age, gender, adverse drug reaction (ADR), date of administration, concomitant administration of other vaccinations, time until onset of ADR, other systemic reactions, and dechallenge and rechallenge data.

RESULTS: A total of 24 case reports of uveitis associated with human papilloma virus vaccination were identified, all cases were female, and the median age was 17. Median time from HPV vaccination to reported ADR was 30 days (range 0-476 days).

DISCUSSION: According to World Health Organization criteria, the relationship between human papilloma virus vaccination and uveitis is "possible." Causality assessments are based on the time relationship of drug administration, uveitis development and re-challenge data.

CONCLUSIONS: Clinicians should be aware of a possible bilateral uveitis and papillitis following HPV vaccination.

[BMJ Case Rep.](#) 2012 May 8;2012. pii: bcr0220125797. doi: 10.1136/bcr.02.2012.5797.

Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80.

[Badiu I](#), [Geuna M](#), [Heffler E](#), [Rolla G](#)

Abstract

A 17-year-old girl reported generalised urticaria, eyelid angioedema, rhino-conjunctivitis, dyspnoea and wheezing 1 h after third intramuscular administration of quadrivalent human papilloma virus vaccine (Gardasil). She was treated with antihistamine, and corticosteroids with prompt relief of rhinitis and dyspnoea, while urticaria and angioedema lasted 24 h. Intradermal test with Gardasil, which contains polysorbate 80 (PS80), resulted positive, while skin tests with the bivalent vaccine were negative. Prick test performed with PS80 resulted positive in the patient and negative in ten healthy controls. The CD203 basophil activation test result was negative for PS80 at all the tested dilutions and specific IgE was not found. As flu vaccine was recommended, the authors skin tested two flu vaccine, one containing PS80 (Fluarix, GSK), which resulted positive and another flu vaccine with no adjuvant or preservative (Vaxigrip, Sanofi Pasteur MSD), which gave negative results. The patient then received Vaxigrip without adverse reactions.

[Dermatology.](#) 2010;221(3):197-200. doi: 10.1159/000319852.

The quadrivalent human papillomavirus vaccine: erythema multiforme and cutaneous side effects after administration.

[Pérez-Carmona L](#), [Aquayo-Leiva I](#), [González-García C](#), [Jaén-Olasolo P](#).

Abstract

The quadrivalent human papillomavirus (qHPV) vaccine, the first vaccine for use in the prevention of cervical cancer and condyloma acuminatum, was approved in June 2006. In 2008, the mass media reported suspected links between the qHPV vaccine and serious adverse events; however, several studies have found that the vaccine is safe and the main adverse events are mild local reactions. Erythema multiforme (EM) is an acute self-limited cutaneous or mucocutaneous syndrome characterized by the abrupt onset of symmetric target lesions. The clinical manifestations and histological features of EM, Stevens-Johnson syndrome and toxic epidermal necrolysis show considerable overlap, and they are classically considered to represent a spectrum of skin disorders. We present a case of EM following qHPV vaccination to review the cutaneous side effects of this vaccine and the possibility of more serious side effects with the administration of booster doses.

[BMJ.](#) 2008 Dec 2;337:a2642. doi: 10.1136/bmj.a2642.

Hypersensitivity reactions to human papillomavirus vaccine in Australian schoolgirls: retrospective cohort study.

[Kang LW](#), [Crawford N](#), [Tang ML](#), [Buttery J](#), [Royle J](#), [Gold M](#), [Ziegler C](#), [Quinn P](#), [Elia S](#), [Choo S](#).

Abstract

OBJECTIVE: To describe the outcomes of clinical evaluation, skin testing, and vaccine challenge in adolescent schoolgirls with suspected hypersensitivity to the quadrivalent human papillomavirus vaccine introduced in Australian schools in 2007.

DESIGN: Retrospective cohort study.

SETTING: Two tertiary paediatric allergy centres in Victoria and South Australia, Australia.

PARTICIPANTS: 35 schoolgirls aged 12 to 18.9 years with suspected hypersensitivity reactions to the quadrivalent human papillomavirus vaccine.

MAIN OUTCOME MEASURES: Clinical review and skin prick and intradermal testing with the quadrivalent vaccine and subsequent challenge with the vaccine.

RESULTS: 35 schoolgirls with suspected hypersensitivity to the quadrivalent human papillomavirus vaccine were notified to the specialised immunisation services in 2007, after more than 380 000 doses had been administered in schools. Of these 35 schoolgirls, 25 agreed to further evaluation. Twenty three (92%) experienced reactions after the first dose. Thirteen (52%) experienced urticaria or angio-oedema, and of these, two experienced anaphylaxis. Thirteen had generalised rash, one with angio-oedema. The median time to reaction was 90 minutes. Nineteen (76%) underwent skin testing with the quadrivalent vaccine: all were skin prick test negative and one was intradermal test positive. Eighteen (72%) were subsequently challenged with the quadrivalent vaccine and three (12%) elected to receive the bivalent vaccine. Seventeen tolerated the challenge and one reported limited urticaria four hours after the vaccine had been administered. Only three of the 25 schoolgirls were found to have probable hypersensitivity to the quadrivalent vaccine.

CONCLUSION: True hypersensitivity to the quadrivalent human papillomavirus vaccine in Australian schoolgirls was uncommon and most tolerated subsequent doses.

[SAGE Open Med.](#) 2019 Jan 8;7:2050312118822650. doi: 10.1177/2050312118822650. eCollection 2019.

A cross-sectional study of the relationship between reported human papillomavirus vaccine exposure and the incidence of reported asthma in the United States.

[Geier DA](#), [Kern JK](#), [Geier MR](#)

Abstract

OBJECTIVES: Asthma is a chronic disorder that affects persons of all ages impacting the quality of their lives. This cross-sectional hypothesis-testing study evaluated the relationship between human papillomavirus vaccine and the risk of an incident asthma diagnosis in a defined temporal period post-vaccination.

METHODS: The 2015-2016 National Health and Nutrition Examination Survey data were examined for a group of 60,934,237 weighted persons between 9 and 26 years old in Statistical Analysis Software.

RESULTS: Reported incident asthma significantly clustered in the year of reported human papillomavirus vaccination. When the data were separated by gender, the effects observed remained significant for males but not females.

CONCLUSION: The results suggest that human papillomavirus vaccination resulted in an excess of 261,475 asthma cases with an estimated direct excess lifetime cost of such persons being US\$42 billion. However, it is unclear what part of the vaccine and/or vaccine medium may have increased an individual's susceptibility to an asthma episode, whether the asthma diagnosis represented one asthma episode or if it is chronic, and how much therapeutic support was needed (if any) and for how long, which would impact cost. Despite the negative findings in this study, routine vaccination is an important public health tool, and the results observed need to be viewed in this context.

[BMC Neurol.](#) 2018 Dec 28;18(1):222. doi: 10.1186/s12883-018-1233-y.

Myasthenia gravis following human papillomavirus vaccination: a case report.

[Chung JY](#), [Lee SJ](#), [Shin BS](#), [Kang HG](#)

Abstract

BACKGROUND: Myasthenia gravis (MG), an autoimmune neuromuscular disorder, occurs owing to autoantibodies against acetylcholine receptors. MG symptoms can be triggered by various vaccines. Many studies have evaluated the safety and adverse events of the human papillomavirus (HPV) vaccine. Here, we present a life-threatening case of ocular and bulbar MG symptoms after HPV vaccination and a brief literature review.

CASE PRESENTATION: A 23-year-old woman presented with binocular diplopia, ptosis, dysarthria, and dysphagia, which occurred on the 3rd day after the second HPV vaccine administration. She was diagnosed with MG based on history, clinical features, and test results. Her symptoms deteriorated on the 3rd day after admission, and she was transferred to the intensive care unit with mechanical ventilation. On the 7th day after admission, due to discomfort in the right chest, pulmonary embolism was suspected. A tracheostomy was performed on the 14th day of mechanical ventilation. In the 4th week, the tracheostomy tube was removed; all symptoms had completely resolved at discharge. She was followed up for 5 months without recurrence or further treatment.

CONCLUSION: HPV vaccination may cause MG owing to unexpected abnormal autoimmune responses. Additional studies are needed to clarify the possible causal relationship between the HPV vaccine and neurological complications and to evaluate the safety of the vaccine.

[Cureus](#). 2018 Sep 24;10(9):e3352. doi: 10.7759/cureus.3352.

Simultaneous Bilateral Optic Neuritis Following Human Papillomavirus Vaccination in a Young Child.

[Michael NDB](#), [Tuan Jaffar TN](#), [Hussein A](#), [Wan Hitam WH](#)

Abstract

Vaccination-induced optic neuritis is not common. The development of optic neuritis following various vaccinations have been reported, suggesting a possible association between optic neuritis and vaccination. Of those reported cases, influenza vaccines have been the most common. Although rare, those patients who developed optic neuritis following HPV vaccination also presented with other central nervous system (CNS) demyelinating syndromes, especially following a booster dose. We present a rare case of simultaneous isolated bilateral optic neuritis following the first dose of an HPV vaccination in a young child. She received treatment with a systemic corticosteroid that resulted in a good clinical outcome without developing any demyelinating disease.

[mmunol Res](#). 2018 Dec;66(6):744-754. doi: 10.1007/s12026-018-9036-1.

Autonomic dysfunction and HPV immunization: an overview.

[Blitshteyn S](#), [Brinth L](#), [Hendrickson JE](#), [Martinez-Lavin M](#).

Erratum in

[Correction to: Autonomic dysfunction and HPV immunization: an overview. \[Immunol Res. 2018\]](#)

Abstract

This article reviews the case series reported from several countries describing patients with suspected severe side effects to the HPV/vaccines. The described symptom clusters are remarkably similar and include disabling fatigue, headache, widespread pain, fainting, gastrointestinal dysmotility, limb weakness, memory impairment episodes of altered awareness, and abnormal movements. This constellation of symptoms and signs has been labeled with different diagnoses such as complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), small fiber neuropathy (SFN), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), or fibromyalgia. It is known that autoimmunity and autoantibodies

are present in a subset of patients with CRPS, POTS, SFN, ME/CFS, and fibromyalgia. This article proposes that vaccine-triggered, immune-mediated autonomic dysfunction could lead to the development of de novo post-HPV vaccination syndrome possibly in genetically susceptible individuals. Being cognizant that a temporal relationship between vaccination and symptom onset does not necessarily equate to causality, mounting evidence of case series calls for well-designed case-control studies to determine the prevalence and possible causation between these symptom clusters and HPV vaccines. Since personalized medicine is gaining momentum, the use of adversomics and pharmacogenetics may eventually help identify individuals who are predisposed to HPV vaccine adverse events.

[Reumatol Clin.](#) 2018 Jul - Aug;14(4):211-214. doi: 10.1016/j.reuma.2018.01.014. Epub 2018 Mar 13.

HPV vaccination syndrome: A clinical mirage, or a new tragic fibromyalgia model.

[Martínez-Lavín M](#)

Abstract

Independent investigators have described the onset of a chronic painful dysautonomic syndrome soon after human papillomavirus (HPV) vaccination. The veracity of this syndrome is hotly debated. Many of the reported post-HPV vaccination cases fulfill fibromyalgia diagnostic criteria. This article discusses the arguments favoring the existence of a syndrome associated to HPV vaccination. We propose that fibromyalgia dysautonomic-neuropathic model could help in the diagnostic and therapeutic process in those patients in whom the onset of a painful chronic illness began after HPV immunization. On the other hand, if its veracity is corroborated, HPV vaccination syndrome may become a new tragic fibromyalgia model.

[Autoimmun Rev.](#) 2014 Jul;13(7):736-41. doi: 10.1016/j.autrev.2014.01.054. Epub 2014 Jan 24.

On the relationship between human papilloma virus vaccine and autoimmune diseases.

[Pellegrino P](#), [Carnovale C](#), [Pozzi M](#), [Antoniazzi S](#), [Perrone V](#), [Salvati D](#), [Gentili M](#), [Brusadelli T](#), [Clementi E](#), [Radice S](#)

Abstract

The human papilloma virus (HPV) vaccines were introduced to reduce the incidence of cervical cancer. The bivalent vaccine is effective against HPV-16, -18, -31, -33 and -45 while the quadrivalent vaccine is effective against HPV-16, 18, 31, 6 and 11 types. The immunisation, recommended for adolescent females, has led to high vaccine coverage in many countries. Along with the introduction of the HPV vaccines, several cases of onset or exacerbations of autoimmune diseases following the vaccine shot have been reported in the literature and pharmacovigilance databases, triggering concerns about its safety. This vaccination programme, however, has been introduced in a population that is at high risk for the onset of autoimmune diseases, making it difficult to assess the role of HPV vaccine in these cases and no conclusive studies have been reported thus far. We have thus analysed and reviewed comprehensively all case reports and studies dealing with either the onset of an autoimmune disease in vaccinated subject or the safety in patients with autoimmune diseases to define the role of the HPV vaccines in these diseases and hence its safety. A solid evidence of causal relationship was provided in few cases in the examined studies, and the risk vs. benefit of vaccination is still to be solved. The on-going vigilance for the safety of this vaccine remains thus of paramount importance.

[J Investig Med High Impact Case Rep.](#) 2014 Mar 18;2(1):2324709614527812. doi: 10.1177/2324709614527812. eCollection 2014 Jan-Mar.

Postural Orthostatic Tachycardia With Chronic Fatigue After HPV Vaccination as Part of the "Autoimmune/Auto-inflammatory Syndrome Induced by Adjuvants": Case Report and Literature Review.

[Tomljenovic L](#), [Colafrancesco S](#), [Perricone C](#), [Shoenfeld Y](#)

Abstract

We report the case of a 14-year-old girl who developed postural orthostatic tachycardia syndrome (POTS) with chronic fatigue 2 months following Gardasil vaccination. The patient suffered from persistent headaches, dizziness, recurrent syncope, poor motor coordination, weakness, fatigue, myalgias, numbness, tachycardia, dyspnea, visual disturbances, phonophobia, cognitive impairment, insomnia, gastrointestinal disturbances, and a weight loss of 20 pounds. The psychiatric evaluation ruled out the possibility that her symptoms were psychogenic or related to anxiety disorders. Furthermore, the patient tested positive for ANA (1:1280), lupus anticoagulant, and antiphospholipid. On clinical examination she presented livedo reticularis and was diagnosed with Raynaud's syndrome. This case fulfills the criteria for the autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA). Because human papillomavirus vaccination is universally recommended to teenagers and because POTS frequently results in long-term disabilities (as was the case in our patient), a thorough follow-up of patients who present with relevant complaints after vaccination is strongly recommended.

[Front Neurol](#). 2014 Nov 28;5:230. doi: 10.3389/fneur.2014.00230. eCollection 2014.

Caratteristiche cliniche in pazienti con miofascite macrofagica di lunga durata

[Rigolet M](#), [Aouizerate J](#), [Couette M](#), [Ragunathan-Thangarajah N](#), [Aoun-Sebaiti M](#), [Gherardi RK](#), [Cadusseau J](#), [Authier FJ](#)

Abstract

La miofascite macrofagica (MMF) è una condizione emergente caratterizzata da specifiche lesioni muscolari che valutano la persistenza anormale a lungo termine dell'idrossido di alluminio all'interno dei macrofagi nel sito della precedente immunizzazione. I pazienti affetti di solito sono adulti di mezza età, che presentano principalmente artromialgia diffusa, affaticamento cronico e deficit cognitivi marcati, non correlati a dolore, affaticamento o depressione. Le caratteristiche cliniche di solito corrispondono a quelle osservate nella sindrome da affaticamento cronico / encefalomielite mialgica. Le caratteristiche rappresentative della disfunzione cognitiva associata a MMF comprendono la sindrome dysexecutive, la menomazione della memoria visiva e l'estinzione dell'orecchio sinistro al test di ascolto dicotico. La maggior parte dei pazienti soddisfa i criteri per il deterioramento cognitivo lieve non amnesico / disesecutivo, anche se alcuni deficit cognitivi appaiono insolitamente gravi. La disfunzione cognitiva sembra stabile nel tempo, nonostante le marcate fluttuazioni. I potenziali evocati possono mostrare anomalie in linea con il coinvolgimento del sistema nervoso centrale, con un pattern neurofisiologico che suggerisce la demielinizzazione. Perfusione cerebrale SPECT mostra un pattern di diffuse anomalie corticali e sottocorticali, con ipoperfusioni correlate a deficienze cognitive. La combinazione di dolore muscolo-scheletrico, stanchezza cronica e disturbi cognitivi genera disabilità croniche con possibile esclusione sociale. Gli approcci terapeutici classici sono solitamente insoddisfacenti e rendono difficile la cura del paziente.

[Autoimmun Rev](#). 2019 May 4. pii: S1568-9972(19)30109-0. doi: 10.1016/j.autrev.2019.05.006. [Epub ahead of print]

Sindrome da mialgia e stanchezza cronica a seguito di immunizzazione: miofascite macrofagica e studi su animali supportano il legame con la persistenza e la diffusione adiuvante dell'alluminio nel sistema immunitario.

[Gherardi RK](#), [Crépeaux G](#), [Authier FJ](#)

Abstract

Encefalomielite mialgica / Sindrome da affaticamento cronico (ME / CFS) è una malattia invalidante multifattoriale e scarsamente deficitaria. Presentiamo evidenze epidemiologiche, cliniche e sperimentali che la ME / CFS costituisce un importante tipo di effetto avverso dei vaccini, in particolare quelli contenenti adiuvanti di alluminio particellamente degradabili. Le prove sono emerse molto lentamente a causa della molteplicità, mancanza di specificità, esordio ritardato e frequente sottovalutazione medica dei sintomi ME / CFS. È stato supportato da uno studio epidemiologico che ha confrontato i militari vaccinati contro quelli non vaccinati che sono rimasti indifesi durante la seconda guerra del Golfo. I pazienti affetti soffrono di disfunzioni cognitive che colpiscono l'attenzione, la memoria e le connessioni inter-emisferiche, ben correlate a difetti di perfusione cerebrale e associate a un modello stereotipato e caratteristico dell'ipometabolismo del glucosio cerebrale. La biopsia del muscolo deltoide eseguita per indagare sulla mialgia produce tipicamente miofascite macrofagica (MMF), un biomarcatore istologico che valuta la persistenza di lunga data degli agglomerati di alluminio all'interno di cellule immunitarie innate nel sito della precedente immunizzazione. L'MMF è apparentemente legata alla disintossicazione delle particelle minerali alterata dal macchinario xeno / autofagia. Il confronto tra tossicologia di diverse forme di alluminio e diversi tipi di esposizione è fuorviante e inadeguato e piccoli esperimenti sugli animali hanno capovolto il vecchio dogma. Invece di essere rapidamente solubilizzate nello spazio extracellulare, le particelle di alluminio iniettate vengono rapidamente catturate dalle cellule immunitarie e trasportate agli organi distanti e al cervello dove provocano una risposta infiammatoria ed esercitano una neurotossicità selettiva a basse dosi selettive. Osservazioni cliniche ed esperimenti su pecore, un grande animale come gli umani, hanno confermato sia la diffusione sistemica che gli effetti neurotossici degli adiuvanti di alluminio. ME / CFS post-immunizzazione rappresenta la manifestazione principale della "sindrome autoimmune / infiammatoria indotta da adiuvanti" (ASIA).

[J Inorg Biochem.](#) 2012 Dec;117:85-92. doi: 10.1016/j.jinorgbio.2012.08.015. Epub 2012 Aug 30.

Detection of human papillomavirus (HPV) L1 gene DNA possibly bound to particulate aluminum adjuvant in the HPV vaccine Gardasil.

[Lee SH](#)

Abstract

Medical practitioners in nine countries submitted samples of Gardasil (Merck & Co.) to be tested for the presence of human papillomavirus (HPV) DNA because they suspected that residual recombinant HPV DNA left in the vaccine might have been a contributing factor leading to some of the unexplained post-vaccination side effects. A total of 16 packages of Gardasil were received from Australia, Bulgaria, France, India, New Zealand, Poland, Russia, Spain and the United States. A nested polymerase chain reaction (PCR) method using the MY09/MY11 degenerate primers for initial amplification and the GP5/GP6-based nested PCR primers for the second amplification were used to prepare the template for direct automated cycle DNA sequencing of a hypervariable segment of the HPV L1 gene which is used for manufacturing of the HPV L1 capsid protein by a DNA recombinant technology in vaccine production. Detection of HPV DNA and HPV genotyping of all positive samples were finally validated by BLAST (Basic Local Alignment Search Tool) analysis of a 45-60 bases sequence of the computer-generated electropherogram. The results showed that all 16 Gardasil samples, each with a different lot number, contained fragments of HPV-11 DNA, or HPV-18 DNA, or a DNA fragment mixture from both genotypes. The detected HPV DNA was found to be firmly bound to the insoluble, proteinase-resistant fraction, presumably of amorphous aluminumhydroxyphosphate sulfate (AAHS) nanoparticles used as adjuvant. The clinical significance of these residual HPV DNA fragments bound to a particulate mineral-based adjuvant is uncertain after intramuscular injection, and requires further investigation for vaccination safety.

[Curr Med Chem.](#) 2014 Mar;21(7):932-40.

Melting profiles may affect detection of residual HPV L1 gene DNA fragments in Gardasil®.

[Lee SH](#)

Abstract

Gardasil® is a quadrivalent human papillomavirus (HPV) protein-based vaccine containing genotype-specific L1 capsid proteins of HPV-16, HPV-18, HPV-6 and HPV-11 in the form of virus-like-particles (VLPs) as the active ingredient. The VLPs are produced by a DNA recombinant technology. It is uncertain if the residual HPV L1 gene DNA fragments in the vaccine products are considered contaminants or excipients of the Gardasil® vaccine. Because naked viral DNA fragments, if present in the vaccine, may bind to the insoluble amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant which may help deliver the foreign DNA into macrophages, causing unintended pathophysiologic effects, experiments were undertaken to develop tests for HPV L1 gene DNA fragments in the final products of Gardasil® by polymerase chain reaction (PCR) and direct DNA sequencing. The results showed that while the HPV-11 and HPV-18 L1 gene DNA fragments in Gardasil® were readily amplified by the common GP6/MY11 degenerate consensus primers, the HPV-16 L1 gene DNA may need specially designed non-degenerate PCR primers for amplification at different regions of the L1 gene and different stringency conditions for detection. These variable melting profiles of HPV DNA in the insoluble fraction of the Gardasil® vaccine suggest that the HPV DNA fragments are firmly bound to the aluminum AAHS adjuvant. All methods developed for detecting residual HPV DNA in the vaccine Gardasil® for quality assurance must take into consideration the variable melting profiles of the DNA to avoid false negative results.

[J Clin Neuromuscul Dis.](#) 2016 Sep;18(1):37-40. doi: 10.1097/CND.000000000000130.

Small Fiber Neuropathy Following Vaccination.

[Kafaie J](#), [Kim M](#), [Krause E](#).

Abstract

OBJECTIVE: To identify clinical and quantitative relationship between vaccinations and small fiber neuropathy (SFN). SFN refers to damaged unmyelinated or thinly myelinated sensory and/or autonomic fibers. Diagnosis is primarily based on clinical presentation. Intraepidermal nerve fiber density can provide diagnostic confirmation with a sensitivity of 88% and a specificity of 91%. However, the possible association between vaccination and small fiber polyneuropathy is not well defined.

METHODS: Case study.

RESULTS: Fourteen-year-old white adolescent girl presented with intractable generalized pain for 1.5 years. Burning dysesthetic pain began in the lower back and progressed to all extremities 9 days following human papillomavirus vaccination. The pain persisted despite various pain medications. Examination was significant for allodynia of right scapula (T4-T6) and decreased pinprick sensation in feet. MRI Brain with and without contrast, MR Face, Orbit with and without contrast, and MR Cervical, Lumbar spines with and without contrast were all normal. Nerve Conduction Studies/Electromyogram studies were unremarkable, and skin biopsy of the right thigh and foot showed low intraepidermal nerve fiber density with normal sweat gland nerve fiber density.

CONCLUSIONS: This case report describes an acute onset of non-length-dependent SFN potentially related to human papillomavirus vaccine administration. Literature review includes several similar case studies, and various pathological processes have been proposed for vaccine-associated polyneuropathies. Some theories describe immune-mediated hypersensitivity to the solvents/adjuvants and/or invasion of nervous system through a prolonged, less virulent infection. However, the lack requires that evidence must be carefully reviewed.

[Intern Med.](#) 2016;55(21):3181-3184. Epub 2016 Nov 1.

Two Cases of Acute Disseminated Encephalomyelitis Following Vaccination Against Human Papilloma Virus.

[Sekiguchi K](#), [Yasui N](#), [Kowa H](#), [Kanda F](#), [Toda T](#).

Abstract

We herein present two cases of acute disseminated encephalomyelitis (ADEM) following vaccination against human papilloma virus (HPV). Case 1 experienced diplopia and developed an unstable gait 14 days after a second vaccination of Cervarix. Brain magnetic resonance imaging (MRI) showed an isolated small, demyelinating lesion in the pontine tegmentum. Case 2 experienced a fever and limb dysesthesia 16 days after a second vaccination of Gardasil. Brain MRI revealed hyperintense lesion in the pons with slight edema on a T2-weighted image. Both cases resolved completely. It is important to accumulate further data on confirmed cases of ADEM temporally associated with HPV vaccination.

[J Toxicol Environ Health A.](#) 2018;81(14):661-674. doi: 10.1080/15287394.2018.1477640. Epub 2018 Jun 11.

A lowered probability of pregnancy in females in the USA aged 25-29 who received a humanpapillomavirus vaccine injection.

[DeLong G](#)

Abstract

Birth rates in the United States have recently fallen. Birth rates per 1000 females aged 25-29 fell from 118 in 2007 to 105 in 2015. One factor may involve the vaccination against the human papillomavirus (HPV). Shortly after the vaccine was licensed, several reports of recipients experiencing primary ovarian failure emerged. This study analyzed information gathered in National Health and Nutrition Examination Survey, which represented 8 million 25-to-29-year-old women residing in the United States between 2007 and 2014. Approximately 60% of women who did not receive the HPV vaccine had been pregnant at least once, whereas only 35% of women who were exposed to the vaccine had conceived. For married women, 75% who did not receive the shot were found to conceive, while only 50% who received the vaccine had ever been pregnant. Using logistic regression to analyze the data, the probability of having been pregnant was estimated for females who received an HPV vaccine compared with females who did not receive the shot. Results suggest that females who received the HPV shot were less likely to have ever been pregnant than women in the same age group who did not receive the shot. If 100% of females in this study had received the HPV vaccine, data suggest the number of women having ever conceived would have fallen by 2 million. Further study into the influence of HPV vaccine on fertility is thus warranted.

[Clin Pediatr \(Phila\).](#) 2018 May;57(5):603-606. doi: 10.1177/0009922817728701. Epub 2017 Sep 4.

Autoimmunity, Autonomic Neuropathy, and the HPV Vaccination: A Vulnerable Subpopulation.

[Schofield JR](#), [Hendrickson JE](#)

[Clin Rheumatol.](#) 2017 Oct;36(10):2169-2178. doi: 10.1007/s10067-017-3768-5. Epub 2017 Jul 20.

Serious adverse events after HPV vaccination: a critical review of randomized trials and post-marketing case series.

[Martínez-Lavín M](#), [Amezcu-Guerra L](#)

Erratum in

[Erratum to: Serious adverse events after HPV vaccination: a critical review of randomized trials and post-marketing case series.](#) [Clin Rheumatol. 2017]

Abstract

This article critically reviews HPV vaccine serious adverse events described in pre-licensure randomized trials and in post-marketing case series. HPV vaccine randomized trials were identified in PubMed. Safety data were extracted. Post-marketing case series describing HPV immunization adverse events were reviewed. Most HPV vaccine randomized trials did not use inert placebo in the control group. Two of the largest randomized trials found significantly more severe adverse events in the tested HPV vaccine arm of the study. Compared to 2871 women receiving aluminum placebo, the group of 2881 women injected with the bivalent HPV vaccine had more deaths on follow-up (14 vs. 3, $p = 0.012$). Compared to 7078 girls injected with the 4-valent HPV vaccine, 7071 girls receiving the 9-valent dose had more serious systemic adverse events (3.3 vs. 2.6%, $p = 0.01$). For the 9-valent dose, our calculated number needed to seriously harm is 140 (95% CI, 79–653) [DOSAGE ERROR CORRECTED]. The number needed to vaccinate is 1757 (95% CI, 131 to infinity). Practically, none of the serious adverse events occurring in any arm of both studies were judged to be vaccine-related. Pre-clinical trials, post-marketing case series, and the global drug adverse reaction database (VigiBase) describe similar post-HPV immunization symptom clusters. Two of the largest randomized HPV vaccine trials unveiled more severe adverse events in the tested HPV vaccine arm of the study. Nine-valent HPV vaccine has a worrisome number needed to vaccinate/number needed to harm quotient. Pre-clinical trials and post-marketing case series describe similar post-HPV immunization symptoms.

[J Investig Med High Impact Case Rep.](#) 2014 Oct 28;2(4):2324709614556129. doi: 10.1177/2324709614556129. eCollection 2014 Oct-Dec.

Adolescent Premature Ovarian Insufficiency Following Human Papillomavirus Vaccination: A Case Series Seen in General Practice.

[Little DT](#), [Ward HR](#)

Abstract

Three young women who developed premature ovarian insufficiency following quadrivalent human papillomavirus (HPV) vaccination presented to a general practitioner in rural New South Wales, Australia. The unrelated girls were aged 16, 16, and 18 years at diagnosis. Each had received HPV vaccinations prior to the onset of ovarian decline. Vaccinations had been administered in different regions of the state of New South Wales and the 3 girls lived in different towns in that state. Each had been prescribed the oral contraceptive pill to treat menstrual cycle abnormalities prior to investigation and diagnosis. Vaccine research does not present an ovary histology report of tested rats but does present a testicular histology report. Enduring ovarian capacity and duration of function following vaccination is unresearched in preclinical studies, clinical and postlicensure studies. Postmarketing surveillance does not accurately represent diagnoses in adverse event notifications and can neither represent unnotified cases nor compare incident statistics with vaccine course administration rates. The potential significance of a case series of adolescents with idiopathic premature ovarian insufficiency following HPV vaccination presenting to a general practice warrants further research. Preservation of reproductive health is a primary concern in the recipient target group. Since this group includes all prepubertal and pubertal young women, demonstration of ongoing, uncompromised safety for the ovary is urgently required. This matter needs to be resolved for the purposes of population health and public vaccine confidence.

[BMJ Case Rep.](#) 2012 Sep 30;2012. pii: bcr2012006879. doi: 10.1136/bcr-2012-006879.

Premature ovarian failure 3 years after menarche in a 16-year-old girl following human papillomavirus vaccination.

[Little DT](#), [Ward HR](#).

Abstract

Premature ovarian failure in a well adolescent is a rare event. Its occurrence raises important questions about causation, which may signal other systemic concerns. This patient presented with amenorrhoea after identifying a change from her regular cycle to irregular and scant periods following vaccinations against human papillomavirus. She declined the oral contraceptives initially prescribed for amenorrhoea. The diagnostic tasks were to determine the reason for her secondary amenorrhoea and then to investigate for possible causes of the premature ovarian failure identified. Although the cause is unknown in 90% of cases, the remaining chief identifiable causes of this condition were excluded. Premature ovarian failure was then notified as a possible adverse event following this vaccination. The young woman was counselled regarding preservation of bone density, reproductive implications and relevant follow-up. This event could hold potential implications for population health and prompts further inquiry.

[Am J Reprod Immunol.](#) 2013 Oct;70(4):309-16. doi: 10.1111/aji.12151. Epub 2013 Jul 31.

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

[Colafrancesco S](#), [Perricone C](#), [Tomljenovic L](#), [Shoenfeld Y](#).

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.

[Curr Opin Obstet Gynecol.](#) 2015 Aug;27(4):265-70. doi: 10.1097/GCO.000000000000183.

A link between human papilloma virus vaccination and primary ovarian insufficiency: current analysis.

[Gruber N](#), [Shoenfeld Y](#)

Abstract

PURPOSE OF REVIEW: The cause of primary ovarian insufficiency (POI) is multifactorial. Known causes include external factors such as chemotherapy, radiotherapy, exposure to endocrine-disrupting chemicals, infections that lead to a permanent insult to the ovary, autoimmune conditions, and genetic causes. An association between the quadrivalent antihuman papilloma vaccine (HPV4) and POI was recently suggested.

RECENT FINDINGS: An increasing number of cases of POI post-HPV4 are being reported. Possible mechanisms for the suspected effect of HPV on female reproductive function are a toxic effect or an autoimmune response. The trigger could be the vaccine immunogen contents or the adjuvants, the latter are used to increase the immune reaction. The adjuvant in HPV4 contains aluminum. Animal models have shown aluminum exposure to inhibit expression of female reproductive hormones and to induce histologic changes in the ovaries. Specific genetic compositions may be more susceptible to developing an autoinflammatory syndrome after exposure to an environmental factor.

SUMMARY: The mechanisms responsible for POI are not yet fully understood. Although case reports cannot establish causation, awareness of a possible link between HPV4 and POI will help to identify and manage future cases that may arise.

[Expert Opin Drug Saf.](#) 2015;14(9):1387-94. doi: 10.1517/14740338.2015.1073710. Epub 2015 Jul 28.

The safety of human papilloma virus-blockers and the risk of triggering autoimmune diseases.

[Baker B](#), [Eça Guimarães L](#), [Tomljenovic L](#), [Agmon-Levin N](#), [Shoenfeld Y](#).

Abstract

INTRODUCTION: With the safety of human papilloma virus vaccine (HPVv) being questioned, this article aims to assess the risks and benefits of the commercially available HPVv. Within the last decade, two vaccines (Gardasil and Cervarix) have been put on the market to prevent infection with the most oncogenic HPV subtypes. Both vaccines contain aluminum adjuvants that are meant to cause a hyper stimulated immune response to prevent HPV infection.

AREAS COVERED: The purpose of this paper is to consider the safety of these two vaccines based on the data from the U.S. VaccineAdverse Event Reporting System (VAERS) and case reports.

EXPERT OPINION: The current HPVv are both effective and generally safe. However, it should be noted that autoimmune side effects have been reported in several studies. Further research should be done to understand the relationship between HPVv and autoimmunity.

[Vaccine.](#) 2017 Aug 24;35(36):4761-4768. doi: 10.1016/j.vaccine.2017.06.030. Epub 2017 Jul 24.

Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study of over 2million young girls in France.

[Miranda S](#), [Chaignot C](#), [Collin C](#), [Dray-Spira R](#)¹, [Weill A](#), [Zureik M](#)

Abstract

BACKGROUND: Whether human papillomavirus (HPV) vaccination could induce or trigger autoimmune diseases (AID) has been questioned, and potentially contributes to low

immunization coverage in France. This study evaluated the association between HPV vaccination and the risk of AID using routinely collected data sources.

METHODS: All girls aged 13-16 years between 2008 and 2012, covered by the general health insurance scheme and without history of HPV vaccination or AID, were included and followed using French nationwide databases. Fourteen neurological, rheumatological, haematological, gastrointestinal or endocrine AID, were identified from ICD-10 codes allocated to hospital stays and long-term illnesses or by marker drugs. Their incidence was compared between girls exposed and non-exposed to HPV vaccination, using a Cox model adjusted for inclusion year, geographic area, socio-economic indicators, healthcare use level and other immunizations.

RESULTS: Among 2,252,716 girls, 37% received HPV vaccine and 4,096 AID occurred during a mean follow-up time of 33 months. The incidence of AID was not increased after exposure to HPV vaccination, except for Guillain-Barré syndrome (GBS) (incidence rate of 1.4 among exposed [20 cases] versus 0.4 per 100,000 PY among unexposed [23 cases]; adjusted HR: 3.78 [1.79-7.98]). This association persisted across numerous sensitivity analyses and was particularly marked in the first months following vaccination. Under the hypothesis of a causal relationship, this would result in 1-2 GBS cases attributable to HPV vaccine per 100,000 girls vaccinated.

CONCLUSIONS: Our study provides reassuring results regarding the risk of AID after HPV vaccination, but an apparently increased risk of GBS was detected. Further studies are warranted to confirm this finding.

[Pharmaceut Reg Affairs](#) S12:001. doi: 10.4172/2167-7689.S12-001

Death after Quadrivalent Human Papillomavirus (HPV) Vaccination: Causal or Coincidental?

Tomljenovic L, Shaw CA (2012)

The proper understanding of a true risk from vaccines is crucial for avoiding unnecessary adverse reactions (ADRs). However, to this date no solid tests or criteria have been established to determine whether adverse events are causally linked to vaccinations. Objectives: This research was carried out to determine whether or not some serious autoimmune and neurological ADRs following HPV vaccination are causal or merely coincidental and to validate a biomarker-based immunohistochemical (IHC) protocol for assessing causality in case of vaccination-suspected serious adverse neurological outcomes. Methods: Post-mortem brain tissue specimens from two young women who suffered from cerebral vasculitis-type symptoms following vaccination with the HPV vaccine Gardasil were analysed by IHC for various immunoinflammatory markers. Brain sections were also stained for antibodies recognizing HPV-16L1 and HPV-18L1 antigen which are present in Gardasil. Results: In both cases, the autopsy revealed no anatomical, microbiological nor toxicological findings that might have explained the death of the individuals. In contrast, our IHC analysis showed evidence of an autoimmune vasculitis potentially triggered by the cross-reactive HPV-16L1 antibodies binding to the wall of cerebral blood vessels in all examined brain samples. We also detected the presence of HPV-16L1 particles within the cerebral vasculature with some HPV-16L1 particles adhering to the blood vessel walls. HPV-18L1 antibodies did not bind to cerebral blood vessels nor any other neural tissues. IHC also showed increased T-cell signalling and marked activation of the classical antibody-dependent complement pathway in cerebral vascular tissues from both cases. This pattern of complement activation in the absence of an active brain infection indicates an abnormal triggering of the immune response in which the immune attack is directed towards self-tissue. Conclusions: Our study suggests that HPV vaccines containing HPV-16L1 antigens pose an inherent risk for triggering potentially fatal autoimmune vasculopathies. Practice implications: Cerebral vasculitis is a serious disease which typically results in fatal outcomes when undiagnosed and left untreated. The fact that many of the symptoms reported to vaccine safety surveillance databases following HPV vaccination are indicative of cerebral vasculitis, but are unrecognized as such (i.e., intense persistent migraines, syncope, seizures, tremors and tingling, myalgia, locomotor abnormalities, psychotic symptoms and cognitive

deficits), is a serious concern in light of the present findings. It thus appears that in some cases vaccination may be the triggering factor of fatal autoimmune/neurological events. Physicians should be aware of this association.

[Int J Pub Health Safe 3: 163. \(2018\)](#)

Vaccines and Neuroinflammation

Giannotta G, Giannotta N

Abstract Background: Post-vaccination adverse reactions (AEs) are a reason of strong debate among scientists. Unfortunately, we often make the mistake of discussing just the epidemiology but not the molecular biology. The action mechanism of the vaccines is still not fully known despite the fact that aluminum adjuvants have been used for about 100 years. **Hypothesis:** We hypothesized a link between vaccinations and neuroinflammation. The peripheral proinflammatory cytokines (IL-1 β , IL-6, and TNF- α), expressed after the injection of the vaccines can reach the brain and can cause neuroinflammation after microglia activation. Elevated pro-inflammatory cytokines, particularly TNF- α , have been described in studies regarding the cytokines profile in autistic children. IL-1 β represents a cytokine that controls the local pro-inflammatory cascade and thereby affects the balance between protective immunity and destructive inflammation. A subgroup of children with ASD (Autism Spectrum Disorder) has developed neuroinflammation. Several postmortem studies have confirmed the activation of microglia and neuroinflammation. A recent study has shown the presence of aluminum in the brain of individuals with autism and this aluminum was also found in microglia cells. Aluminum from vaccines is redistributed to numerous organs, including brain, where it accumulates. Each vaccine adds to this tissue different level of aluminum. Aluminum, like mercury, activates microglia leading to chronic brain inflammation and neurotoxicity. **Conclusion:** The molecular mechanisms presented here demonstrate how peripheral cytokines, expressed after vaccination, can cause neuroinflammation in some subjects, after microglia activation, depending on the immunogenetic background and the innate immune memory.

[Clin Case Rep Rev](#), 2019 doi: 10.15761/CCRR.1000454 Volume 5: 1-12

Post-vaccination inflammatory syndrome: a new syndrome

Giannotta G1 * and Giannotta N2

Abstract

Background: The relationship between vaccines and neuroinflammation have consistent molecular biology bases. In a recent paper we have already analyzed this kind of relationship.

Hypothesis: In this paper, we have gained additional evidence to support the link between vaccines and neuroinflammation. Furthermore, we found the molecular bases that support the link between HPV vaccines and certain adverse events (AEs). The peripheral proinflammatory cytokines (IL-1 β , IL-6, and TNF- α), expressed after the injection of the vaccines can reach the brain and can cause neuroinflammation after microglia activation. After vaccine injection significant systemic immune activation may occur with signs suggesting reactive brain inflammation, such as acute crying, fever, restlessness and failure to eat. It is a warning of danger to the brain in front of which we should reflect before causing irreversible damage. We also hypothesized the existence of a post-vaccination inflammatory syndrome caused by the proinflammatory cytokines strongly expressed after HPV vaccine injections. In addition, the molecular explanation of the chronic pain that has affected many girls in the world, including the complex regional pain syndrome (CRPS) in Japanese girls.

Conclusion: All vaccines can cause neuroinflammation. HPV vaccines can cause a post-vaccination inflammatory syndrome characterized by chronic pain and neuroinflammation. In this case, the phenomena of central sensitization is responsible for all the symptoms associated with chronic pain. The strong expression of proinflammatory cytokines, secreted

after HPV vaccinations, brings to process that can produce irreversible neurological results in HPV vaccinated girls.

Tratto da: <https://www.corvelva.it/it/approfondimenti/pubblicazioni/reazioni-avverse-da-vaccino-hpv.html?fbclid=IwAR251Kc8VtHApfydPP8KcGKY5MNUqzG3bcxAmaEL5kZrSAj-GUKvPVg5SVA>