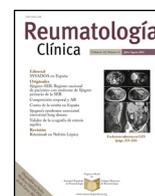




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Review Article

HPV Vaccination Syndrome: A Clinical Mirage, or a New Tragic Fibromyalgia Model[☆]

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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 fulfil 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.

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Síndrome posvacunal VPH. ¿Un espejismo clínico, o un nuevo modelo trágico de fibromialgia?

RESUMEN

Investigadores independientes han descrito la emergencia de un síndrome doloroso-disautonómico crónico enseguida de la vacunación contra el virus del papiloma humano (VPH). La veracidad de este síndrome es objeto de un encendido debate. Muchos de los casos reportados cumplen los criterios diagnósticos de fibromialgia.

Este artículo discute los argumentos a favor de la existencia de este nuevo síndrome. Propone que el modelo neuropático-disautonómico de la fibromialgia podría ayudar en el proceso diagnóstico y terapéutico de los casos que presentan un padecimiento doloroso crónico después de haber sido inmunizados frente al VPH. Por otro lado, de corroborarse su veracidad, el síndrome posvacunal VPH se erigiría como un nuevo modelo trágico e indeseado de fibromialgia.

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Palabras clave:

Vacuna del papiloma

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Neuropatía de fibras pequeñas

Disautonomía

Síndrome de fatiga crónica

Síndrome posvacunal de VPH

Introduction

Vaccination has been one of the most successful public health strategies in the history of medicine. Dreadful diseases like smallpox and poliomyelitis have practically been eradicated. This undeniable success has multiple programs of universal immuniza-

tion. However, as in any effective biological therapy, an excessive dosage can provoke damage. This would appear to be the situation of vaccination against human papillomavirus (HPV).

The present review reports how having seen two cases of a serious syndrome that appeared to be like fibromyalgia that developed soon after HPV vaccination¹ led us to investigate the strength of the possible link between these two events. The study suggests that there is an actual relationship between vaccination against HPV and the development of chronic painful conditions.² This article proposes that the controversial HPV vaccination syndrome could become a new tragic and undesirable model of fibromyalgia. On the other hand, recent research on the pathogenesis and treatment

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of fibromyalgia could provide diagnostic and therapeutic guidelines for those individuals affected by a chronic condition soon after immunization against HPV.

Background

Our group has been dedicated to investigate the mechanisms that lead to fibromyalgia. We propose that dysautonomia is the common underlying pathogenesis of fibromyalgia and other related syndromes, such as complex regional pain syndrome and chronic fatigue.³ We also suggest that fibromyalgic pain is of neuropathic origin⁴ and, moreover, that the sodium channels located in the dorsal root ganglia may have an important role as sympathetic-nociceptive short-circuit sites.⁵ This proposal has recently been supported by the finding of small fiber neuropathy in a considerable percentage of individuals with fibromyalgia⁶ and complex regional pain syndrome.⁷

The First Cases of Adverse Events Following Human Papillomavirus Vaccination: An Anecdote in the Setting of Evidence-based Scientific Medicine

In 2014, we published the findings in two girls who developed a serious condition that was similar to fibromyalgia soon after receiving the HPV vaccine.¹ In evidence-based scientific medicine, case reports are located in the lowest level of the hierarchy of evidence. However, the issuing of case reports is also considered an early and important warning in the process of drug surveillance.⁸

After the publication of those cases, we received messages from a number of countries in which physician, but especially the mothers of patients, wrote about similar incidents. Prior to this, the association between vaccination against HPV and another type of dysautonomia—postural orthostatic tachycardia syndrome—had also been reported.⁹ A short time later, two case series similar to ours were published by authors from Denmark¹⁰ and Japan.¹¹ The symptoms reported were very similar, but the diagnoses differed. The Japanese patients were mostly considered to have complex regional pain syndrome, whereas the Danish patients were often diagnosed with postural orthostatic tachycardia syndrome or chronic fatigue syndrome. The clinical manifestations of those affected included repetitively headache, myalgia, arthralgia, fatigue, dizziness, nausea and, less frequently, myoclonic disorders.^{10,11} On the basis of our research on fibromyalgia, we speculated that dysautonomia and small fiber neuropathy could be the hypothetical pathogeneses underlying HPV vaccination syndrome.¹²

This type of reaction to vaccination against HPV appears to be rare. With our current knowledge it is not possible to calculate the incidence. However, there is general information about reports of adverse events in HPV vaccination. In a study performed in the Spanish Valencian Community between 2007 and 2011, the rate of reports of adverse effects was approximately 1 of 1000 doses of HPV vaccine administered. The reports were made by qualified healthcare professionals (physicians or nurses). Approximately a third of these undesirable events were classified as “serious”. This rate of notification was 10 times higher than that reported for other vaccines administered during the same period to girls of similar ages.¹³

Subsequently, we asked individuals who had had a chronic disease after vaccination against HPV to complete three validated questionnaires: the 2010 American College of Rheumatology (ACR-2010), which enabled the diagnosis of fibromyalgia and established its severity; the Composite Autonomic Symptom Score (COMPASS-31), which detects symptoms of dysautonomia; and the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS), which

measures the neuropathic component of chronic pain. Over a period of one month, we received 45 completed questionnaires from 13 different countries. In all, 29% of those surveyed detected the onset of their condition within 24 h after HPV vaccination. The most frequent presenting symptoms were headache, musculoskeletal pain, fatigue, dizziness/vertigo and paresthesias/allodynia. Overall, 53% of those surveyed met the diagnostic criteria of fibromyalgia. The high COMPASS-31 and S-LANSS scores indicated the presence of severe dysautonomia and severe neuropathic pain. After an average of 4.2 ± 2.5 years, 92% of those affected remained disabled.¹⁴ In those patients who met the criteria for fibromyalgia, there was a correlation between the severity of the fibromyalgia measured by ACR-2010 and the intensity of dysautonomia scored by COMPASS-31.¹⁵

The reaction of international health authorities to these independent publications was firm and adverse. The European Medicines Agency judged that there was no relationship between the vaccine against HPV and the development of complex regional pain syndrome or postural orthostatic tachycardia.¹⁶ Reviews conducted by British,¹⁷ Canadian¹⁸ and Spanish¹³ health authorities supported the safety of immunization against HPV. A powerful argument put forward by the defenders of this vaccine was that the large, double-blind, randomized preclinical studies guaranteed the safety of the HPV vaccine. These randomized studies have a higher level of reliability in evidence-based scientific medicine. Randomized studies eliminate the contrivances that have nothing in common with the intervention and the results are totally independent of the judgment of the researchers. Our next step was to analyze in detail the randomized preclinical studies and the case series that reported adverse incidents involving vaccination against HPV.

An In-depth Analysis of the Randomized Studies Involving the Human Papillomavirus Vaccine Discovers Disturbing Data Regarding Its Safety

A critical analysis of the safety profile of the vaccine against HPV² reveals the following data:

1. The great majority of the randomized trials with the HPV vaccine did not utilize as control a true placebo, but an aluminum adjuvant. In clinical trials, the placebo is defined as an inert substance. Obviously, the aluminum adjuvant does not have this property. The innocuousness of the aluminum adjuvant has been put into question.² Strictly speaking, these controlled trials do not compare the efficacy or the safety of the HPV vaccine. They compare only the part of the vaccine that contains particles similar to HPV.
2. Two of the large preclinical randomized trials demonstrated more serious adverse incidents after vaccination against HPV. The VIVIANE study compared 2881 women injected with the bivalent HPV vaccine versus 2871 injected with the aluminum “placebo”. Over the 4-year follow-up period, there were 14 deaths in the immunized group versus 3 deaths in the control group. The difference is statistically significant. Fisher’s exact test produced a *P*-value of .01. The researchers who conducted this randomized trial deemed that none of the deaths were attributable to the injections administered.¹⁹

The largest double-blind study involving Gardasil compared the efficacy and safety of the new Gardasil-9 versus the tetravalent Gardasil employed at the present time. Gardasil-9 contains more than twice the HPV virus-like particles and more than twice the aluminum adjuvant than its predecessor. Serious adverse incidents were more frequent with Gardasil-9 (3.3%) than with the tetravalent formula (2.6%). We calculate a *P*-value of .012. The researchers

considered that 0% of the adverse events in the two arms of the study were due to the intervention.²⁰

The results of the statistical analyses of these two pivotal studies are distressing. There are more serious adverse effects in the patients who received the HPV vaccine being investigated. Nevertheless, these findings were avoided by the authors, who turned to stressing the fact that the researchers in both cases deemed that 0% of the adverse incidents were related to the intervention. In these two fundamental studies of vaccination against HPV, the solid and disturbing statistical results were ignored and subordinated to the opinion of the investigators.

Independent Researchers Report Similar Symptoms After Vaccination Against Human Papillomavirus

Other data that support the veracity of HPV vaccination syndrome lie in the fact that independent reports from different parts of the world describe a similar group of post-vaccine symptoms that include headache, fatigue, myalgias, paresthesias and dizziness, among others.^{9–11,13} This composite of adverse symptoms had been mentioned in randomized preclinical trials. The difficulty arises upon attempting to label this pleiad of symptoms with a precise diagnosis. The study of the database of adverse effects of the World Health Organization (VigiBase) highlights this problem. Cases of headache, dizziness, fatigue and syncope were reported more frequently and were more severe after vaccination against HPV when compared with other types of immunizations administered to individuals of a similar age. However, a minority of the reports mentioned a specific diagnosis.²¹ The lack of an explicit diagnosis and the dilution of the vaccine employed in cases of the HPV vaccination syndrome in different diagnoses is a possible explanation for the failure to recognize the adverse effects of this vaccine on the part of drug regulatory agencies.

In many cases, the syndrome reported as an adverse effect of immunization against HPV meets the diagnostic criteria of fibromyalgia. This was the situation of approximately half of the patients with whom we contacted.¹³

Human Papillomavirus Vaccination Syndrome: A Model of Fibromyalgia?

Human papillomavirus vaccination syndrome described independently by a number of researchers could become a model that would aid in the understanding of the pathogenesis of fibromyalgia. This disabling disease generally presents in healthy young individuals. It could be that, in some cases, vaccination against HPV acts as a trigger for fibromyalgia or chronic fatigue in predisposed persons or with a history of previous disorders. A study conducted in Denmark demonstrated that the patients who developed symptoms after HPV vaccination had a significantly higher rate of pre-vaccination care-seeking than those who did not.²²

In cases of HPV vaccination syndrome, the date of onset of the condition and that of administration of the trigger are well identified. The most widespread symptoms are typical of fibromyalgia: headache, generalized pain, paresthesias and fatigue. It must be stressed that some of these individuals have also mentioned movement disorders such as tremors and myoclonus. These motor disorders are a well-recognized complication of complex regional pain syndrome. Those affected by HPV vaccination syndrome have severe dysautonomia.¹³ In these cases, there is a correlation between the severity of fibromyalgia and the severity of dysautonomia.¹⁴ Individuals who develop a chronic condition after vaccination against HPV have antibodies against key elements of the autonomic nervous system, such as antibodies against adrenergic and muscarinic receptors.^{23,24} In the few patients in whom

this has been investigated, physicians encountered small fiber neuropathy.^{9,11,24} Should this be verified, this new tragic model would support the dysautonomic and neuropathic pathogenesis of fibromyalgia.

Advances in the Understanding of the Pathogenesis of Fibromyalgia Could Provide Diagnostic Strategies for Patients With Adverse Effects to Vaccination Against Human Papillomavirus

The dysautonomic–neuropathic model of fibromyalgia could provide diagnostic guidelines for those individuals who develop a chronic condition after HPV vaccination. A major problem in these cases has been the absence of a proper diagnosis. The application of the COMPASS-31, S-LANSS and ACR-2010 questionnaires would help to identify the existence of dysautonomia, neuropathic pain and fibromyalgia, respectively. The tilt-table test would recognize postural orthostatic tachycardia or other syndromes involving orthostatic intolerance. Skin biopsy would identify the presence of small fiber neuropathy. The search for antibodies to adrenergic and muscarinic receptors could become a useful tool in the diagnostic process of HPV vaccination syndrome.

New Pathogenetic Knowledge on Fibromyalgia Could Provide Therapeutic Indications for Human Papillomavirus Vaccination Syndrome

At the present time, drug treatment for fibromyalgia leaves much to be desired. However, based on new pathophysiological knowledge, there is investigation underway involving selective blockers of sodium channels located in the dorsal root ganglia.²⁵ These substances could become an effective analgesic for HPV vaccination syndrome. The infusion of immunoglobulins or plasmapheresis could be useful in those cases of HPV vaccination syndrome in which there are antibodies against adrenergic or muscarinic receptors.^{23,24} Pyridostigmine, fludrocortisone and propranolol utilized in orthostatic intolerance syndromes⁹ could be extrapolated to the therapeutic armamentarium for HPV vaccination syndrome.

It is evident that these diagnostic and therapeutic considerations are hypothetical and need to be subjected to the judgment of investigation.

Conclusions

Independent investigators have reported the development of a fibromyalgia-like chronic syndrome after HPV vaccination. It is difficult to categorize the condition within a specific diagnosis. Recent advances in our understanding of fibromyalgia could provide diagnostic and therapeutic guidelines for the hypothetical HPV vaccination syndrome. On the other hand, should the veracity of HPV vaccination syndrome be corroborated, it could become a new tragic and undesired model of fibromyalgia. International health authorities deny the existence of such a syndrome. More research will be necessary to define HPV vaccination syndrome as a clinical mirage or as a new clinical entity.

Conflicts of Interest

The author declares he has no conflicts of interest.

References

1. Martínez-Lavín M. Fibromyalgia-like illness in 2 girls after human papillomavirus vaccination. *J Clin Rheumatol.* 2014;20:392–3.

2. Martínez-Lavín M, Amezcua-Guerra L. Serious adverse events after HPV vaccination: a critical review of randomized trials and post-marketing case series. *Clin Rheumatol.* 2017;36:2169–217.
3. Martínez-Martínez A, Mora T, Vargas A, Fuentes-Iniestra M, Martínez-Lavín M. Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome and interstitial cystitis. A review of case-control studies. *J Clin Rheumatol.* 2014;20:146–50.
4. Martínez-Lavín M, López S, Medina M, Nava A. The use of the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire in fibromyalgia patients. *Semin Arthritis Rheum.* 2003;32:407–11.
5. Vargas-Alarcon G, Alvarez-Leon E, Fragoso JM, Vargas A, Martinez A, Vallejo M, et al. A SCN9A gene-encoded dorsal root ganglia sodium channel polymorphism associated with severe fibromyalgia. *BMC Musculoskeletal Dis.* 2012;13:23.
6. Ramírez M, Martínez-Martínez LA, Hernández-Quintela E, Velazco-Casapia J, Vargas A, Martínez-Lavín M. Small fiber neuropathy in women with fibromyalgia: An in vivo assessment using corneal confocal bio-microscopy. *Semin Arthritis Rheum.* 2015;45:214–9.
7. Oaklander AL, Rissmiller JG, Gelman LB, Zheng L, Chang Y, Gott R. Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). *Pain.* 2006;120:235–43.
8. Vandenbroucke JP. In defense of case reports and case series. *Ann Intern Med.* 2001;134:330–4.
9. Blitshteyn S. Postural tachycardia syndrome following human papillomavirus vaccination. *Eur J Neurol.* 2014;21:135–9.
10. Brinth L, Theibel AC, Pors K, Mehlsen J. Suspected side effects to the quadrivalent human papilloma vaccine. *Dan Med J.* 2015;62(A5064).
11. Kinoshita T, Abe RT, Hineno A, Tsunekawa K, Nakane S, Ikeda S. Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine. *Intern Med.* 2014;53:2185–200.
12. Martínez-Lavín M. Hypothesis. Human papillomavirus vaccination syndrome Small fiber neuropathy and dysautonomia could be its underlying pathogenesis. *Clin Rheumatol.* 2015;34:1165–9.
13. Rodríguez-Galán MA, Pérez-Vilar S, Díez-Domingo J, Tuells J, Gomar-Fayos J, Morales-Olivas F, et al. Adverse reactions to human papillomavirus vaccine in the Valencian Community (2007–2011). *An Pediatr (Barc).* 2014;81:303–9.
14. Martínez-Lavín M, Martínez-Martínez LA, Reyes-Loyola P. HPV vaccination syndrome. A questionnaire-based study. *Clin Rheumatol.* 2015;34:1981–3.
15. Martínez-Lavín M, Reyes-Loyola PK, Martínez-Martínez LA. Human Papilloma virus vaccination, fibromyalgia and dysautonomia. *Arthritis Rheumatol.* 2016; 68 (suppl 10) [accessed 26 oct 2017]. Available from: <http://acrabstracts.org/abstract/human-papilloma-virus-vaccination-fibromyalgia-and-dysautonomia/>
16. HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS. [accessed 5 mar 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/European_Commission_final_decision/WC500196773.pdf
17. Donegan K, Beau-Lejdstrom R, King B, Seabroke S, Thomson A, Bryan P. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. *Vaccine.* 2013;31:7–4961.
18. Liu XC, Bell CA, Simmonds KA, Svenson LW, Russell ML. Adverse events following HPV vaccination Alberta 2006–2014. *Vaccine.* 2016;34:1800–5.
19. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazzcano-Ponce E, Salmerón J, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. *Lancet.* 2014;84:2213–27.
20. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med.* 2015;372:711–23.
21. Chandler RE, Juhlin K, Fransson J, Caster O, Edwards IR, Norén GN. Current safety concerns with human papillomavirus vaccine: A cluster analysis of reports in VigiBase. *Drug Saf.* 2017;40:81–90.
22. Molbak K, Hansen ND, Valentiner-Branth P. Pre-vaccination care-seeking in females reporting severe adverse reactions to HPV vaccine. A registry based case-control study. *PLOS One.* 2016;11:e0162520.
23. Hendrickson JE, Tormey CA. Human papilloma virus vaccination and dysautonomia: Considerations for autoantibody evaluation and HLA typing. *Vaccine.* 2016;34:4468.
24. Schofield JR, Hendrickson JE. Autoimmunity autonomic neuropathy, and the HPV vaccination: a vulnerable subpopulation. *Clin Pediatr (Phila).* 2017. <http://dx.doi.org/10.1177/0009922817728701> [Epub ahead of print].
25. Martínez-Martínez LA, Pérez LF, Becerril-Mendoza LT, Rodríguez-Henriquez P, Muñoz OE, Acosta G, et al. Ambroxol for fibromyalgia: one group pretest-postest open-label pilot study. *Clin Rheumatol.* 2017;36:1879–84.