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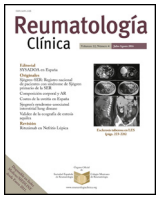

Review Article

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.

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

Palabras clave:
Vacuna del papiloma
Fibromialgia
Neuropatía de fibras pequeñas
Disautonomía
Síndrome de fatiga crónica
Síndrome posvacunal de VPH

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.

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 immunization. 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 vaccination[1] 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 origin[4] 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 fibromyalgia[6] 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 Denmark[10] 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] Canadian[18] and Spanish[13] 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 HPV[2] 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 administrated.[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