

# HPV vaccination syndrome. A questionnaire-based study

Manuel Martínez-Lavín<sup>1</sup> · Laura-Aline Martínez-Martínez<sup>1</sup> · Paola Reyes-Loyola<sup>1</sup>

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**Abstract** Isolated cases and small series have described the development of complex regional pain syndrome, postural orthostatic tachycardia, and fibromyalgia after human papillomavirus (HPV) vaccination. These illnesses are difficult to diagnose and have overlapping clinical features. Small fiber neuropathy and dysautonomia may play a major role in the pathogenesis of these entities. We used the following validated questionnaires to appraise the chronic illness that might appear after HPV vaccination: The 2010 American College of Rheumatology Fibromyalgia Diagnostic Criteria, COMPASS 31 dysautonomia questionnaire, and S-LANSS neuropathic pain form. These questionnaires and a “present illness” survey were e-mailed to persons who had the onset of a chronic ailment soon after HPV vaccination. Forty-five filled questionnaires from individuals living in 13 different countries were collected in a month’s period. Mean ( $\pm$ SD) age at vaccination time was  $14\pm 5$  years. Twenty-nine percent of the cases had immediate (within 24 h) post-vaccination illness onset. The most common presenting complaints were musculoskeletal pain (66 %), fatigue (57 %), headache (57 %), dizziness/vertigo (43 %), and paresthesias/allodynia (36 %). Fifty-three percent of affected individuals fulfill the fibromyalgia criteria. COMPASS-31 score was  $43\pm 21$ , implying advanced autonomic dysfunction. Eighty-three percent of the patients who had ongoing pain displayed S-LANSS values  $>12$ , suggesting a neuropathic component in their pain experience. After a

mean period of  $4.2\pm 2.5$  years post-vaccination, 93 % of patients continue to have incapacitating symptoms and remain unable to attend school or work. In conclusion, a disabling syndrome of chronic neuropathic pain, fatigue, and autonomic dysfunction may appear after HPV vaccination.

**Keywords** Complex regional pain syndrome · Dysautonomia · Fibromyalgia · Gulf War Illness · HPV vaccine · Myalgic encephalomyelitis · Small fiber neuropathy

## Introduction

Vaccination has been one of the most effective public health measures in the history of medicine. Terrible diseases such as smallpox or poliomyelitis have been practically eradicated. Nevertheless, it seems as the pendulum has swung too far. Nowadays, children are subjected to multiple vaccination protocols not only to prevent common infectious diseases, but also to prevent the late appearance of cancer. The human papillomavirus (HPV) vaccine is the case in point [1]. Adverse reactions appear to be more frequent after HPV vaccination when compared to other types of immunizations. A study done in the Valencian Community of Spain showed that the adverse HPV vaccination side effects reported by health professionals (doctors or nurses) to the health authorities have an approximate incidence rate of 1 per 1000 inoculations. This incidence was ten times higher than the ones described with other types of vaccines administered to girls of similar age. Thirty-two percent of the HPV vaccine adverse reaction was classified as “severe” [2]. Different isolated cases and small series have described the development of syncope, complex regional pain syndrome [3], postural orthostatic tachycardia syndrome [4, 5], and fibromyalgia [6] after HPV vaccination. These illnesses are difficult to diagnose and have overlapping

✉ Manuel Martínez-Lavín  
drmartinezlavin@gmail.com

<sup>1</sup> Departamento de Reumatología, Instituto Nacional de Cardiología Ignacio Chávez, Juan Badiano 1, 14080 Mexico City, Mexico

clinical features. Recently published evidence suggests that dysautonomia and small fiber neuropathy may be the common underlying pathogenesis for these overlapping clinical entities [1].

There are three recently validated self-applied questionnaires that may help to appraise these syndromes: the 2010 American College of Rheumatology Fibromyalgia Diagnostic Criteria survey is able to detect the presence of fibromyalgia [7], COMPASS 31 evaluates the burden of autonomic symptoms [8], and S-LANSS questionnaire may suggest a neuropathic component in the pain experience [9].

Our objective was to use these questionnaires as tool to investigate if a patterned illness might develop after HPV vaccination.

## Material and methods

The three validated questionnaires together with a “present illness” survey were e-mailed to individuals who had the onset of a chronic disease soon after HPV vaccination. The target population was identified with the help of HPV vaccine blog managers. Patients who had previously e-mailed us after publication of an article discussing this topic [1], and two cases personally seen by one of the authors [6] were also contacted. Individuals were asked to fill-out the questionnaire only if they have reasons to believe that the HPV vaccination was related to the onset of their chronic illness. The cases that had symptoms onset within 3 months post-vaccination were reviewed.

The protocol was approved by the Institutional Research and Ethics committees.

## Results

The outstanding results of 45 filled questionnaires collected in a month’s period are summarized in Table 1. Patients reside in 13 different countries. Mean ( $\pm$ SD) age at vaccination time was  $14\pm 5$  years; all except 1 affected individual were female. The mean time span between vaccination and onset of symptoms was  $2.3\pm 3.1$  weeks. Twenty-nine percent of the cases had immediate (within 24 h) post-vaccination illness onset. The most common presenting complaints were musculoskeletal pain (66 %), fatigue (57 %), headache (57 %), dizziness/vertigo (43 %), paresthesias/allodynia (36 %), and nausea/vomiting (27 %). After a mean period of  $4.2\pm 2.5$  years post-HPV vaccination, all except two patients have escalating vexing symptoms. At this point in time, the most common reported symptoms were fatigue/tiredness (88 %), muscle pain (76 %), headache (74 %), muscle weakness (69 %), thinking or remembering problem (63 %), dizziness (63 %), pain/cramps in the abdomen (60 %), numbness/tingling

**Table 1** Outstanding features of 45 patients who describe adverse HPV vaccination reactions

| Feature   |               |
|---|---------------|
| Age (mean $\pm$ SD)   | 19 $\pm$ 6    |
| Female (%)  | 98            |
| Age at vaccination time (mean $\pm$ SD)                         | 14 $\pm$ 5    |
| Quadrivalent vaccination (%)                                    | 79            |
| Bivalent vaccination (%)  | 21            |
| Time elapsed between HPV vaccination and symptoms onset (weeks) | 2.3 $\pm$ 3.1 |
| Most common presenting complaints (%)                           |               |
| Musculoskeletal pain  | 66            |
| Fatigue   | 57            |
| Headache  | 57            |
| Dizziness/vertigo   | 43            |
| Paresthesias/allodynia  | 36            |
| Nausea/vomiting   | 27            |
| Most frequent complaints at survey time (%)                     |               |
| Fatigue/tiredness   | 88            |
| Muscle pain   | 76            |
| Headache  | 74            |
| Muscle weakness   | 69            |
| Thinking or remembering problem                                 | 63            |
| Dizziness   | 63            |
| Pain/cramps in the abdomen                                      | 60            |
| Numbness/tingling   | 60            |
| Nausea  | 60            |
| Questionnaire score   |               |
| % of cases fulfilling fibromyalgia 2010 diagnostic criteria     | 53            |
| COMPASS 31 score  | 43 $\pm$ 21   |
| % of cases with S-LANSS score >12 <sup>a</sup>                  | 83            |
| % of cases able to go to school (or work) on a regular basis    | 7             |

<sup>a</sup> Measured only in patients with ongoing pain

(60 %), and nausea (60 %). Because of these symptoms, 93 % of patients are unable to regularly attend school or work.

Fifty-three percent of affected individuals fulfill the fibromyalgia diagnostic criteria. COMPASS-31 score was  $43\pm 21$ ; these values imply advanced autonomic dysfunction. Eighty-three percent of the patients who had ongoing pain displayed S-LANSS values >12, suggesting a neuropathic component in their pain experience.

## Discussion

These results suggest that a patterned illness of neuropathic pain and autonomic dysfunction may appear after HPV vaccination. The HPV post-vaccination cluster of symptoms

described in this study from individuals residing in 13 different countries is analogous to the ones reported in 53 Danish patients by Brinth et al. Similar to our results, the most common complaints in the Danish study were headache (100 %), orthostatic intolerance (96 %), fatigue (96 %), cognitive dysfunction (89 %), and nausea (91 %) [5]. Likewise, the most common symptoms in 40 HPV-vaccinated Japanese girls published by Kinoshita et al were headache (70 %), fatigue (53 %), coldness of the legs (53 %), limb pain (50 %), and limb weakness (48 %) [3].

HPV vaccination syndrome bears resemblance to fibromyalgia, myalgic encephalomyelitis/chronic fatigue syndrome, ASIA syndrome, macrophagic myofasciitis, and to Gulf War Illness. These syndromes have overlapping clinical features and have been previously associated to other aluminum-containing vaccines [10–12]. The obvious difference is that HPV vaccination syndrome affects mostly girls in the initial period of their lives.

HPV vaccination syndrome appears to be a neurotoxic disease affecting mainly the sensory and the autonomic nervous system. Based on our previous research on fibromyalgia [13], we speculate that in susceptible individuals the vaccine recombinant virus-like particles adsorbed on aluminum-containing adjuvant may damage dorsal root ganglia. This damage may induce small fiber neuropathy and dysautonomia [1].

The clear limitation of our study is the lack of direct medical examination of affected individuals.

In conclusion, emerging evidence suggests that a disabling syndrome of chronic neuropathic pain, vexing fatigue, and profound autonomic dysfunction may appear after HPV vaccination.

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## References

1. Martínez-Lavin M (2015) Human papillomavirus vaccination syndrome. Small fiber neuropathy and dysautonomia could be its underlying pathogenesis. *Clin Rheumatol* 34:1165–1169
2. Rodríguez-Galán MA, Pérez-Vilar S, Díez-Domingo J, Tuells J, Gomar-Fayos J, Morales-Olivas F, Pastor-Villalba E (2014) Adverse reactions to human papillomavirus vaccine in the Valencian Community (2007–2011). *An Pediatr (Barc)* 81:303–309
3. Kinoshita T, Abe RT, Hineno A, Tsunekawa K, Nakane S, Ikeda S (2014) Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine. *Intern Med* 53:2185–2200
4. Blitshteyn S (2014) Postural tachycardia syndrome following human papillomavirus vaccination. *Eur J Neurol* 21:135–139
5. Brinth L, Theibel AC, Pors K, Mehlsen J (2015) Suspected side effects to the quadrivalent human papilloma vaccine. *Dan Med J* 62:A5064
6. Martinez-Lavin M (2014) Fibromyalgia-like illness in 2 girls after human papillomavirus vaccination. *J Clin Rheumatol* 20:392–393
7. Wolfe F, Clauw D, Fitzcharles MA, Goldenberg D, Katz RS, Mease P et al (2010) The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* 62:600–610
8. Sletten DM, Suarez GA, Phillip A, Low PA, Mandrekar J, Singera W (2012) COMPASS 31: a refined and abbreviated composite autonomic symptom score. *Mayo Clin Proc* 87:1196–1201
9. Bennett MI, Smith BH, Torrance N, Potter J (2005) The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *J Pain* 6:149–158
10. Agmon-Levin N, Zafrir Y, Kivity S, Balofsky A, Amital H, Shoenfeld Y (2014) Chronic fatigue syndrome and fibromyalgia following immunization with the hepatitis B vaccine: another angle of the 'autoimmune (auto-inflammatory) syndrome induced by adjuvants' (ASIA). *Immunol Res* 60:376–83
11. Hotopf M, David A, Hull L, Ismail K, Unwin C, Wessely S (2000) Role of vaccinations as risk factors for ill health in veterans of the Gulf war: cross sectional study. *BMJ* 320:1363–1367
12. Rigolet M, Aouizerate J, Couette M, Ragunathan-Thangarajah N, Aoun-Sebaiti M, Gherardi RK, Cadusseau J, Authier FJ (2014) Clinical features in patients with long-lasting macrophagic myofasciitis. *Front Neurol* 28:230
13. Vargas-Alarcon G, Alvarez-Leon E, Fragoso JM, Vargas A, Martinez A, Vallejo M, Martinez-Lavin M (2012) A SCN9A gene-encoded dorsal root ganglia sodium channel polymorphism associated with severe fibromyalgia. *BMC Musculoskelet Dis* 13: 23