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ORIGINAL ARTICLE

Autonomic dysfunction and HPV immunization: an overview

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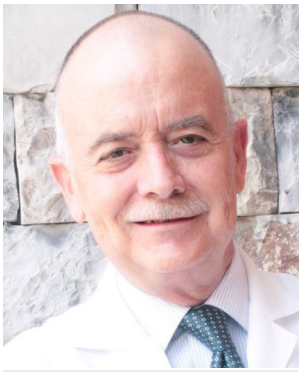

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Abstract

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.

Keywords HPV vaccine · Autonomic dysfunction · Autoimmunity · Postural orthostatic tachycardia syndrome · Chronic regional pain syndrome · Small fiber neuropathy · Fibromyalgia · Myalgic encephalomyelitis · Chronic fatigue syndrome

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Introduction

Vaccines are considered a global and ground-breaking healthcare success with impressive impact on both mortality and morbidity worldwide. This accomplishment has multiplied the recommended vaccine regimens. In recent years, three vaccines directed to prevent human papilloma virus (HPV)-related malignancies have been approved for global use; Cervarix protecting against HPV serotypes 16 and 18, Gardasil 4 aimed at serotypes 6, 11, 16, and 18, and Gardasil 9 against serotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58 [1–3]. Both the antigenic component of the vaccines and the adjuvant of the vaccines are different. Cervarix contains aluminum hydroxide and monophosphoryl lipid whereas both the quadrivalent and nonavalent vaccines contain amorphous aluminum hydroxyphosphate sulfate in different dosages [4, 5].

Since Gardasil FDA approval in 2006, case series and case reports describing patients with suspected severe side effects to the HPV vaccines have been emerging from several

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countries [6–18]. The symptoms described by independent researchers are quite similar and include long-lasting excessive fatigue, severe headache, cognitive dysfunction, gastrointestinal discomfort, widespread neuropathic pain, sleep disturbance, and motor alteration such as tremor and/or myoclonus. Autonomic dysfunction has been proposed as the common underlying pathogenesis for these symptom clusters [19].

The aim of this article is to update the emerging evidence of a symptom complex, involving the autonomic nervous system dysfunction as suspected side effect of the HPV vaccine. This article will also examine the possible relationship of immune-mediated autonomic dysfunction in the development of these perplexing syndromes and discuss the diagnostic investigations to support the clinical evaluation in patients affected by these disorders. Our search strategy included PubMed database review using the key word HPV vaccine linked to the following words: adverse events, autonomic nervous system, postural orthostatic tachycardia syndrome, complex regional pain syndrome, chronic fatigue syndrome, fibromyalgia, or small fiber neuropathy. We also reviewed the literature on the presence of antibodies in these syndromes.

Autonomic dysfunction

Autonomic dysfunction encompasses changes in autonomic nervous system function that adversely affect health. This dysfunction may range from episodes of neurally mediated hypotension or syncope, POTS, and sympathetically maintained pain syndromes, to progressive neurodegenerative disorders, such as multiple system failure and pure autonomic failure [20]. Dysautonomia is sometimes used as an umbrella term that includes all autonomic disorders, from the orthostatic hypotension found in Parkinson disease and multiple system atrophy to the autonomic dysfunction of postural orthostatic tachycardia syndrome (POTS), complex regional pain syndrome (CRPS), fibromyalgia, and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [21]. The autonomic nervous system plays a key role in maintaining orthostasis, a physiologic mechanism that allows humans to maintain an upright posture via the adaptability of blood pressure, heart rate, and cerebral perfusion in response to gravitational forces. Thus, a key feature of most autonomic disorders is the orthostatic intolerance.

Autonomic dysfunction may also induce chronic vexing pain. Different traumatic events can trigger the development of sympathetically maintained pain syndromes. Animal models have helped to advance our understanding of sympathetically maintained pain syndromes. An animal model has consistently shown that after trauma, there is sympathetic sprouting within the dorsal root ganglia establishing abnormal connections between the sympathetic nervous system and the nociceptive system [22]. Dorsal root ganglia contain small nerve fiber cell bodies, particularly SCN9A gene-encoded dorsal root ganglia sodium channels, that are involved in pain transmission and sympathetic function [23].

Common autonomic syndromes

Traditionally, autonomic dysfunction has been linked to well-defined diseases such as Parkinson disease and diabetes. The use of autonomic function tests, including a tilt table test, deep breathing, Valsalva maneuver, and quantitative sudomotor axon reflext test (QSART), as well as other tests, such as a skin biopsy to diagnose small fiber neuropathy and heart rate variability tests, led to the identification and defined diagnostic criteria for many other autonomic disorders, such as POTS, neurocardiogenic syncope, autonomic and small fiber neuropathy, and autoimmune autonomic ganglionopathy (AAG) [24]. Utilizing these tests in patients with ME/CFS, fibromyalgia and CRPS demonstrated abnormalities in the autonomic nervous system, involving adrenergic, cardiovagal, or sudomotor function as common findings in these overlapping conditions [21].

In the overwhelming majority of cases, these autonomic syndromes develop without prior vaccination.

Postural orthostatic tachycardia syndrome

POTS is a heterogeneous disorder of the autonomic nervous system characterized by orthostatic tachycardia, orthostatic intolerance, and non-orthostatic symptoms, such as weakness, headache, nausea, dizziness, sleep disturbance, and fatigue [24]. POTS is not rare, but can be easily missed by clinicians who may not be aware of POTS as a diagnosis. It is estimated that at least 1,000,000 people have POTS in the USA, 85% of whom are women between ages 15 and 50 [25].

POTS is diagnosed via a stand test or tilt table test, demonstrating an increase in heart rate by at least 30 bpm from supine to standing position in the first 10 min of tilt and associated with symptoms of the orthostatic intolerance; at least 40 bpm rise in heart rate is required for the diagnosis in children and adolescents [21, 26–28]. POTS is often considered "the final common pathway" for multiple etiologies. Pathophysiologic mechanisms resulting in POTS include an autonomic neuropathy, hypovolemia, elevated sympathetic tone, mast cell activation, secondary deconditioning, and the presence of antibodies [29]. About 50% of POTS patients have small fiber neuropathy, 20% have co-morbid autoimmune disorders [30], at least 18% have Ehlers-Danlos syndrome [31], and 20% have mast cell activation syndrome [32]. In an attempt to categorize and further define autonomic disorders, some experts consider POTS to be a limited form of the autoimmune autonomic neuropathy [33].

Vaccination has been reported as an important triggering event in at least 4% of POTS patients [34]. Despite the isolated reports [9, 11, 35], the incidence of de novo POTS and other autonomic disorders after vaccination of healthy individuals is unknown, largely because many patients are undiagnosed or mis-diagnosed with other conditions involving altered consciousness and awareness [36]. These conditions may include seizure disorders, cardiac arrhythmias, migraine variants, and psychiatric entities, such as conversion disorder, somatization disorder, factitious disorder, anxiety disorders, or malingering. Correct diagnosis of POTS is often delayed by months to years and is usually established by a physician with expertise in autonomic disorders or clinicians with a high index of clinical suspicion. A comprehensive physical examination, including an orthostatic blood pressure and heart rate measurement, and thorough cardiac and neurologic examinations are necessary. Additionally, a tilt table test or complete autonomic function tests support the diagnosis of POTS and other autonomic disorders.

Complex regional pain syndrome

CRPS is a chronic pain condition affecting one of the limbs, usually after trauma or injury to that limb. The International Association for the Study of Pain diagnostic criteria for CRPS requires (i) preceding noxious event; (ii) spontaneous pain or hyperalgesia/hyperesthesia not limited to a single nerve territory and disproportionate to the inciting event; and (iii) edema, temperature, or sudomotor abnormalities present in the affected limb, in particular distal sites [37]. Sympathetic dysfunction is evident in the affected limb. CRPS can evolve into a full fledged widespread pain syndrome.

Fibromyalgia

Fibromyalgia is characterized by widespread pain, widespread allodynia, paresthesias, fatigue, sleep disorders, and cognitive difficulties. Besides these defining features, patients with fibromyalgia frequently display an array of multisystem complaints [38]. Physical, infectious, and/or mental stressors could trigger fibromyalgia. Growing evidence suggests that autonomic dysfunction plays a key part in the development of fibromyalgia and that fibromyalgia is a sympathetically maintained neuropathic pain syndrome [39].

Myalgic encephalomyelitis/chronic fatigue syndrome

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterized by extreme fatigue resulting in significant functional impairment. Several diagnostic criteria for ME/CFS have been developed and used in both clinical practice and research. The Canadian Criteria defines ME/CFS as a condition lasting at least 6 months characterized by fatigue, post-exertion malaise, pain, and disordered sleep accompanied by neurologic, autonomic, neuro-endocrine, and immune dysfunction [40]. In 2015, The Institute of Medicine renamed ME/CFS as "Systemic Exertion Intolerance Disease," defined as a condition characterized by impaired day-to-day function, post-exertional malaise, and unrefreshing sleep, coupled with cognitive impairment and/or orthostatic tolerance with symptoms at least half the time for 6 months or more [41]. The recent re-definition of ME/CFS as "systemic exertion intolerance disease" highlights its dysautonomia component.

Isolated reports and small case-series have described the development of CRPS, ME/CFS, or fibromyalgia after hepatitis B vaccination [42].

Autoimmunity and autoantibodies in POTS, CRPS, EM/CFS, and fibromyalgia

Considering that vaccines could elicit autoimmunity in genetically susceptible individuals, it is hypothesized that molecular mimicry with cross-reacting antibodies against potential targets of the autonomic ganglia (such as AchR ganglionic neuronal receptor), neurons, cardiac proteins, alpha 1 adrenergic, β1/2-adrenergic, and M2/3 muscarinic receptors could be a possible mechanism of injury in those cases that had the onset of a chronic illness after HPV immunization [30]. We will now examine the literature on autoantibodies associated to POTS, CRPS, EM/CFS, and fibromyalgia.

Autoantibodies and POTS

Although POTS is a heterogeneous disorder, there is an increasing appreciation that autoimmunity is involved in at least a subset of cases. A report from the Mayo Clinic described 6/42 POTS patients as testing positive for low levels of nicotinic acetylcholine ganglionic receptor autoantibodies [26]. A case series of 82 children with POTS found 20 to have acetylcholine ganglionic receptor autoantibodies [43]. Li et al. described B1 adrenergic receptor autoantibodies in 14/14 patients with POTS, with B2 adrenergic receptor autoantibodies being detected in approximately half of these patients. Further, all of the studied POTS patients had α1 adrenergic receptor autoantibodies detected that were capable of altering contractility via a perfused rat cremaster arteriole assay [42]. In a case series of 100 patients with POTS, 25% had a positive ANA, 7% had at least one positive anti-phospholipid antibody, 3% had elevated tissue transglutaminase, and 1 in 5 had a co-

morbid autoimmune disorder [29]. Watari et al. analyzed the serum of 34 patients with POTS, who were a median of 22 years old. Twenty-nine percent of them have antiganglionic acetylcholine receptor antibodies. None of the 73 healthy controls who were tested were positive [44].

The co-existence of diverse forms of autoimmunity in POTS patients [17, 26, 30] further strengthens the hypothesis that some cases of POTS likely represent a form of autoimmunity. There remains a paucity of knowledge of the autoimmune basis of POTS, due in part to a lack of commercially available laboratory testing and due in part to a lack of comprehensive knowledge about the putative autoantigen targets. However, no Clinical Laboratory Improvement Amendment (CLIA)-certified commercial testing for α or β adrenergic receptor autoantibodies is currently available in the USA. Assays for detecting autoantibodies against G protein-coupled receptors such as α or β adrenergic receptors are difficult to commercialize, given that optimal assays investigate not only the presence but also the agonistic or antagonistic function of such autoantibodies.

Autoantibodies in complex regional pain syndrome

Like POTS, CRPS is also a heterogeneous disease, and like POTS patients, some CRPS patients have recently been described to have detectable autoantibodies against G protein-coupled receptors (Table 1). Blaes et al. first described the presence of autoantibodies against the sympathetic nervous system in a subset of CRPS patients in 2004 [49], with a 2009 study showing that the antibodies, present in 13/30 CRPS patients, were specific for differentiated neurons with a cholinergic phenotype [50]. Kohr and colleagues subsequently identified the antibodies as binding to the second extracellular loop of β2-adrenergic and muscarinic-2 receptors, with functional significance demonstrated using a fetal cardiomyocyte bioassay. One of these antibodies was detected in 90% of tested CRPS patients, with both antibodies being detected in 55% of tested CRPS patients ($n = 20$ patients studied) [51]. In addition, another laboratory recently reported the presence of activating autoantibodies against α adrenergic receptors of adult cardiac myocytes in 10/18 patients with longstanding CRPS compared to 1/57 controls, with the effect being abrogated by α-1a adrenergic receptor blockade [52]. Further, the fact that passive transfer of serum IgG from humans with CRPS to mice results in CRPS-like symptoms lends additional support to the pathologic role that these G protein-coupled-receptor autoantibodies play in vivo [53].

Autoantibodies in ME/CFS and fibromyalgia

ME/CFS is heterogeneous disease, with many decades of research having been dedicated to investigating infectious or other etiologies and to studying immune abnormalities and potential autoantibody associations. Autoantibodies against nuclear components, phospholipids, neuronal components, neurotransmitters, and G protein-coupled receptors have all been described in patients with ME/CFS [54]. A recent study, using an ELISA with recombinant G protein-coupled receptors expressed in CHO cells (Celltrend GmbH), detected β2-adrenergic receptor autoantibodies or muscarinic receptor autoantibodies (M3 or M4) in 29% of 268 ME/CFS patients [55]. Positron emission tomography studies of CFS patients suggest the functional significance of these antibodies, with a reduction of neurotransmitter ([11C](+)methyl-3-piperidyl benzilate) binding observed in the brains of autoantibody-positive CFS patients compared to antibody-negative CFS patients or healthy controls [56].

Autoantibodies to many targets (including nuclear, rheumatoid factor, thyroglobulin, thyroperoxidase, smooth muscle, myelin basic protein, and others) have been detected in patients with fibromyalgia attributed to the hepatitis B vaccine [42], as well as in others with fibromyalgia [57]. Autoimmune autonomic ganglionopathy (AAG), a disease with some degree of symptomatic overlap with POTS, CRPS, and ME/CFS, is associated with high levels of nicotinic acetylcholine ganglionic receptor autoantibodies [33].

In summary, a subset of patients with POTS, CRPS, ME/CFS, and fibromyalgia have laboratory evidence of autoimmunity. Recent publications have demonstrated the findings of autoantibodies directed against, and in many instances activating, receptors of the autonomic nervous system [48, 51, 55]. These are in most cases preliminary studies in small groups of patients, but they are significant and should be tested in larger cohorts with well-selected and characterized patients and compared to well-matched subjects. More widespread laboratory testing for surface binding antibodies may provide diagnostic assistance in these and other diseases in the future.

Case series of autonomic dysfunction following HPV vaccination

Independent clinicians from different countries have described the onset of severe dysautonomia syndromes soon after HPV vaccination. The described cases have similar clinical features and include long-lasting excessive fatigue, severe headache, cognitive dysfunction, gastrointestinal discomfort, widespread neuropathic pain [6–9, 14, 16, 58], sleep disturbance, and motor alteration such as tremor and/or myoclonus [6, 7, 9]. Patients with these clusters of symptoms have been labeled with diagnoses such as CRPS, POTS, fibromyalgia, or ME/CFS.

Table 1 Case series of HPV vaccine adverse events. Outstanding clinical features (modified from refernce [45])

First author, year of publication (reference)	# of cases	Age Range (years)	Main diagnosis	Presenting symptoms	Outcome at the time of publication	Proposed pathogenesis	Other features
Richards 2012 [46]	4	12–16	CRPS	Headache, fatigue	Improved	Injection trauma	
Colafrancesco /2013 [15]	3	13–21	Premature ovarian insufficiency	Amenorrhea, nausea, headache, sleep disturbances, arthralgia	Amenorrhea persisted	ASIA syndrome	Anti-ovarian and anti-thyroid antibodies
Kinoshita 2014 [45]	40	11–17	CRPS	Headache, fatigue, limb pain and coldness	Not defined	Peripheral sympathetic nerve dysfunction	Limb tremors
Blitshteyn 2014 [11]	6	12–20	POTS	Dizziness, fatigue, syncope, paresthesias	Improved	Cross reacting antibodies to autonomic ganglia	3/6 patients with small fiber neuropathy
Tomljenovic 2014 [16]	1	14	POTS, chronic fatigue syndrome	Headache, dizziness, fatigue, myalgias	Remained ill	ASIA syndrome	+ antinuclear antibodies
Brinth 2015 [7]	35	13–39	POTS (21/35), chronic fatigue syndrome	Orthostatic intolerance, nausea, headache, fatigue	24/35 remained disabled	Dysautonomia	Segmental dystonia, neuropathic pain
Martinez-Lavin 2015 [14]	45	9–33	Fibromyalgia (53%)	Fatigue, myalgia, headache	93% remain disabled	Dysautonomia, small fiber neuropathy	Muscle weakness, dyscognition
Hendrickson 2016 [47]	1	14	CRPS/POTS	Fatigue, stomach pain, arthralgias	Improved with immunotherapy	Dysautonomia	+ adrenergic and muscarinic receptor antibodies
Palmieri 2016 [48]	18	12–24	ASIA syndrome	Myalgia, vascular skin abnormalities, headache	10/18 disabled	Cross-reactive adaptive immune response	Memory impairment, asthenia.
Kafaie 2016 [14]	1	14	Small fiber neuropathy	Generalized pain and paresthesias	Not defined	Immune-mediated phenomena	
Bitshteyn 2017 [17]	1	18	POTS	Fatigue, presyncope, nausea	Improved with immunotherapy	Cross reacting antibodies	+ anti NMDA, beta2 and muscarinic 2 antibodies

Two of the largest case series on HPV vaccine adverse events describe a short time interval between HPV vaccination and illness onset. Brinth et al. published 35 patients in whom the symptoms appeared on an average of 9.3 days after vaccination (range 0–30 days) [7]. Martínez Lavín et al. reported 45 patients. The time elapsed between HPV vaccination and symptoms onset was 2.3 ± 3.1 weeks (mean ± standard deviation). Twenty-nine percent of these cases had the illness onset within 24 h after the jab [14].

Available information suggests that the affected girls were healthy before vaccination. Case series describe them as previously healthy and athletic [7]. Nevertheless, a large Danish registry-based case-control study found that females who developed adverse events to HPV vaccination had more pre-immunization symptoms and health care-seeking pattern than those individuals without post-immunization illness. The authors provide two possible explanations for the background health-seeking behavior imbalance: The illness may have been already present at the time of vaccination, and/or in certain situations, HPV vaccine may trigger an illness in a vulnerable subpopulation [59].

Postural orthostatic tachycardia syndrome following HPV vaccination

The quadrivalent HPV vaccine Gardasil was approved by the United States Food and Drug Administration for prevention of cervical cancer in women, age 9–26, in 2006. In 2009, a post-licensure safety surveillance analysis revealed a reported rate of 8.2/100,000 doses of HPV vaccine distributed for syncope and 6.8/100,000 for dizziness [47]. Although syncope immediately following the injection is noted as the most common adverse effect of Gardasil, the rate of chronic, recurrent neurocardiogenic syncope, or the rate of other autonomic disorders, such as POTS, was not assessed in this post-licensure safety study.

In 2010, Blitshetyn described the first case of new-onset POTS after HPV vaccination, followed by a case series of six patients with POTS after vaccination with Gardasil [10, 11]. All six previously healthy young women developed symptoms of POTS within 6 days to 2 months after immunization, and all patients were initially misdiagnosed with other conditions. Three patients also had neurocardiogenic syncope, and three patients were diagnosed with possible small fiber neuropathy. Two of the six patients had positive antinuclear antibody (ANA) test, and all patients had significant fatigue, weakness, orthostatic tachycardia, and impaired functional status, including inability to participate in sports. Symptoms in all patients improved over 3 years with pharmacotherapy and non-pharmacologic measures, but residual symptoms persisted [11].

Subsequently, another case of a young woman who developed POTS after vaccination with Gardasil was reported, and this patient also had a positive antinuclear and antiphospholipid antibodies [60]. The authors proposed that post-vaccination autoimmune disorders, post-vaccination autoantibodies, and symptoms of arthralgia, myalgia, weakness, fatigue, and other manifestations are all part of the criteria for the diagnosis of ASIA syndrome [16]. The term "ASIA-Autoimmune/inflammatory Syndrome Induced by Adjuvants" (ASIA) encompasses an array of clinical conditions and has been reported as a suspected side effect to the HPV vaccine [46].

In 2014, 40 adolescent patients with various neurological symptoms developed following HPV vaccination were reported from Japan. Symptoms in these girls included pain and weakness in the extremities, orthostatic dysregulation, fatigue, and significant functional impairment, such as inability to concentrate and participate in previous activities. Four of 40 patients (10%) tested positive for POTS [6]. In a larger case series of 53 patients with autonomic symptoms after HPV vaccine from Denmark, 28 patients had objective evidence of POTS [7].

Complex regional pain syndrome after HPV vaccination

In 2014, Kinoshita et al. described peripheral sympathetic nerve dysfunction in 40 Japanese girls following HPV vaccination. Similar to other reports, these HPV-vaccinated girls had a multisystem disorder. Fourteen of them fulfilled the diagnosis of CRPS [6]. Richards et al. from Australia published four similar cases of CRPS as suspected side effects to HPV vaccine [61].

Fibromyalgia after HPV vaccination

In a preliminary abstract publication, Nishioka et al. described 25 Japanese girls with fibromyalgia-like symptoms after HPV vaccination [13]. Martínez-Lavín et al. reported that 23 out of 45 patients from 13 different countries who had the onset of a chronic illness soon after HPV vaccination fulfill the 2010 American College of Rheumatology criteria for fibromyalgia [14].

Myalgic encephalomyelitis/chronic fatigue syndrome after HPV vaccination

Brinth et al. reported that 35 out of 39 Danish patients referred to their Syncope Unit with the suspicion of HPV vaccination untoward reactions fulfilled the new criteria for system exertion intolerance disease also known as ME/CFS [9]. Both the Danish and the Dutch health authorities found a signal with

long-lasting fatigue as suspected side effect to HPV vaccines [4]. Palmieri et al. reported 18 Italian girls with similar severe dysautonomia symptoms to those described by other clinicians. A proportion of them could be classified as having fibromyalgia or ME/CFS [58].

Studies reporting no association between HPV vaccines and POTS or fatigue-related conditions

Several studies have found no association between HPV vaccines and POTS or fatigue-related conditions. Donegan et al. reported no association between Cervarix vaccination and fatigue related conditions in United Kingdom [62], and a large Scandinavian cohort study by Arnheim Dahlström et al. found no evidence supporting associations between Gardasil and an array of well-defined autoimmune conditions [63]. More recently, Arana et al. searched the 40,735 VAERS reports following HPV vaccination and identified only 29 POTS cases who fully met the diagnostic criteria for POTS. The authors concluded that POTS is rarely reported following HPV vaccination and that no unusual or unexpected reporting patterns suggesting a safety problem was detected [64].

Although we fully acknowledge the value of these large studies, it is important to recognize their inherent limitations. POTS is notoriously under-diagnosed, misdiagnosed, and therefore under-reported in the VAERS passive surveillance system. The very diffuse symptoms experienced by the affected patients and the lack of diagnostic biomarkers will inevitably lead to marked diversity in diagnostic practice between countries and clinical specialties.

Case-series and evidence-based medicine

Case series and case reports rank low in evidence-based medicine hierarchy. Nevertheless, they have their own role in the progress of medical science. They permit discovery of unexpected drug effects [65]. The fact that very similar post-HPV vaccination syndromes have been described by independent investigators raises the possibility of a real association between HPV vaccine and autonomic dysfunction syndromes [45].

This proposed HPV vaccine-dysautonomia link is reinforced by the VigiBase study. VigiBase is the largest international data base on drug adverse events. Symptom clusters of headache and dizziness with either fatigue or syncope were found to be more commonly described, and more severe, in HPV vaccine notifications compared with non-HPV vaccine reports for females of similar age. The minority of reports contained specific diagnosis [66].

After preparation of our manuscript, a large case-control postal survey from Nagoya Japan was published. The study included 29,846 females born between 1994 and 2001. No significant increase in occurrence of any of the 24 reported post-HPV vaccination symptoms was found in vaccinated girls when compared to unvaccinated individuals. Nevertheless, a subgroup analysis excluding individuals who had the onset of symptoms before the first HPV vaccination did find several statistical differences. This subgroup analysis revealed that hospital visits due to menstrual irregularity, abnormal amounts of menstrual bleeding, pain in the joints or other parts of the body, severe headache, fatigue, poor endurance, difficulty concentrating, dizziness, loss of ability to walk in a normal way, sudden loss of strength, and weakness in the hand and feet were significantly more frequent in the vaccinated cohort [67].

Is there an HPV vaccination syndrome?

While acknowledging that temporality cannot confirm causality, we, the four authors of this review, have directly evaluated patients with severe chronic autonomic dysfunction developed shortly after HPV vaccination. We are impressed not only by the illness severity, but also by the diagnostic and therapeutic difficulties. The multiplicity of symptoms that these patients have makes it complicated to label them with a specific diagnosis. Japanese investigators have proposed preliminary diagnostic criteria for this apparently new syndrome [13, 68]. According to these guidelines, after HPV vaccination, the most frequent symptoms these patients have are prolonged fatigue, chronic headache, widespread pain, tremor, myoclonus, fainting, altered gastrointestinal motility, limb weakness, gait disturbances, paresthesias, photophobia, sleep disturbances, memory impairment, difficulties in concentration, and menstrual abnormalities. This set of symptoms may serve as a guideline to consider the possibility of an HPV vaccine adverse reaction. The use of COMPASS questionnaire, neuropathic pain questionnaires, tilt table testing, and skin biopsies may help in the clinical assessment of such cases. These tools may help to identify a neuropathic component in the pain experience, autonomic symptom burden, POTS, or small fiber neuropathy [7, 10, 14].

Case reports of autoantibodies in dysautonomia syndromes following HPV vaccination

Isolated reports have described the presence of antibodies directed to different autonomic nervous system domains in dysautonomia syndromes following HPV vaccination. Hendrickson and Tormey reported a 14-year-old girl with severe post-HPV vaccine dysautonomia displaying antibodies to nicotinic acetyl-choline ganglionic receptors, as well as adrenergic and muscarinic M2 receptors [60, 69]. In another

case report, Blitshteyn described an 18-year-old girl who developed POTS after Cervarix, associated with serum anti-NMDAR antibody, as well as beta 2 adrenergic and muscarinic M2 antibodies, without evidence of encephalitis [17]. A similar case of an 11-year-old who developed POTS and NCS after Gardasil with positive adrenergic and muscarinic antibodies was published by Schofield and Hendrickson [70].

Additionally, there is new evidence that patients with neurologic symptoms developed after HPV vaccine have abnormalities in the spinal fluid consistent with neuro-inflammation and neuro-immune process. In a study of 32 patients with persistent neurologic symptoms after HPV vaccine, researchers found increased pro-inflammatory cytokines and antibodies to GluN2B-NT2, GluN2B-CT, and GluN1-NT receptors compared to the healthy controls [71].

Considering that vaccines can elicit autoimmunity in genetically susceptible individuals, we believe that further investigation of the prevalence of the autoantibodies, utilizing a large well-designed case-control study is warranted. The presence of autoantibodies does not necessarily equate to the occurrence of a specific disease and does not answer the question of causality with regard to the HPV vaccine. The hope, however, is that increased awareness of these disorders brought about by the controversy surrounding the HPV vaccines will lead to a more coordinated research effort worldwide, with the goal of developing improved diagnostic and therapeutic strategies for patients affected by these disorders.

Bradford-Hill criteria for causality and HPV vaccine adverse events

Bradford Hill proposed 9 item criteria to assess the cause–effect relationship between an environmental factor and an undesirable event. The nine items include strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy [72]. When these criteria are applied to HPV vaccine adverse events, we find a temporal association between HPV vaccination and the development of autonomic dysfunction. This association has also shown consistency. A similar syndrome has been observed by independent clinicians, in different places, circumstances, and times. There appears to be a biological gradient for HPV adverse events. As already stated [45], the largest Gardasil randomized trial evaluated 7071 women immunized with the HPV 9-valent dose vs. 7078 women injected with the quadrivalent HPV formula [73]. The 9-valent dose has more than twice the amount of virus-like particles and aluminum adjuvant compared to the 4-valent counterpart. Severe (> 5 cm) injection site swelling was seen more often in the 9-valent group; 3.8% vs. 1.5% $p < 0.01$. Vaccine-related systemic events occurred significantly more frequently in the 9-valent group ($n = 2086$ or 29.5%) than in the 4-valent group, ($n = 1929$ or 27.3%, $p = 0.003$). Serious systemic adverse events were more frequent in the 9-valent arm of the study; 233 (3.3%) vs.183 (2.6%) $p = 0.01$. These data raise the possibility that HPV vaccine adverse events may be dose-related. Furthermore, HPV vaccine triggered immune mediated autonomic dysfunction is being proposed as plausible pathogenetic mechanism. Additional clinical and experimental research is needed to investigate any HPV vaccine–autonomic dysfunction relationship.

Personal predisposition to vaccine untoward reactions: adversomics

The relative rareness of suspected HPV vaccine-related events suggests that there may be a personal susceptibility to the development of adverse reactions. Gender may play a possible role. HPV vaccine has been given predominantly to females, who are much more vulnerable to developing autonomic disorders such as POTS, CRPS, and fibromyalgia. Furthermore, it is known that some individuals are genetically predisposed toward autoimmune disorders and have a higher risk of adverse events following vaccination [60]. This fact is underscored by the emerging field of adversomics focusing on genetically determined vaccine-associated adverse events [74]. Narcolepsy was seen after the influenza vaccine Pandemrix in subjects of a specific HLA subtype, and common variants of certain genes have been associated with an increased risk of febrile seizures after measles, mumps, rubella vaccination [75, 76].

Concluding remarks

There is substantial evidence from case series reported from various countries that the HPV vaccine may be associated with phenotypic syndromes that share common pathogenesis involving the autonomic nervous system, potentially including underlying autoimmune processes. Being cognizant that a temporal relationship between vaccination and symptom onset does not necessarily equate to causality, the mounting evidence calls for further investigation to determine the prevalence and possible causation between these post-vaccination syndromes and HPV vaccines.

Recent publications concerning ME/CFS, CRPS, and POTS have demonstrated autoantibodies with agonistic effects on receptors in the autonomic nervous system [44, 48, 51, 55]. Such agonistic autoantibodies could help explain the autonomic dysfunction described in many patients with suspected side effects to the HPV vaccines. Considering that vaccines can elicit autoimmunity in genetically susceptible individuals, we believe that further investigation of prevalence of the autoantibodies utilizing a large well-designed case-control study is warranted. As we enter the era of personalized medicine, our hope is that eventually, we would be able to identify individuals with a

genetic predisposition toward vaccine-related adverse events via the use of high-throughput technology (adversomics).

Authors' contributions All authors actively participated in the design and writing of the article. All authors approved the final version of the manuscript.

Compliance with ethical standards

Conflicts of interest Manuel Martínez-Lavín declares no conflict of interest. Jeanne Hendrickson declares no conflict of interest. Svetlana Blitshteyn has served as a medical expert witness on cases of POTS and other neurologic syndromes after Gardasil vaccine. Louise Brinth declares no conflict of interest.

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