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REVIEW ARTICLE

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

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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 syndromes.

Keywords Complex regional pain syndrome · Dysautonomia · Fibromyalgia · HPV vaccination · Postural orthostatic tachycardia syndrome · Small fiber neuropathy · Sympathetic pain

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Vaccination has been one of the most effective public health measures in the history of medicine http://www.cdc.gov/vaccines/ (accessed 6 April 2015). 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]. Different adverse reactions have been reported from several parts of the world after HPV vaccination. A patterned illness of chronic pain and autonomic dysfunction seems to be emerging from these reports [2–5]. Kinoshita et al. [2] and Brinth et al. [4] have recently published well-documented evidence of different expressions of sympathetic dysfunction in sizable groups of girls that received the HPV vaccine.

There appears to be a disconnection between the self-reported severe reactions that frequently appear in the social media blogs http://sanevax.org (accessed 4 April 2015), in contrast with the opinion of health authorities that classify the purported side effects as coincidental or not specific for a definite diagnosis [6]. Some investigators have classified these post-vaccination responses as "mass psychogenic illness" [7]. Nevertheless, during the last months, the medical scientific literature has documented case reports and small series describing severe adverse reactions to the HPV vaccine that might have common underlying pathogenesis. HPV vaccine-induced illnesses include complex regional pain syndrome (CRPS) [2], postural orthostatic tachycardia syndrome (POTS) [2–4], and fibromyalgia [8, 9], among others. These illnesses are often difficult to recognize. Various traditional physicians deny the mere existence of these syndromes disregarding them as somatization disorders or psychogenic illnesses [10, 11].

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This piece proposes that HPV vaccine-induced small fiber neuropathy and dysautonomia could be the common underlying pathogenesis to the group of rare, but severe, reactions that follow HPV vaccination.

Dysautonomia and small fiber neuropathy

The term dysautonomia refers to a change in autonomic nervous system function that adversely affects health. The changes range from episodes of neurally mediated hypotension and/or tachycardia, sympathetically-maintained pain syndromes, to progressive neurodegenerative disorders [12].

Small fiber neuropathy is a disease of the most distal nociceptive and sympathetic fibers. The outstanding clinical features of small fiber neuropathy are pain paresthesias and autonomic dysfunction. Neurological examination is usually normal, as are the electromyography and clinically available nerve conduction studies. The diagnosis of small fiber neuropathy is confirmed by skin biopsy [13, 14]. Corneal confocal microscopy is a new method to assess small nerve fiber pathology [15]. These objective procedures show diminished intraepidermal or corneal small fiber innervation.

Adverse events that follow HPV vaccination

Adverse reactions appear to be more frequent after HPV vaccination when compared to other type 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 had 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 HVP vaccine adverse reaction was classified as "severe" [16]. Similar percentage of HPV vaccine adverse reactions events was reported to the Danish Health Authorities in 2013. There were 511 adverse events (177 serious) per 488,224 HPV vaccine doses sold [6]. In 2013, the Japanese Health Ministry stopped actively recommending HPV vaccination while investigating 24 cases of an illness similar to CRPS that emerged after HPV vaccination [1].

Adverse reaction after HPV vaccination described in medical literature Syncope

Syncope is defined as a short loss of consciousness and muscle strength, characterized by a fast onset, short duration, and spontaneous recovery. It is due to a decrease in blood flow to the brain. The syncope has been recognized by the World Health Organization ad Hoc committee, as HPV vaccine side-effect [1]. Several studies concur with this opinion [2–4, 16]. As a response to this untoward reaction, a 15-min observation period following vaccination has been officially recommended. Convulsive episodes might accompany syncope.

Postural Orthostatic Tachycardia Syndrome

POTS is a heterogeneous disorder of the autonomic nervous system characterized by orthostatic tachycardia, other symptoms of orthostatic intolerance such as syncope, and non-orthostatic symptoms such as fatigue, gastrointestinal disturbance and migraine headache, an overwhelming majority of affected individuals are young women [17]. POTS is diagnosed with the head up tilt table test proving orthostatic intolerance and a sustained heart rate increment of >30/min or to levels above 120/min within 10 min of postural change in the absence of overt orthostatic hypotension. An increase of >40/min was required for patients aged 12 to 19 years [18].

Several groups of investigators described POTS onset after HPV vaccination. Blitshteyn published six cases presenting this association. Three of the six cases had possible small fiber neuropathy with abnormal quantitative sensory testing [3]. Four of the 40 Japanese girls with HPV vaccine untoward reactions described by Kinoshita had POTS [2]. Brinth et al. studied 53 Danish girls referred to a syncope clinic with symptoms of orthostatic intolerance that appeared post HPV vaccination. Half of these 53 patients were diagnosed with POTS. It is notable that these POTS patients also complained of widespread pain paresthesias, disordered sleep, cognitive dysfunction, and fatigue [4]. These symptoms suggest the concomitant presence of fibromyalgia.

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 [19]. As already stated, the Japanese Healthy Ministry is investigating cases of CRPS related to HPV vaccination [1]

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 [2]. Richards et al. from Australia

published four similar cases of HPV vaccine that evoked CRPS [20].

Fibromyalgia

Fibromyalgia is a syndrome that predominately affects women. Widespread pain, widespread allodynia, paresthesias, fatigue, sleep disorders, and cognitive difficulties characterize this illness. Besides these defining features, patients with fibromyalgia frequently display an array of multisystem complaints [21]. Physical and/or mental stressors could trigger fibromyalgia [22]. I have personally taken care of two girls who develop severe incapacitating fibromyalgia-like illness after HPV inoculation [8]. Follow-up observation has shown that similar to what has been reported in other post HPV vaccine cases [2, 4] these two girls have developed intermittent motor problems with myoclonus. In a preliminary abstract publication, Nishioka et al. described 25 Japanese girls with fibromyalgia-like symptoms after HPV vaccination [9].

Dysautonomia as the common underlying dysfunction linked with the HPV vaccination syndrome

A yin-yang harmonic interaction of the two autonomic nervous system branches (sympathetic and parasympathetic) keeping homeostasis is crucial. In healthy circumstances, the autonomic nervous system immediately responds to any gravitational force in order to preserve adequate cerebral perfusion. The autonomic nervous system also plays a key role in the proper function of all internal organs. The sympathetic branch of the autonomic network is an important part of the stress response system. Sympathetic dysfunction may induce chronic vexing pain syndromes [21]. Different traumatic events can trigger the development of sympathetically-maintained pain syndromes [22]. Animal models have helped to advance our understanding of sympathetically-maintained pain syndromes. A murine 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. Dorsal root ganglia contain the small nerve fibers cell bodies. Particular SCN9A gen encoded dorsal root ganglia sodium channels are involved in pain transmission and sympathetic function [23].

Dysautonomia is a fundamental pathogenetic substrate in cases of syncope and POTS leading to diminished cerebral perfusion and/or the development of tachycardia [4, 17, 18]. Autonomic dysfunction likely plays a major role in CRPS, inducing local temperature and sweat alterations as well as a sympathetically-maintained pain state [24]. Our group has presented evidence suggesting that autonomic dysfunction plays a key part in the development of fibromyalgia and that fibromyalgia is a sympathetically maintained neuropathic pain syndrome [21, 22].

The three dysautonomic syndromes under discussion have a clear clinical overlap. Patients with syncope or POTS frequently have concurrent fibromyalgia [25]. As already stated, the clinical features of the HPV vaccine-related POTS described by Birth et al. also include widespread pain, paresthesias, fatigue, cognitive dysfunction, and disordered sleep suggesting the presence of concomitant fibromyalgia [4]. CRPS may evolve into a fibromyalgia-like widespread pain syndrome [26].

Small fiber neuropathy considered as possible underlying pathological substrate in post HPV vaccination syndrome

As mentioned before, small fiber neuropathy induces pain, paresthesias, and autonomic dysfunction [13]. These are alterations commonly found in CRPS [19], POTS [17], fibromyalgia [21, 22], and also in the post HPV vaccination reports [2, 4].

Haensch et al. performed skin biopsies in 84 patients with POTS. Forty-five percent had intraepidermal nerve fiber density below the normal range. Decreased nerve fiber density correlated with reduced myocardial metaiodobenzylguanidine uptake, suggesting cardiac denervation [27]. Oaklander et al. described evidence of small-fiber axonal degeneration in 17/18 individuals with CRPS [28]. Different groups of investigators have found that fibromyalgia patients frequently have skin biopsy abnormalities or corneal confocal microscopic changes consistent with small fiber neuropathy [14, 15].

This recently gathered evidence suggests that small fiber neuropathy could be the underlying mechanism for the pain and autonomic dysfunction seen in CRPS, POTS, and fibromyalgia. This common pathogenesis may also explain their overlapping clinical features. Therefore, this article proposes as a hypothesis that small fiber neuropathy may also explain the pain and autonomic dysfunction seen in post HPV vaccination syndrome.

How HPV vaccination could possibly induce small fiber neuropathy and autonomic dysfunction?

At this stage of knowledge in which a possible association between HPV vaccine and clinical syndromes is being explored, it seems risky to propose any potential pathogenetic mechanism. Yet, some speculations may be put forward: The rareness of HPV vaccine-related events described so far suggests that there is a personal susceptibility to develop adverse

reactions. Gender may play a role. HPV vaccine has been given (so far) mostly to women who are much more vulnerable to develop painful dysautonomic syndromes such as POTS, CRPS, and fibromyalgia. The vaccine adjuvant aluminum remains a culprit. An altered process of inactivated HPV virus and aluminum adjuvant that damage dorsal root ganglia could be suggested as a preliminary pathogenetic speculation for the development of small fiber neuropathy. In animal models, aluminum is able to damage dorsal root ganglia [29]

Other types of aluminum containing vaccines have been associated to inflammatory—autoimmune syndromes such as ASIA syndrome [30] and macrophagic myofasciitis [31].

Divergence between self-reported HPV vaccination illness and health authority's assessment

The self-reported (or mom's reported) HPV vaccination illness that appear in different social media blogs http://sanevax.org (accessed 4 April 2015) are in many instances similar to the cases described in medical literature. There is no reason to believe that these self-described cases are fabricated. Except for the Japanese Health Minister that declared a moratorium on HPV vaccination, other health authorities have not found enough evidence to modify the current WHO recommendation. One possible reason for this stance is the lack of specific diagnosis of the untoward vaccine reactions. In the third quarter of 2014, the Danish Health and Medicines Authority received 14 cases of serious adverse events to HPV vaccine. Five of them were described by the Health Authorities as having "multiple symptoms with pain" (or dizziness), with no specific diagnosis. The lack of explicit diagnosis led to the conclusion that it was "not possible to assess any causality" [6]. It would seem valid to speculate that some of these undiagnosed cases may have one of the painful syndromes under discussion.

A cluster of cases that occurred after HPV vaccination in Australia [7] and in Colombia http://news.yahoo.com/mystery-illness-plagues-girls-colombia-052825963.html (accessed on 4 April 2015) was classified as "mass psychogenic response". Regardless of the etiology of such cases, the fact remains that a severe illness, whatever it was, started after HPV vaccination. There is no scientific information on the final outcome of these "psychogenic cases".

Anecdotal cases and small series in no way prove causality, but a patterned illness of chronic pain paresthesias and autonomic dysfunction after HPV vaccination seems to be emerging. Kinoshita et al. [2] and Brinth et al. [4] series are compelling.

Thalidomide and cisapride side effects were recognized thanks to initial case reports describing severe untoward reactions. HPV vaccination has a very special setting. The vaccine is given to healthy girls (and now boys) during a crucial period of their lives. Therefore, the outmost attention should be paid to any possible untoward reaction.

HPV vaccine efficacy on cervical cancer mortality is inference based

There is solid scientific information linking HPV infection with the subsequent cervical cancer development [32]. Nonetheless, the majority of HPV infections will be cleared by cell-mediated immune responses within 3 years of infection. On the other hand, the duration of HPV vaccine-induced antibodies is not known [33]. So, it will take decades to define the actual HPV vaccine efficacy on cervical cancer mortality. The linear-reductionist approach of a vaccine application for the global prevention of a neoplastic disease although attractive may be routed by human physiology complexity. Guo et al. described in an abstract form that women who received the quadrivalent HPV vaccine were more likely to be infected with other high-risk HPV strains not included in the vaccine, when compared with women that did received the HPV vaccine [34]. The proposal that HPV vaccine will have an impact on cervical cancer prevalence and mortality needs factual corroboration.

Conclusions

Case reports and small series have described the onset of CRPS, POTS, and fibromyalgia after HPV vaccination. Dysautonomia plays an important role in the pathogenesis of these overlapping syndromes. Small fiber neuropathy has been recently described in CRPS, POTS, and fibromyalgia. Pain and dysautonomia are the clinical manifestations of small fiber neuropathy and of HPV vaccination syndrome. Clinicians should be aware of the possible association between HPV vaccination and the development of the puzzling CRPS POTS and/or fibromyalgia symptoms.

Disclosures None.

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