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RESEARCH ARTICLE

Human papillomavirus (HPV) vaccine and autonomic disorders: a position statement from the American Autonomic Society

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Abstract

Introduction Human papillomavirus (HPV) vaccination has been anecdotally connected to the development of dysautonomia, chronic fatigue, complex regional pain syndrome and postural tachycardia syndrome.

Objectives To critically evaluate a potential connection between HPV vaccination and the above-noted conditions.

Methods We reviewed the literature containing the biology of the virus, pathophysiology of infection, epidemiology of associated cancers, indications of HPV vaccination, safety surveillance data and published reports linking HPV vaccination to autonomic disorders.

Results At this time, the American Autonomic Society finds that there are no data to support a causal relationship between HPV vaccination and CRPS, chronic fatigue, and postural tachycardia syndrome to other forms of dysautonomia.

Conclusion Certain conditions are prevalent in the same populations that are vaccinated with the HPV vaccine (peri-pubertal males and females). This association, however, is an insufficient proof of causality.

Keywords Consensus statement · Postural tachycardia syndrome · HPV · Vaccine · Autonomic dysfunction

Impact of human papilloma virus on human health

Human papillomaviruses (HPV) are non-enveloped viruses with a double-stranded circular DNA genome. The genome is enclosed in an icosahedral capsid, which is made up of two proteins: the major capsid protein (L1) and the minor capsid protein (L2). HPV is the most common sexually transmitted infection in the USA. An estimated 14 million persons are newly infected with HPV each year in the USA with nearly half occurring in adolescents and young adults [1]. Although HPV infection is common (40–80% lifetime probability of infection) [2], most infections are cleared by a cell-mediated immune response [3].

Epidemiological data support the existence of a group of high-risk human papilloma viruses associated with cancer: HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 [3, 4]. These high-risk viruses cause dysfunction of cell cycle regulators and cause neoplasia [3, 5]. Inability of the immune system to clear this high-risk infection is another hypothesized pathway leading to cancer [6]. HPV infection causes cancers at transformation zones between different kinds of epithelium: cervix, anus, and oropharynx [7]. In addition to oncogenic HPV infection, concomitant sexually transmitted diseases, multiparity, smoking, and hormonal contraceptive use are other identified risk factors for cervical cancer [7]. There is a severity-dependent infection prevalence: tests for HPV DNA are positive in 11.7% with normal cervical cytology, 50–70% of cervical intraepithelial neoplasia (CIN) 1, 85% of CIN 2, 90–100% of CIN 3, 85% of vaginal cancer,

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80–96% of anal cancer, 40–70% of invasive penile cancer, and 72% of squamous cell head and neck cancer [3, 4].

Infection with HPV is recognized as one of the major causes of infection-related cancer worldwide [8]. Persistent oncogenic HPV infections cause over 500,000 cancers worldwide and 30,000 cancers [7, 9, 10] in the USA annually, with more than half of those cases leading to death [11]. Cervical cancer is the fourth most common cancer in women and the second largest cause of mortality from cancer in the developing world [11–15]. HPV also has a major role in the etiology of squamous cell carcinoma of the anus (men and women), vulva, vagina, penis, mouth, and oropharynx [16–18].

Current approach to treatment of HPV-related diseases

Education, abstinence, and condom use can all reduce infection risk, but even strict condom use is not completely protective in males [7]. Current treatments cannot eliminate HPV, thus contributing to high infection prevalence [4].

HPV vaccination is effective in preventing infection and thus development of high-grade precancerous lesions [7, 19]. Phase III randomized controlled trials of prophylactic HPV vaccination were designed to prevent incident-related HPV infection and thus pre-neoplastic lesions [20, 21]. All vaccines demonstrated high immunogenicity and efficacy in preventing persistent infection (90% infection reduction, 90% reduction in genital warts) and precancerous (CIN3) lesions (85% reduction) [20]. This makes HPV vaccination a high-value public health intervention [8].

Three HPV vaccines licensed in the USA (Cervarix, Gardasil, and Gardasil 9) protect against infection with HPV types 16 and 18 which cause over 60% of cervical and oropharyngeal HPV-related cancers. In addition, quadrivalent (Gardasil) and nonavalent (Gardasil 9) HPV vaccines protect against HPV types 6 and 11, which cause 90% of genital warts, and Gardasil 9 protects against five additional oncogenic HPV serotypes. These vaccines are composed of virus-like particles (VLPs) derived from the major capsid protein (L1) of HPV, contain no genetic viral material, and are highly immunogenic. All three available vaccines are most effective in preventing HPV-related disease in naïve patients only and ideally should be administered before onset of sexual activity. As the vaccines induce humoral immunity and not cell-mediated immunity, they have no therapeutic effect in patients who already have genital lesions or HPV-related cancer [19].

On the basis of phase III trial data, in 2006, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommended routine vaccination of females 11–12 years of age and catch-up vaccination of females 13–26 years of age with a series of three doses of Gardasil given at baseline, 1–2 months after initiation, and 6 months after initiation [13]. Routine Gardasil vaccination of males 11–12 years of age, with catch-up vaccination of males 13–21 years of age, was recommended by the ACIP in 2011 [22]. The US Food and Drug Administration (FDA) licensed the nonavalent Gardasil vaccine in 2009 for females and in 2014 for males [23]. Given the high immunogenicity of Gardasil among males (97.4–99.2% seroconversion at 7 months) [24] and suboptimal vaccination coverage among females, HPV vaccination of males benefits females through herd immunity [23]. Furthermore, HPV vaccination will play an important role in stemming the increasing incidence of HPV-related oropharyngeal cancers in males which is expected to exceed that of cervical cancer in the USA by 2020 [22].

HPV vaccine safety

Population-based vaccination program implementation includes monitoring of coverage, impact, and safety [8]. There are passive monitoring programs which have limitations, like incomplete reporting and coincidental associations. Because of this shortcoming, routine formal evaluations of the passive report systems are performed. There have been multiple post-licensure vaccine safety evaluations, independent of the manufacturers, both in the USA and internationally [8]. In addition, comprehensive, independent scientific reviews have been conducted to assess the safety of the HPV vaccines [25, 26].

The most common adverse events associated with HPV vaccines (as a group) reported in the literature are injection site-related: local pain, redness, and swelling. Reported systemic side effects include fatigue, fever, GI symptoms (diarrhea, nausea, vomiting), headache, myalgia, and arthralgia [19, 22, 27, 28]. Syncope is a manageable side effect of vaccination in general and simple measures can be adopted to avoid it [26]. All reported symptoms are transient and do not worsen with subsequent vaccine doses. To date, the data from clinical trials and available post-marketing periodic safety updates have indicated acceptable safety of HPV vaccines. In fact, systemic side effects did not differ between vaccinated and placebo groups for bivalent, quadrivalent, and nonavalent vaccines, and there is no increased risk of death associated with HPV vaccination [26, 29].

Data released by the Global Advisory Committee on Vaccine Safety (GACVS) in June 2017 [30] included a safety update on HPV vaccines. Since licensure in 2006, over 270 million doses of HPV vaccines have been distributed. The committee evaluated safety data for this vaccine in 2007, 2008, 2009, 2013, 2014, and 2015. Evaluation of large population-based data by the GACVS from multiple countries

found no causal association between HPV vaccination and diverse symptoms that included chronic pain, motor dysfunction, complex regional pain syndrome (CRPS), or postural tachycardia syndrome (POTS) [30].

A review of reports of POTS following HPV vaccination by the Vaccine Adverse Reporting System (VAERS), commissioned by the CDC and the FDA, found approximately one POTS case for every 6.5 million worldwide distributed HPV vaccine doses (29 cases total) between 2006 and 2015. Twenty of these cases had a history of pre-existing medical conditions: chronic fatigue, asthma, and chronic headaches. For this time period, the crude reporting rate of POTS after HPV vaccination was rare, measuring 0.07% [31].

To understand the association between HPV vaccination and autonomic and/or pain disorders, a large registry-based hospital study in Finland investigated the incidence of autonomic or pain disorders for the years 2002–2012, which were *prior* to the introduction of the HPV vaccine in Finland. In 2002, there were two cases of POTS per 100,000 person-years, and this increased by 2012 to almost 13 cases of POTS per 100,000 person-years [32]. The investigators found that one cause for the higher annual incidence rate for POTS and chronic fatigue syndrome (CFS) was increased physician awareness of these diagnoses. It is imperative that this general increase in incidence and/or awareness of autonomic disorders is accounted for in the interpretation of data concerning any potential impact of HPV vaccination on autonomic disorders.

Dissenting opinions regarding safety

Anecdotal reports alleging possible adverse events following HPV vaccination have been published [33–40]. Cited adverse events include dysautonomia, CFS, CRPS, and POTS [39].

A presumed immunological or inflammatory response to vaccination is considered the linking mechanism to the development of POTS, pain syndrome, or other form of dysautonomia [33–40]. In a review of these publications, several key factors are apparent:

1. Some of the reported cases labeled as post HPV vaccine POTS did not have a well-defined diagnosis [37, 38], did not take into consideration effects of physical deconditioning on bedside testing [40], and clinical descriptions did not fit the accepted definition of POTS for both adolescents and children [37, 41].
2. Overall, the number of reported or observed POTS cases after vaccination was generally lower compared to the expected incidence that would occur naturally in the target population under almost all assumptions for all regions and countries, except for Denmark, where the majority of POTS cases that have been reported come from one syncope unit [42, 43].
3. Critical analysis of the Danish cohort study revealed a flawed scientific approach [43]. The Scientific Advisory Group of the European Medicines Agency investigated the Danish Syncope Unit Cohort in more detail and concluded: "this was a highly selected sample of patients, apparently chosen to fit a pre-specified hypothesis of vaccine-induced injury" [43]. All patients were referred to the same syncope unit for evaluation for an existing concern of HPV vaccine-induced illness, which makes the case series unrepresentative of the general population, and there was no control group [42]. The methods used to ascertain the trigger and time to onset of specified symptoms of autonomic dysfunction may inherently have biased patient recall [31]. There was no consistent relationship with the dose sequence to support the notion that this case series is suggestive of a specific autoimmune response to the vaccine [43].

Despite having issues in case ascertainment and classification, unsuitable analytic methods, and misleading conclusions [26], these case reports have drawn media attention to a small numbers of individuals with purported adverse reactions to HPV vaccination. The reports influence how providers communicating risks associated with not vaccinating [44, 45] are confounded by patient care-seeking behavior patterns pre- and post-vaccination [46], thus reducing the number of vaccinated individuals. In fact, the reports have created widespread fear, resulting in decreased vaccination rates or even dismantling of vaccination programs in some countries [32, 47].

It is common for a diagnosis of any syndrome or disease, including a persistent autonomic or pain disorder, to be attributed to a recent life event such as a recent illness, trauma, or even vaccination [25, 26]. The fact that certain conditions peak in incidence at the same age, and in the same population that is being vaccinated (peri-pubertal males and females), is insufficient proof of causality, especially with chronic illness such as dysautonomia and POTS, which have relapsing–remitting courses and frequent exacerbations caused by a variety of factors. Attribution of causality requires solid epidemiological data demonstrating evidence for causality at the population level, with supporting evidence of biological plausibility [48, 49].

American Autonomic Society position

At this time, the American Autonomic Society (AAS) finds that the data do not support a causal relationship between HPV vaccination and CRPS, POTS, or other forms of dysautonomia. Large population studies and exposure of over 270

million people to the HPV vaccine have not resulted in an identifiable pattern of adverse events, and no evidence of an increase in dysautonomia or POTS with use of the vaccine.

The AAS acknowledges that several groups have dissenting opinions [33–40, 47]. However, the data at this time constitute only weak temporal associations between events, and their hypothesized mechanisms have not been scientifically proven. The small sample sizes, inherent selection biases, and lack of control populations preclude drawing any scientifically valid conclusions of causality [31, 42, 47].

The AAS recognizes that HPV increases the risk of cancer in patients who become infected. In the absence of compelling data for harm from vaccination, we are concerned that isolated reports linking HPV vaccination to autonomic disorders or chronic pain disorders may cause needless panic in those at risk for HPV infection and decrease the rate of HPV vaccinations. Neglecting HPV vaccination has the potential for significant public harm by eliminating equitable protection from vaccination against HPV-related cancer [26]. For example, in Japan where HPV vaccination was not proactively recommended, mortality from cervical cancer increased by 3.4% between 2005 and 2015 [44]. In contrast, herd immunity seems to develop in countries with a vaccination rate greater than 50%, with an associated decline in cancer rates [12, 50].

As with any reported autonomic disorder, the AAS supports ongoing surveillance and collection of data including the type and timing of symptom onset after vaccination, and the objectively measured severity of potential autonomic adverse effects related to HPV vaccination [23, 32, 46, 51–57]. The AAS also supports ongoing, well-designed, long-term population-based epidemiological studies that assess the safety and efficacy of vaccines of any sort. However, the AAS warns against drawing premature conclusions from poorly designed trials or small cohort studies that do not adequately assess the risks and benefits of population-level vaccination.

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Compliance with ethical standards

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