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[Nicole Schipperjin](#) * , [Megan Wijensinghe](#) , [Aisa Romo](#) , [Benjamin Brooks](#)

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Case Report

Postural Orthostatic Tachycardia Syndrome (POTS) as an Adverse Event to the Human Papilloma Virus (HPV) Vaccine and Its Relationship to Ehlers Danlos Syndrome (EDS)

Nicole Schipperijn *, Megan Wijesinghe, Aisa Romo and Benjamin Brooks

Rocky Vista University College of Osteopathic Medicine; megan.wijesinghe@co.rvu.edu (M.W.); aisa.romo@ut.rvu.edu (A.R.); bbrooks@rvu.edu (B.B.)

* Correspondence: nicole.schipperijn@co.rvu.edu

Abstract: Gardasil 4, a human papilloma virus vaccine, has been shown to protect against various cancers, including cervical cancer. Common side effects include injection site pain, fever, headaches, and muscle aches. In some individuals, the severe side effect of postural orthostatic tachycardia syndrome (POTS) has been reported. POTS is characterized by the abnormal response of lightheadedness, blurry vision, and dizziness while transitioning to an upright posture. POTS predominately affects women, with more than eighty-five (85) percent of POTS patients being female. POTS on average, takes five years and eleven months to receive the diagnosis. Additionally, A strong association between POTS and Ehlers Danlos Syndrome Type III (EDS) exists. Eighty (80) percent of patients with EDS have POTS. This severe side effect dictates that providers need to be aware of this strong association of HPV vaccinations and POTS. In this report we will present a case of a young women with a past medical history significant for EDS type III who was diagnosed with POTS after receiving Gardasil 4 vaccination. This case demonstrates the need for physicians to be aware of the association of POTS with EDS type III and HPV vaccination. Physician awareness of the associations, signs and symptoms of POTS and earlier testing at the first presentation of signs and symptoms will limit the negative impact on patient's quality of life.

Keywords: Ehlers Danlos syndrome; vaccine adverse events; postural orthostatic Tachycardia syndrome

1. Introduction

The Gardasil 9 vaccine, which protects against nine strains of the Human Papilloma Virus (HPV), was first approved in December of 2014 [1] and has been shown to reduce the risk of developing various cancers, including cervical cancer [2]. Common side effects of the vaccine include injection site pain, fever, headaches, and muscle aches; however, the vaccine has been known to cause severe adverse events for some individuals, such as postural orthostatic tachycardia syndrome (POTS).

POTS is a form of orthostatic intolerance associated with excessive tachycardia upon standing, which is typically relieved by recumbence and often accompanied by many other symptoms [3,4]. Before the COVID-19 pandemic, POTS was estimated to impact 1 to 3 million Americans, with the majority being women between the ages of 15 and 50 [5,6]. POTS morbidity derives primarily from symptom burden and functional impairment, including profound fatigue, cognitive dysfunction, headaches, gastrointestinal disturbance, syncope, and presyncope, which limit physical activity [3,4]. POTS has significant impacts on daily life, including a 52% unemployment rate among patients, 70.5% with income loss, and 95% with significant medical expenses. POTS-related work and financial instability highlight the need for improved diagnosis and treatments [7].

POTS can be triggered by diverse initiating events, often making its exact initiating event challenging to pinpoint. Commonly, POTS is preceded by a viral infection, which can disrupt the autonomic nervous system's functioning. In some individuals, POTS may also emerge following



significant physical or emotional stress, surgery, or pregnancy, indicating a potential link to bodily stressors and changes [8]. Additionally, while rare and not well understood, there are documented cases where POTS symptoms have developed after vaccination [9,10]. While the initiating events are poorly understood, some potential risk factors have been identified. Further, evidence is limited that vaccination, including the HPV vaccination in the initiating events for POTS [11].

Ehlers-Danlos Syndrome (EDS) Type III, now commonly referred to as Hypermobility EDS (hEDS), is considered by some to be a risk factor for Postural Orthostatic Tachycardia Syndrome (POTS). The joint hypermobility and connective tissue fragility characteristic of hEDS can impact the cardiovascular system, potentially predisposing individuals to POTS [12]. This relationship highlights the potential for shared underlying pathophysiological mechanisms between hEDS and POTS, possibly leading to common symptoms such as rapid heart rate upon standing and autonomic dysregulation [13].

Here, we report on one young woman with a past medical history significant for hEDS who was diagnosed with POTS after receiving the Gardasil 4 vaccine. This case highlights the importance of physicians' ability to recognize associations, signs, and symptoms of POTS to reach a quicker diagnosis and highlights associated with EDS, POTS, and HPV vaccination.

2. Case Presentation Section

A 42-year-old female received the Gardasil 4 vaccine in January 2014. Past medical history is significant for migraines and EDS type III. The patient was diagnosed with EDS in 2010 and presented with a Beighton score of 7 out of 9.

A few days after, the patient experienced symptoms of POTS, specifically tachycardia and syncope. The patient experienced frequent bouts of syncope, impacting her daily life. The patient states that when her POTS worsens, she has more than 20 POTS episodes per day. While the patient began experiencing symptoms of POTS in 2014, it took several doctor visits complaining of POTS symptoms before a table tilt test was performed. This resulted in a diagnosis not being made until 2021. Table 1 shows the patient's positive table tilt test with pulses measuring to a maximum of 158 bpm with seventy (70) degrees of tilting. After the patient's POTS diagnosis, Modafinil was prescribed and resolves the patient's POTS symptoms.

Adverse symptoms of POTS following the Gardasil 4 vaccine has had a severe impact on the patient's daily life. The patient claimed she went from a very sociable person to an introvert. The patient fears having a POTS episode when she is alone. She also fears leaving home and having an episode away from home.

Table 1. Vital signs recorded during the patient's table tilt test. Results show a positive table tilt test diagnostic for POTS.

Degree of Tilt	02/17/21 1020	02/17/21 1019	02/17/21 1018
Degree of Tilt	70 degrees	70 degrees	70 degrees
Heart Rate	144 bpm	145 bpm	136 bpm
Blood Pressure	115/82	122/90	132/84

3. Discussion

Case reports have documented adolescent girls developing symptoms of orthostatic intolerance and excessive tachycardia consistent with POTS in the days and weeks following a Gardasil immunization [10,14]. Butts et al. (2017) provide a review of the current literature on the potential association between the HPV vaccine and POTS. Chandler et al. (2016) discusses safety concerns with the HPV vaccine and reports of adverse events, including POTS. Barboi et al. (2020) present a position statement from the American Autonomic Society on the HPV vaccine and autonomic disorders, including POTS [11]. The mechanisms linking the Gardasil vaccination to POTS are not well understood but may involve autoimmune or autonomic dysfunction triggered by the vaccine.

Further research is warranted to elucidate the potential association between POTS and the Gardasil vaccination, given the potential impact on the lives of young vaccine recipients.

POTS symptoms can take months or even years to manifest fully, making accurate tracking and quantification of POTS incidence following vaccination challenging. Furthermore, lack of awareness of POTS diagnostic criteria among providers and terminology varying from postural orthostatic tachycardia syndrome to chronic fatigue syndrome confound efforts to definitively diagnose and document POTS cases that may be linked to vaccinations. These factors make determining the true prevalence and causal association between POTS and vaccination, like Gardasil, difficult to ascertain [15].

POTS can have a significant impact on patients' lives. Some patients report mild symptoms and can continue normal daily activity. Others live through symptoms severe enough that everyday activities, such as walking, bathing, housework, and even eating, are significantly limited [3,4]. High out-of-pocket medical costs related to POTS are a burden on patients seeking a diagnosis or treatment [7].

Accurate diagnosis of POTS is a crucial yet difficult milestone for patients. POTS can be misdiagnosed because patients may present with a variety of symptoms without any clinically significant findings. Physicians may misdiagnose POTS as anxiety, panic attacks, vasovagal syncope, or inappropriate sinus tachycardia. Many patients are inappropriately diagnosed with psychiatric disorders and consequently may distrust the medical community [16–18]. Symptoms can be present for months or years before a final diagnosis of POTS is made. Some patients may wait two to seven years before receiving a diagnosis, and many patients who first suggest a diagnosis of POTS to their physicians must present to several practitioners before receiving a POTS diagnosis [17]. In this case, it took six years before a table tilt was performed and POTS was diagnosed.

The long period from symptom presentation to diagnosis is frustrating to patients because medical costs can accumulate, and they may not receive the proper medical treatment when the correct diagnosis is not made. Knowing the strong association between hEDS and POTS, and POTS as a potential adverse event to the HPV vaccine is crucial to reduce the time between presentation and diagnosis of POTS. Patients with hEDS should be more frequently tested for POTS, especially after receiving an HPV vaccine. Patients with hEDS should also be educated about the potential risk for developing POTS as part of pre-vaccination education.

A potential association between POTS and hEDS exists [19]. We recognize that the incidence of POTS associated with hEDS is low; however, given the clear considerations and impacts for patients with hEDS, additional monitor in these cases is warranted before administering HPV vaccinations, as the vaccine may initiate POTS. Here, we recommend additional research and vigilance to identify potential associations with patients with hEDS developing POTS after HPV vaccination.

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