Vaccine 33 (2015) 2602–2605

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus

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ARTICLE INFO

Article history:
Received 5 February 2015
Received in revised form 17 March 2015
Accepted 30 March 2015
Available online 14 April 2015

Keywords:
Autonomic nervous system
Human papilloma virus vaccination

ABSTRACT

Background: Infections with human papilloma virus (HPV) can result in cervical, oropharyngeal, anal, and penile cancer and vaccination programs have been launched in many countries as a preventive measure. We report the characteristics of a number of patients with a syndrome of orthostatic intolerance, headache, fatigue, cognitive dysfunction, and neuropathic pain starting in close relation to HPV vaccination.

Methods: Patients were referred for orthostatic intolerance following HPV vaccination. Symptoms of autonomic dysfunction were quantified by standardised questionnaire. The diagnosis of postural orthostatic tachycardia syndrome (POTS) rested on finding a sustained heart rate increment of >30 min^{-1} (>40 min^{-1} in adolescents) or to levels >120 min^{-1} during orthostatic challenge.

Results: 35 women aged 23.3 ± 7.1 years participated. Twenty-five had a high level of physical activity before vaccination and irregular periods were reported by all patients not on treatment with oral contraception. Serum bilirubin was below the lower detection limit in 17 patients. Twenty-one of the referred patients fulfilled the criteria for a diagnosis of POTS (60%, 95%CI 43–77%). All patients had orthostatic intolerance, 94% nausea, 82% chronic headache, 82% fatigue, 77% cognitive dysfunction, 72% segmental dystonia, 68% neuropathic pain.

Conclusions: In a population referred for symptoms of orthostatic intolerance and other symptoms consistent with autonomic dysfunction that began in close temporal association with a quadrivalent HPV vaccination, we identified a 60% prevalence of POTS. Further work is urgently needed to elucidate the potential for a causal link between the vaccine and circulatory abnormalities and to establish targeted treatment options for the affected patients.

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Vaccinations are generally safe, warranted and will most likely reduce morbidity and mortality, but they also carry an inherent risk of provoking autoimmune phenomena. Though numerous case reports have caused discussion in the medical literature as well as in the lay press on a possible association between vaccination and development of autoimmunity, these do not provide evidence for a causal link. Postlicensure monitoring may be superior in detecting rare adverse event than prelicensure reviews. Based on the Vaccine Adverse Events Reporting System, Slade et al. [1] analysed 12,424 reports following HPV vaccination and found syncope, dizziness, nausea and head-ache to be the most prevalent events. A large Scandinavian study comparing almost 300,000 cases and 700,000 controls found increased risk ratios for three autoimmune manifestations, where further assessment could not demonstrate consistent evidence for a plausible association [2].

In a retrospective analysis of six cases, Blitshteyn [3] suggested that postural orthostatic tachycardia syndrome (POTS) could be caused by the adjuvanted HPV vaccine and Kinoshita suggests symptoms of dysautonomia caused by the vaccine [4]. POTS is a heterogeneous condition of dysautonomia and suspected autoimmunity characterized by abnormal increments in heart rate upon assumption of the upright posture accompanied by orthostatic intolerance and symptoms of cerebral hypoperfusion and sympathoexcitation. An increase in heart rate equal to or greater than 30 min^{-1} or to levels higher than 120 min^{-1} during a head-up tilt test is the main diagnostic criterion [5]. POTS can be diagnosed with a standing test or tilt table test, although tilt tests are not always available. A routine physical examination will not

Abbreviations: HPV, Human papilloma virus; POTS, Postural orthostatic tachycardia syndrome.

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http://dx.doi.org/10.1016/j.vaccine.2015.03.098
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diagnose POTS, nor, in most instances, will orthostatic vital sign testing that lasts less than 1–2 min. Before diagnosing a patient with POTS other medical conditions causing tachycardia should be ruled out. POTS is more common in women with a 5:1 female-to-male ratio [6]. The overall prevalence is not known but it is estimated that POTS is found in 500,000 patients in the USA [7] which would translate to 10,000 in Denmark. The orthostatic symptoms consist of lightheadedness, visual blurring or tunnel vision, palpitations, tremulousness, and weakness (especially of the legs). Other symptoms include fatigue, exercise intolerance, hyperventilation, nausea, concentration difficulties, and headaches. Studies on the pathophysiology of POTS have found attenuated cardiovagal baroreflex control coupled with increased vasomotor tone which corresponds well with the clinical finding of a destabilized blood pressure regulation [8]. According to an overview by Grubb [9] many patients will report abrupt onset of symptoms after a febrile illness [10] as well as after pregnancy, immunizations, sepsis, surgery, or trauma. The cause or causes of POTS are not well established, but two small studies have suggested an immune-mediated pathogenesis [11,12]. Symptoms of orthostatic intolerance and often severe headaches may be of such intensity that the patient may be functionally disabled [10].

In the present study, we present the characteristics of 35 patients in whom an apparent syndrome of orthostatic intolerance, headache, fatigue, cognitive dysfunction, and neuropathic pain started in close relation to HPV vaccination.

1. Patients and methods

We included 35 patients consecutively referred to our syncope unit for head-up tilt test under the diagnosis of orthostatic intolerance as a suspected adverse event following vaccination with the quadrivalent HPV vaccine (Gardasil®). Informed consent was obtained from all patients. Due to the retrospective nature of the study, approval by the authorities was not required.

The patients were interviewed with special focus on symptoms from the central and peripheral nervous system, exercise habits, salt and water consumption, menstrual cycle, and medication. As most patients described a gradual development in both number and severity of symptoms we asked them to specify the time passed from vaccination to development of the first symptom suspected to be related to the vaccine. The narrative report was supplemented by two questionnaires: The COMPASS-31 [13] provides a global autonomic severity score as well as domain scores specifying and quantifying symptoms and severity of autonomic dysfunction. COMPASS 31 is developed from the well-established Autonomic Symptom Profile (ASP) [14] and is compatible with data previously acquired using the ASP. The International Physical Activity Questionnaire—Short Form (IPAQ-SF) [15] was used to quantify physical activity prior to the vaccinations using a categorical score of physical activity (low, moderate and high) based on reports on physical activity during a week. Blood samples were drawn for standard laboratory analysis including: serum concentrations of sodium, potassium, calcium, vitamin-D, cobalamin, creatinin, albumin, C-reactive protein, bilirubin, alanin transaminase, alkaline phosphatase, thyroid stimulating hormone, plasma concentration of glucose and whole blood for concentration of haemoglobin, haemoglobin A_{1C}, and white blood cell count.

Postural challenge was performed by active stand and head-up tilt. After 5 min in the supine position, patients were asked to rise quickly and stand quietly beside the tilt table for 3 min (active stand). The patients then rested for 10 min in the supine position and were tilted head-up to 60 degrees on a tilt table (Head-up Tilt, HUT). If symptoms did not force the tilt test to be aborted they remained in the tilted position for at least 10 min. RR-interval length and blood pressure levels were measured continuously from one precordial ECG-lead and by photopletysmography (CNAP-500 monitor CN Systems Medizintechnik AG, Austria), respectively. RR-intervals were converted to instantaneous heart rate and systolic and diastolic blood pressures were derived from the continuous blood pressure recording on a beat-by-beat basis.

The diagnosis of POTS rested on finding a sustained heart rate increase of $\geq 30\,min^{-1}$ (in adults), $\geq 40\,min^{-1}$ (in adolescents), or to levels $\geq 120\,min^{-1}$ at all ages during a 10 min head-up tilt table test and presence of orthostatic symptoms during test in the absence of orthostatic hypotension [6]. We calculated heart rate and blood pressure as a mean of instantaneous values in 30 s in the supine and upright position and the latter values were obtained at the time of maximum heart rate during the first 3 min of active stand and during the first 10 min during HUT.

2. Statistics

Data are given as mean values and standard deviations. Comparisons between groups were made with the Student's *t*-test for unpaired data and calculations were made in IBM SPSS statistics version 19. A two sided significance level of 0.05 was used.

3. Results

The study included 35 females aged 23.3 ± 7.1 years (mean ± sd) (range 13–39). Seventeen per cent were aged between 12 and 15 years, 21% between 15 and 19 years, 37% between 19 and 27 years, and 25% were 27 years or older. Body weight and height were (mean + sd) 62.4 ± 15.7 kg and 168 ± 7.2 cm, respectively resulting in a BMI of $22.1 \pm 4.7\,kg/m^2$. The mean delay between vaccination and onset of symptoms was 9.3 days (range: 0–30). The mean age at onset of symptoms was 22.0 years (range: 12–39). Mean time between onset of symptoms and examination was 1.9 years (range: 0–5). In the resting supine position, heart rate (HR) was $81 \pm 16.7\,min^{-1}$ with systolic and diastolic blood pressures of 123 ± 11.6 mmHg and 82 ± 9.1 mmHg, respectively. Three patients had sinus tachycardia in supine rest ($HR > 100\,min^{-1}$), three and five patients had elevated systolic (>140 mmHg) and diastolic (>90 mmHg) blood pressures, respectively. Twenty-one of the referred patients (60%) fulfilled the criteria for a diagnosis of POTS. During tilt test, heart rate increased from 75 to 109 min^{-1} and from 73 to 94 min^{-1} in patients with and without POTS, respectively ($p < 0.001$).

Median serum bilirubin level was 5 (range: below detection limit—13 $\mu mol\,l^{-1}$). All other laboratory tests were within normal range.

All patients had orthostatic intolerance and the following symptoms were present at the time of examination in more than half of the patients: nausea (94%), chronic headache (82%), fatigue (82%), palpitations (77%), reduced cognitive function (77%), skin changes (76%), intermittent tremor/myoclonic twitches (72%), neuropathic pain (68%), sleep disturbances (61%), and muscular weakness (61%). Gastrointestinal symptoms appeared as nausea and abdominal pain, the latter with varying character, intensity and location. Headache was described as continuous, daily headache with intermittent exacerbation and occasionally pain-free periods. The headache was typically described as severe, chronic and bilateral. Cognitive dysfunction was reported as mental fatigability, difficulties in concentrating, impairment of memory, diminished attention span and verbal dyspraxia. Skin disorders appeared primarily as relapse of acne. Motor symptoms were described as a weakness starting distally, progressing proximally and usually lateralized. The intensity varied in parallel with other symptoms and in five cases lead to dependency on a wheelchair.

Segmental dystonia appeared in the form of intermittent tremor and myoclonic twitches. Sensory symptoms were described as "burning", "a deep stabbing", or "jolts of electricity" starting distally, progressing proximally and usually lateralized in one limb and then spreading proximally and to the contralateral. Most patients also described dysaesthesia/allodynia. Disturbances in sleeping pattern were described as new onset insomnia and nocturia.

The total weighted COMPASS 31 score was 50.3 ± 16.4 and did not differ significantly between those with POTS (52.7 ± 16.2) and those without this diagnosis (45.6 ± 15.3; $p = 0.194$). Based on the IPAQ-SF questionnaire 71% of the patients had a high and 29% had a moderate activity level before symptom-onset. Half of those with a high activity level were competing at a national or international level in their sport. Twenty-four of the 35 patients used oral contraception. The remaining 11 patients all reported irregular periods. Thirty-four out of 35 patients reported that their activities of daily living were seriously affected and 21 had quit school or work due to their symptoms.

Symptoms were reported to appear after the first vaccination in 24%, after the second vaccination in 51%, and after the third vaccination in 25%. The development of symptoms is illustrated by the following case:

Case: A 12-year-old, healthy and physically active girl had general malaise, sore throat, and a slight fever a few days after her first HPV_4 vaccination. Two days after her second vaccination she fainted and in the following days she developed orthostatic intolerance with dizziness, palpitations, and frequent near-syncope. She reported deep limb pain and a burning sensation in her feet and hands. This was accompanied by exercise intolerance and fatigue.

In the following months, she developed chronic, severe headache with intermittent exacerbations accompanied by cognitive dysfunction with impaired memory, concentration difficulties, and verbal dyspraxia. She was nauseated, lost her appetite, and had abdominal pain. Limb pain progressed and was accompanied by intermittent paraesthesia and muscle weakness. Presently she is limited in her daily activities, socially isolated, and cannot attend school.

Antibodies for rheumatoid arthritis, synaptic encephalitis, and cerebral vasculitis were negative. All lab tests were normal except for low vitamin-D. Neurologic, ophthalmological and otological examination revealed no explanation for the headaches or any other symptoms. MRI and CT of the brain including MRI-angiography were normal. A head-up tilt table test showed an increase in heart rate from 77 min^{-1} supine to 121 min^{-1} during tilt with marked orthostatic discomfort. Maximal heart rate during tilt was 137 min^{-1}.

4. Discussion

The present study is a case review of patients referred to our unit for orthostatic intolerance and other symptoms consistent with autonomic dysfunction as suspected side effects to a quadrivalent vaccination against human papilloma virus. Patients stories were consistent as were the reported symptoms and hemodynamic response to tilt with a 60% prevalence of POTS. These patients are in many ways "typical" POTS-patients—both with regard to gender, age of symptom-onset and the presence of orthostatic intolerance coupled with nausea, cognitive dysfunction, impaired sleep and excessive fatigue. However, there are symptoms beyond orthostatic intolerance including: neuropathic pain, myoclonic twitches, and headache which is more severe than that of the "typical" POTS-patients.

Our findings correlate well with other case reports of dysautonomia as suspected side effect to the vaccine [3,4,16]. The patients have presented with quite similar histories and pattern of clinical manifestations possibly constituting a post vaccination syndrome on an autoimmune basis in a specific group of young women.

All the patients had received the quadrivalent Human Papillomavirus Virus-Like Particle vaccine containing capsid protein of HPV Types 6, 11, 16, and 18 with aluminium-containing adjuvant. Adjuvants are commonly used in vaccines to boost the immune response through activation of the innate and adaptive immune systems [17]. The most widely used adjuvant is aluminium salt and this as well as other types of adjuvant have in some cases been associated with autoimmune disease manifestations in predisposed individuals as exemplified by a number of narcolepsy cases suspected to be induced by the H1N1 (Pandemrix) swine flu vaccine [18].

All patients, also the 40% who did not have POTS, reported symptoms of orthostatic intolerance and had a very high score on the structured questionnaire on autonomic dysfunction comparable to patients diagnosed with neurogenic autonomic failure [13,14].

We are aware of several study limitations. The first being the lack of a control group and the possibility of reduced representativeness of our cases compared to the underlying population – as patients are not referred to our unit because of suspected side effects – but because of orthostatic intolerance. The second major limitation is the long and variable delay between the onset of symptoms and orthostatic testing. It is perceivable that the incidence of POTS would be higher if the orthostatic test was conducted after a shorter delay between onset of symptoms and testing as the 40% who did not receive a POTS diagnosis also reported symptoms of orthostatic intolerance. On the other hand, the incidence could have been lower if performed in closer proximity to symptom onset as patients may become deconditioned in the interval between symptom onset and testing. A third limitation is our frequent use of 10-min tilt table test as this study would miss other forms of chronic orthostatic intolerance such as delayed orthostatic hypotension or neurally mediated hypotension (also known as vaso-vagal hypotension). These generally require an orthostatic stress duration of more than 10 min [19]. POTS has been suggested to have an immune-mediated pathogenesis [11,12] and has been proposed to carry a relationship to HPV-vaccination in a report on six patients in whom there was a close correlation between the time of vaccination and appearance of symptoms [3]. POTS may be related to other autoimmune conditions as pointed out in two recent publications linking an increased incidence of POTS to multiple sclerosis [20] and to the antiphospholipid syndrome [21].

The patients in our study were characterised by high levels of physical activity before symptom onset, a high incidence of irregular menstruation, and low levels of bilirubin all of which may have affected their immune response to vaccination. Exercise may increase both pro- and anti-inflammatory cytokines as well as leukocyte subsets [22] and exercise has been found to enhance the response to vaccination [23,24]. Although data are limited, some gender-based differences in immune responses to endurance exercise have been observed [25] and evidence suggests that gender differences may be specific to physically trained women [26]. All patients in our study had irregular periods if not on oral contraception treatment and this could contribute to development of an autoimmune condition as sex steroids play an important role in immune system modulation and development [27,28].

The serum bilirubin levels in our patients were low and bilirubin acts as an inhibitor of the complement cascade (35) suggesting that low levels of bilirubin may enhance the immune and inflammatory response to antigens. We do not know if these patients had low levels of bilirubin before vaccination and symptom onset but the apparent hypobilirubinemia in our patients could have contributed to an increased susceptibility to autoimmune manifestations.

Our findings do not confirm or dismiss a causal link to the HPV-vaccine—but suggest that further research is urgently warranted

in order to clarify the pathophysiology of the symptoms experienced and elucidate the probability and nature of a causal link to the vaccine. We suggest that further clinical description of these patients should be supplemented by case-control studies recruiting age-matched controls for comparison of hemodynamic response to orthostatic stress and other relevant parameters and/or examination of presence of pre-vaccine autonomic symptoms or other phenotypic characteristics as potential risk factors. Most important is research and other initiatives directed at establishing targeted treatment options for the affected patients.

5. Conclusions

The present study has reported on symptoms and signs in patients referred for orthostatic intolerance suspected to be secondary to vaccination against human papilloma virus. The patients were generally older than the current target population for HPV vaccination programs. We found remarkable consistency in the reported symptoms and in the hemodynamic responses to the upright posture. The patients were characterised by a high level of physical activity prior to vaccination and by signs of possible neuroendocrine disturbances. The majority could be diagnosed as having postural orthostatic tachycardia syndrome according to current guidelines and had a very high score on a standardised questionnaire targeted at symptoms of autonomic dysfunction. Our findings do not confirm or dismiss a causal link to the HPV-vaccine—but suggest that further research is urgently warranted in order to clarify the pathophysiology of the symptoms experienced, elucidate the probability and nature of a causal link to the vaccine, and to establish targeted treatment options for the affected patients.

Funding

None.

Conflict of interest statement

Jesper Mehlsen has received fees for speaking and for consulting from Merck, Sharpe & Dohme. Jesper Mehlsen has received fees for speaking from Sanofi Pasteur. The other authors have no competing interests related to the contents of this manuscript or part thereof.

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