Suspected side effects to the quadrivalent human papilloma vaccine

Louise Brinth[1, 2], Ann Cathrine Theibel[1, 2], Kirsten Pors[1] & Jesper Mehlsen[1, 2]

ABSTRACT

INTRODUCTION: The quadrivalent vaccine that protects against human papilloma virus types 6, 11, 16 and 18 (Q-HPV vaccine, Gardasil) was included into the Danish childhood vaccination programme in 2009. During the past years, a collection of symptoms primarily consistent with sympathetic nervous system dysfunction have been described as suspected side effects to the Q-HPV vaccine.

METHODS: We present a description of suspected side effects to the Q-HPV vaccine in 53 patients referred to our Syncope Unit for tilt table test and evaluation of autonomic nervous system function.

RESULTS: All patients had symptoms consistent with pronounced autonomic dysfunction including different degrees of orthostatic intolerance, severe non-migraine-like headache, excessive fatigue, cognitive dysfunction, gastrointestinal discomfort and widespread pain of a neuropathic character.

CONCLUSION: We found consistency in the reported symptoms as well as between our findings and those described by others. Our findings neither confirm nor dismiss a causal link to the Q-HPV vaccine, but they suggest that further research is urgently warranted to clarify the pathophysiology behind the symptoms experienced in these patients and to evaluate the possibility and the nature of any causal link and hopefully establish targeted treatment options.

FUNDING: not relevant.

TRIAL REGISTRATION: not relevant.

Genital human papilloma virus (HPV) infections are commonly acquired soon after sexual debut, and persistent HPV infections can cause cervical cancer. In Denmark, the incidence of cervical cancer is around 370 annual cases, and approximately 100 women die from this disease each year [1].

The quadrivalent vaccine that protects against HPV types 6, 11, 16 and 18 (Q-HPV vaccine) was introduced in Denmark in 2006 and was included into the Danish childhood vaccination programme in 2009. The HPV vaccine is the only vaccine included in the childhood vaccination programme that has also been offered free of charge to women outside the childhood programme in catch-up programmes.

The vaccine is based on virus-like particles containing aluminum adjuvant to enhance and tailor the immune response for more effective and longer lasting protection. To date, approximately 480,000 girls and young women have been vaccinated with the Q-HPV vaccine in Denmark [1].

While vaccinations are generally safe, warranted and will most likely reduce morbidity and mortality, they also carry an inherent risk of provoking side effects. Post-licensure monitoring may be superior to pre-licensure reviews in detecting rare adverse events. A large Scandinavian study comparing almost 300,000 cases and 700,000 controls found that the Q-HPV vaccine is generally well tolerated in the target population with no significant increase in the incidence of predefined autoimmune diseases 180 days post vaccination [2].

During the past years, a collection of symptoms has been described that does not readily fit into an existing diagnostic entity, but seemingly represents or involves a dysfunction in the autonomic nervous system. The symptoms have been described as suspected side effects to both the Q-HPV vaccine and the divalent HPV vaccine and they have been denoted differently, possibly depending on the medical specialty of those evaluating the patients [3-7].

In the following, we describe 53 patients referred to our Syncope Unit for a tilt table test and evaluation of autonomic nervous system function with suspected side effects to the Q-HPV vaccine.

METHODS

This was a retrospective analysis based on 75 patients consecutively referred to the Syncope Unit from May 2011 to December 2014 for a head-up tilt test due to orthostatic intolerance and symptoms compatible with autonomic dysfunction as suspected side effect following vaccination with the Q-HPV vaccine.

In our analysis, we chose to include only those patients who reported onset of symptoms consistent with autonomic dysfunction within the first two post-vaccination months; this meant that 11 patients were excluded. Patients with known chronic diseases pre-vaccination as well as patients in whom other possible eliciting factors could be recognised (seven patients) were also excluded as were patients who were unable to account for the temporal association between vaccination and symptom

ORIGINAL ARTICLE

1) Coordinating Research Centre/ Syncope Unit, Frederiksberg Hospital
2) Department of Clinical Physiology and Nuclear Medicine, Frederiksberg Hospital, Denmark

Dan Med J 2015;62(4):A5064

TABLE 1

Baseline characteristics of the included subjects.

	Mean	SD	Range
Age, yrs	23	7	12-39
Weight, kg	64	15	49-106
Height, cm	169	6	149-180
Body mass index, kg/m²	22	5	15-37
Systolic blood pressure, mmHg	123	10	103-144
Diastolic blood pressure, mmHg	83	8	65-98
Heart rate, bpm	79	15	54-130

SD = standard deviation.

onset (four patients); in total, 53 patient were left for further analysis.

All patients underwent a 60-degree head-up tilt table test (HUT). The postural orthostatic tachycardia syndrome (POTS) was diagnosed according to current guidelines requiring 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 [8].

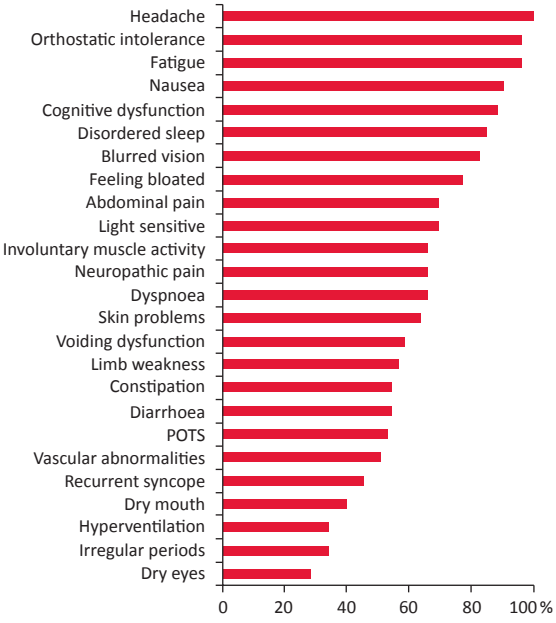
The patients were interviewed with a special focus on symptoms and on the temporal association between vaccination and symptom onset. The narrative report was supplemented by the short form of the International Physical Activity Questionnaire (IPAQ-SF) quantifying the patient's physical activity at the time of referral and just before vaccinations on a recall basis [9].

We described the frequency of the most common symptoms in this group of patients. As the diagnosis POTS has been debated in relation to this group of patients, we did a subgroup analysis describing the frequency of the different symptoms in patients with and without the POTS diagnosis.

Trial registration: not relevant.

FIGURE 1

Symptoms suspected to be side effects to vaccination against human papilloma virus. The frequency of the symptoms is given as percentages of patients reporting the given symptom out of all patients included in the descriptive analysis.



POTS = postural orthostatic tachycardia syndrome.

RESULTS

The analysis includes a total of 53 girls/women aged 12-39 years at the time of examination. Clinical characteristics are given in **Table 1**.

The mean age at symptom onset was 21.0 ± 7.4 years (range: 12-39 years). Mean time between vaccination and onset of symptoms was 11.1 ± 12.5 days (range: 0-58 days) and symptoms were reported to appear after the first vaccination in 21 patients (40%), after the second vaccination in 19 patients (36%), and after the third vaccination in 13 patients (25%).

In **Figure 1**, we present the symptoms that were experienced in more than 25% of the patients; and in the following, we present the typical manifestations of these symptoms:

Headache: 53 (100%) of the included patients reported new-onset headache. Most of the patients described continuous, daily, severe, debilitating headache with intermittent exacerbations and occasionally pain-free periods. Only a few patients described typical migraine.

Orthostatic intolerance: 51 (96%) of the patients reported pronounced symptoms of orthostatic intolerance. In all, 24 (45%) patients experienced recurrent syncopal attacks, and 28 (53%) patients were diagnosed with POTS at tilt table test.

Fatigue: 51 (96%) of the patients complained of excessive fatigue and increased mental and physical fatigability.

Cognitive dysfunction: 47 (89%) of patients complained of inability to concentrate, impairment of short-term memory, diminished attention span – often accompanied by "mental fog", verbal dyspraxia and new-onset dyslexia.

Disordered sleep: 45 (85%) patients reported a change in sleep pattern – primarily described as new-onset insomnia and non-refreshing sleep.

Visual symptoms: 37 patients (70%) reported new-onset hypersensitivity to bright light and (44 patients,

83%) experienced intermittent blurring of vision.

Gastrointestinal symptoms: Patients reported new-onset gastrointestinal discomfort such as nausea (48 patients, 91%); feeling bloated (41 patients, 77%); abdominal pain of varying character, intensity and location (37 patients 70%); and changes in bowel habits (29 patients, 55%).

Neuropathic pain: 35 (66%) of the patients complained of pain described as "burning", "a deep stabbing", or "jolts of electricity" starting distally, often in one limb, and then progressing proximally and often spreading to the contralateral side.

Motor symptoms: 35 (66%) of the patients experienced involuntary muscle activity in the form of intermittent tremor and myoclonic twitches.

Dyspnoea: 35 (66%) reported new-onset intermittent dyspnoea often described as air hunger combined with chest tightness or actual chest pain.

Skin disorders: 34 (64%) of the patients experienced a relapse or – in the adolescent girls – aggravation of acne.

Voiding dysfunction: Only one patient reported new-onset incontinence, but 31 (59%) patients reported voiding dysfunction with respect to frequency, urge, nocturia and incomplete bladder emptying.

Limb weakness: 30 (57%) of the patients experienced muscle weakness in the extremities, most often intermittent in nature, confined to the lower extremities and usually lateralised. The intensity varied in parallel with other symptoms, and in six cases it led to invalidity with very limited walking distances and confinement to a wheelchair for longer periods of time.

Vascular abnormalities: 27 (51%) patients described intermittent changes in skin colour to blue, red, pale or blotchy in the lower parts of the legs and in fingers and toes – the colour changes were often accompanied by painful swelling of the involved limbs. Many patients reported side differences in temperature during these episodes combined with exacerbation of pain in the affected extremity.

Irregular periods: Of the 31 patients who were not on treatment with oral contraception, 15 (48%) reported irregular periods and many reported hypermenorrhoea and worsening of menstrual discomfort and pain.

Sicca symptoms: 21 (40%) patients experienced new-onset dry mouth, and 15 patients (28%) complained of dry eyes.

Hyperventilation: 18 (34%) patients reported a new-onset tendency for hyperventilation or excessive sighing.

Besides the actual orthostatic intolerance (syncope and dizziness), the patients described that fatigue, cognitive dysfunction, hyperventilation and dyspnoea and to some degree headache and nausea were accentuated in the upright position.

In **Figure 2**, we present the frequency of the above-mentioned symptoms in patients with and without the POTS diagnosis, respectively, demonstrating that the two groups have similar patterns and severities of symptoms regardless of the POTS diagnosis. The apparent trend towards POTS patients having a more severe symptom-burden did not reach statistical significance.

Based on the IPAQ-SF questionnaire, 67% had a high and 33% had a moderate activity level before symptom onset. Five patients had a very high activity level and were competing on a national or international level in their sport.

Fifty-two out of 53 patients (98%) reported that their activities of daily living were seriously affected and 40 (75%) had had to quit school or work for more than two months due to their symptoms.

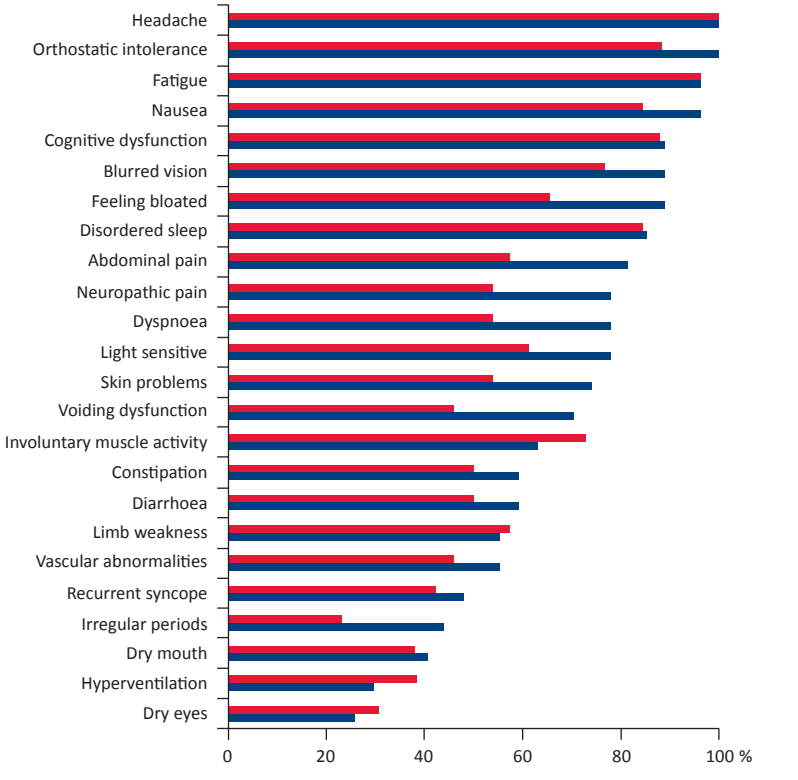
DISCUSSION

The present study is a systematic review of 53 patients referred to our unit with symptoms of orthostatic intolerance and generalised dysautonomia as a suspected side effect of vaccination against human papilloma virus.

The main finding of our study was a high degree of

FIGURE 2

Symptoms suspected of being side effects to vaccination against human papilloma virus in patients with postural orthostatic tachycardia syndrome (POTS) and without the POTS-diagnosis. The frequency of the symptoms is given as percentages of patients reporting the given symptom out of all patients with (■) and without (■) the POTS diagnosis, respectively.



consistency in the symptoms experienced by these patients. The most common symptoms reported were headache, dysautonomia symptoms, excessive fatigue, cognitive dysfunction and widespread pain of a neuropathic character.

Many of the symptoms described in our review as well as in the product resume and adverse event reports may at first seem both diffuse and very common. However, having evaluated more than 70 patients with the suspected side effects, we believe that there is a recognisable pattern of symptoms. Our findings correlate well with the clinical picture presented by Kinoshita et al [6] and Nishioka et al [7], except for the greater proportion of patients suffering from orthostatic intolerance in our group of patients – which may be expected as patients are primarily referred to our unit due to orthostatic intolerance.

The patients in our study were characterised by remarkably high levels of physical activity before symptom onset, which may have affected their immune response to vaccination [10].

In analysing our data, we have considered the possibility of the phenomenon known as mass psychogenic illness, which has been defined as the collective occurrence of a constellation of symptoms suggestive of organic illness, but without an identified cause in a group of people with shared beliefs about the cause of the symptoms [11]. However, we do not find it likely that such a reaction constitutes the background for symptoms and signs found in our patients given their prevaccination history, the chronicity of their symptoms and the temporal and geographical dispersion.

Some of the patients have been suspected of suffering from a functional disorder. However, as the autonomic nervous system innervates, monitors and controls most of the tissues and organs in the body – autonomic dysfunction often presents with a very diffuse and widespread pattern of symptoms [12]. The differential diagnostic procedure – especially with emphasis on the differentiation between functional disorder and autonomic dysfunction – is highly important in this group of patients and may require a faceted approach with involvement of expertise from different medical specialties.

We may have diagnosed more than half of these patients with POTS – but POTS should probably be looked upon as a symptom secondary to another yet unidentified condition rather than as a disease entity of its own. This is underscored by the fact that patients experienced the same degree and pattern of symptoms regardless of the POTS diagnosis. The underlying aetiology behind POTS is still somewhat elusive and the prevalence of POTS is most common in the same subset of the population that are receiving the HPV vaccine (young women) [13], which complicates the aetiological discussion. We found a close chronologic association to the vaccination, but are well aware that this does not necessarily imply a causal relationship.

It is our clinical experience that substantial improvement is possible in POTS patients with multifaceted treatment consisting of a variety of both pharmacological and non-pharmacological treatment modalities [13].

A clarification of the probability and nature of a possible causal link between the symptoms and the HPV vaccine is important in order to ensure that future vaccines may give informed consent based on updated information about possible side effects.

Establishing a relevant and coherent diagnosis and treatment for these patients would contribute to maintaining the trust and credibility in this vaccine which is important as a preventive measure against HPV-related cancer.

CONCLUSION

In this study we present symptoms reported by patients referred for orthostatic intolerance suspected to be secondary to vaccina tion against HPV. We found consistency in the reported symptoms as well as between our findings and those reported by others. Given the symptomatology, we suggest that the pathogenic alteration is located in the autonomic nervous system. Our findings do not confirm or dismiss a causal link to the HPV vaccine – but they do suggest that further research is urgently warranted in order to clarify the pathophysiology of the symptoms experienced, to evaluate the possible link to the vaccine and to establish targeted treatment options for the affected patients.

CORRESPONDENCE: *Louise Brinth,* Koordinerende Forskningsenhed/Synkopecenteret, Vej 3, Indgang 4, Frederiksberg Hospital, Nordre Fasanvej 57, 2000 Frederiksberg, Denmark. E-mail: Louise.Schouborg.Brinth@regionh.dk

ACCEPTED: 25 February 2015

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

LITERATURE

1. Danish Health and Medicines Authority. Personal communication. 2014.
2. Arnheim-Dahlstrom L, Pasternak B, Svanstrom H et al. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013;347:f5906.
3. Blitshteyn S. Postural tachycardia syndrome following human papillomavirus vaccination. Eur J Neurol 2014;21:135-9.
4. Blitshteyn S. Postural tachycardia syndrome after vaccination with Gardasil. Eur J Neurol 2010;17:e52.
5. Martinez-Lavin M. Fibromyalgia-like illness in 2 girls after human papillomavirus vaccination. J Clin Rheumatol 2014;20:392-3.
6. Kinoshita T, Abe RT, Hineno A et al. Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine. Intern Med 2014;53:2185-200.
7. Nishioka K, Yokota S, Matsumoto Y. Clinical features and preliminary diagnostic criteria of human papillomavirus vaccination associated with neuroimmunopathic syndrome (HANS). Int J Rheu Dis 2014;17(suppl 2):6-29. Abstract.
8. Freeman R, Wieling W, Axelrod FB et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 2011;21:69-72.
9. Kurtze N, Rangul V, Hustvedt BE. Reliability and validity of the International Physical Activity Questionnaire in the Nord-Trondelag health study (HUNT) population of men. BMC Med Res Methodol 2008;8:63.

10. Edwards KM, Burns VE, Allen LM et al. Eccentric exercise as an adjuvant to influenza vaccination in humans. Brain Behav Immun 2007;21:209-17.
11. Clements CJ. Mass psychogenic illness after vaccination. Drug Saf 2003; 26:599-604.
12. Jänig W. Integrative action of the autonomic nervous system neurobiology of homeostasis. Cambridge: Cambridge University Press, 2008.
13. Kizilbash SJ, Ahrens SP, Bruce BK et al. Adolescent fatigue, POTS, and recovery: a guide for clinicians. Curr Probl Pediatr Adolesc Health Care 2014;44:108-33.