Suspected side effects to the quadrivalent human papilloma vaccine

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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.
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.

**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
consistency in the symptoms experienced by these patients. The most common symptoms reported were headache, dyssympathetics, 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 Nishioka 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 vaccination 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.

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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.