Is Chronic Fatigue Syndrome/Myalgic Encephalomyelitis a Relevant Diagnosis in Patients with Suspected Side Effects to Human Papilloma Virus Vaccine?

Abstract

The quadrivalent human papilloma virus vaccine (Q-HPV-vaccine) was included into the Danish childhood vaccination program in 2009. During the past years possible side effects have been described in several countries encompassing a collection of symptoms consistent with pronounced autonomic dysfunction coupled with severe non-migraine-like headache, excessive fatigue, cognitive dysfunction, gastrointestinal discomfort and widespread pain of a neuropathic character.

The assessment of the prevalence and the possible pattern in symptoms suspected to be side effects has been hampered by a lack of consistency in the diagnostic criteria applied on seemingly similar symptom complexes. As fatigue and fatigability is a prominent symptom in many of the patients with suspected side effects to the vaccine, chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) could be suspected to be a suitable diagnosis.

We have performed a retrospective analysis on the applicability of the CFS/ME diagnosis in 39 patients referred to our Syncope Unit from May 2011 to April 2015 for clinical evaluation including a head-up tilt test. The patients were referred due to orthostatic intolerance and symptoms compatible with autonomic dysfunction occurring in a close temporal association to vaccination with the Q-HPV vaccine. We found that 34 (87%) and 35(90%) of the patients fulfilled the diagnostic criteria for CFS/ME regarding to the Canadian and the IOM (Institute of Medicine) criteria respectively and suggest that CFS/ME may be a suitable diagnosis for patients with severe and persistent suspected side effects to the Q-HPV vaccine.

For the time being we can neither confirm nor dismiss a causal link between the vaccine and the disabling symptoms, but a consensus on the classification of the patients is needed in order to attain a more systematic clinical and scientific approach to this challenge. Common diagnostic criteria could hopefully result in a specific treatment protocol and thereby strengthen the worldwide program to combat cancers caused by human papilloma virus.

Keywords: Human papilloma virus vaccine; Side effects; Myalgic encephalomyelitis; Chronic fatigue syndrome; Autonomic nervous system

Abbreviations: CFS/ME: Chronic Fatigue Syndrome/Myalgic Encephalomyelitis; HPV: Human Papilloma Virus; IOM: Institute of Medicine; POTS: Postural Orthostatic Tachycardia Syndrome; Q-HPV Vaccine: Quadrivalent Human Papilloma Virus Vaccine; SEID: Systemic Exertion Intolerance Disease; HUT: Head-Up Tilt Table Test

Introduction

The quadrivalent recombinant vaccine protecting against human papilloma virus types 6, 11, 16, and 18 (Q-HPV vaccine, Gardasil®) was included in the Danish childhood vaccination program in 2009. The vaccine administered in 3 separate intramuscular injections over a 6-month period. Since 2014, Danish girls below the age of 14 are only given two doses.

During the past years, a collection of symptoms consistent with pronounced autonomic dysfunction coupled with severe non-migraine-like headache, excessive fatigue, cognitive dysfunction, gastrointestinal discomfort, and widespread pain of a neuropathic character has been described as suspected side effects to the Q-HPV vaccine and to the bivalent HPV-vaccine in Denmark as well as other countries [1-7].

Vaccine safety is extremely important as vaccines are typically given to a vast number of subjects – and as a preventive measure. Continuous focus on the safety evaluation processes with involvement of advances in both vaccine technologies, understanding of the interaction between vaccine and the human body and in the diagnostic tools used in patients with suspected side effects should be applied. The knowledge obtained should be communicated to the public as updated risk-benefits profile in order to qualify the informed consent given at immunization and maintain public confidence in vaccines [8].

Post licensure monitoring may be superior in detecting rare adverse events compared to pre licensure reviews. Many post licensure studies are register studies comparing the incidence of
selected and well defined diagnostic entities in a cohort vaccinated with the vaccine compared to controls and are thus diagnosis dependent. Several studies have been published regarding the safety profiles of the HPV-vaccines [9-11]. A large Scandinavian study comparing almost 300,000 cases vaccinated with the Q-HPV vaccine and 700,000 controls found increased risk ratios for three autoimmune manifestations, where further assessment could not demonstrate consistent evidence for a plausible association [11]. These are powerful studies demonstrating a positive safety profile of the Q-HPV vaccine regarding the investigated diagnostic entities. However, case series describing suspected side effects to the Q-HPV vaccine clearly demonstrates, that the symptoms are many and complex and do not necessarily fit into an existing diagnostic entity making it difficult to assess the prevalence of these suspected side effects. The patients with suspected side effects have been denoted differently, possibly depending on the medical specialty of those evaluating the patients [1-7]. It is a substantial problem in terms of pharmacovigilance and thus in the evaluation of the probability and prevalence of suspected side effects to the Q-HPV vaccine that a specific diagnosis has not been attributed to these apparently quite similar cases presenting around the world.

We have had 90 patients referred to our Syncope Unit from May 2011 to April 2015 for clinical evaluation including 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. As we have found fatigue, pain, and orthostatic intolerance to be central symptoms in these patients [1,2], we decided to investigate to what extent these patients fulfilled the diagnostic criteria for Chronic fatigue syndrome/Myalgic encephalomyelitis (CFS/ME) as this diagnosis somewhat encompasses the symptoms found.

A study from the UK found that the (bivalent) HPV-vaccine was not associated with an increased prevalence of chronic fatigue syndrome [9]. However, as CFS/ME is a somewhat debated and controversial diagnosis with overlap to other syndrome diagnosis we suspect that most patients are not given the diagnosis CFE/ME even if they fulfill the diagnostic criteria neither in the UK nor in Denmark, which would obviously hamper this assessment.

CFS/ME is a debilitating, complex, and controversial disorder with many uncertainties regarding both etiology and delimitation toward other syndrome diagnosis such as fibromyalgia and neurasthenia and somatization. These uncertainties along with a lack of valid biomarkers and effective treatment modalities have limited the possibility for exact diagnosis and treatment.

CFS/ME is characterized by extreme mental and physical fatigue and fatigability with associated symptoms of pain and instability in the control of a broad range of organ systems. Studies suggest irregularities in the nervous system, in hormonal metabolism, in the immune system, and in relation to oxidative stress with a compromised mitochondrial function [12-16]. One of the characteristics is that the range of symptoms are worsened by exertion of any kind and this has a significant impact on the activities of daily life. In spite of an increasing interest the cause and consequences of the condition have not been established. The condition is often found to be precipitated by infections or prolonged or extreme physiological or psychological strain [17].

Several diagnostic criteria have been developed and used in both clinical practice and research. The different criteria are impairing the scientific evaluation of the condition. We have adopted the Canadian Clinical working definition developed by Carruthers et al. [18] in 2003 and revised by Jason et al. [19] in 2010 as it encompasses both the fatigue and the pain seen in our patients. The Canadian Criteria defines ME/CFS as a condition lasting at least 6 months characterized by fatigue, postexertional malaise, pain, and disordered sleep accompanied by neurologic, autonomic, neuroendocrine, and immune dysfunction (Table 2).

In the report by the Institute of Medicine in 2015: Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness they proposed a new and simplified diagnostic criterion and recommended the disorder renamed “systemic exertion intolerance disease” (SEID). The IOM defines CFS/ME/SEID as a condition characterized by impaired day-to-day function, post-exertional malaise, and unrefreshing sleep coupled with cognitive impairment and/or orthostatic intolerance with symptoms at least half the time for 6 months or more [20] (Table 3).

Patients with CFS/ME are often diagnosed with comorbid postural orthostatic tachycardia syndrome (POTS), which suggests a shared pathophysiology [21] and in the diagnostic criteria for CFS/ME/SEID proposed by the IOM orthostatic tolerance is a central component [20]. POTS is a heterogeneous condition of dysautonomia characterized by abnormal increments in heart rate upon assumption of the upright posture accompanied by orthostatic intolerance and symptoms of cerebral hypoperfusion and sympatho excitation. 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 [22]. POTS can be diagnosed with a standing test or tilt table test, although tilt tests are not always available. More than half of the patients we have seen with suspected side effects to the Q-HPV vaccine have fulfilled the diagnostic criteria for POTS [1]. However, we suggest that POTS should be looked upon as a symptom or comorbidity to another and perhaps more severe condition and we believe that this is underscored by the fact that patients with possible side effects expressed the same pattern and burden of symptoms irrespective of whether they fulfilled the POTS diagnosis or not. As fatigue and fatigability are very dominant traits in the patients we found it relevant to assess to what extent they would fulfill the diagnostic criteria for CFS/ME/SEID.

Table 1: Baseline Characteristics of the included subjects.

| Age (years) | Weight (kg) | Height (cm) | BMI (kg/m2) | SBP (mmHg) | DBP (mmHg) | HR (bpm) |
|-------------|-------------|-------------|-------------|------------|------------|----------|
| Mean        | SD          | Range       | Mean        | SD         | Range      | Mean     |
| 23          | 7           | 13-39       | 64          | 14         | 40-110     | 171      |
| 171         | 5           | 153-180     | 21.8        | 4.6        | 14.3-35.9  | 126      |
| 84          | 10          | 63-98       | 80          | 16         | 54-130     |          |

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate
Table 2: Revised Canadian Consensus Criteria for ME/CFS (2010).

| All of the Following Four Criteria Must be Fulfilled |
|---------------------------------------------------|
| 1. Fatigue                                        |
| 2. Post-exertional malaise and/or post-exertional fatigue |
| 3. Unrefreshing sleep or disturbance of sleep quantity or rhythm disturbance |
| 4. Pain (or discomfort) that is often widespread and migratory in nature |

| Two or more neurological and/or cognitive manifestations |
|---------------------------------------------------------|
| At least one symptom from two of the three categories |
| 1. Autonomic manifestations Orthostatic intolerance, palpitations, fainting, nausea, bladder dysfunction etc. |
| 2. Neuroendocrine manifestations Recurrent feelings of feverishness and cold extremities, subnormal body temperature, sweating episodes, marked weight change etc. |
| 3. Immune manifestations Recurrent flu-like symptoms, tender lymph nodes, sore throat etc. |

ME/CFS: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Persistent or recurring symptoms for ≥ 6 months but not lifelong [18].

Table 3: Proposed Diagnostic Criteria for ME/CFS by the Institute of Medicine (IOM).

| Diagnosis Requires that the Patient have the Following Three Symptoms |
|------------------------------------------------------------------------|
| 1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest |
| 2. Post-exertional malaise |
| 3. Unrefreshing sleep |

At least one of the two following manifestations is also required

| 1. Cognitive impairment |
| 2. Orthostatic intolerance |

ME/CFS: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; IOM: Institute of Medicine

The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity [19].

Materials and Methods

Patients

This is a retrospective analysis based on 90 patients referred to the Syncope Unit from May 2011 to April 2015 for clinical evaluation due to suspected side effect following vaccination with the Q-HPV vaccine. Only those patients who had returned the relevant questionnaires (see below) (39 patients) where included in the analysis.

Methods

The patients were submitted to a narrative, clinical interview and to schematic questioning using a checklist of symptoms filled in by the patients at home and by the staff at the clinic elucidating symptom burden and pattern and the temporal association between vaccination and symptom onset. This was supplemented by the COMPASS-31 questionnaire specifying and quantifying symptoms and severity of autonomic dysfunction.

All patients underwent a 60-degree head-up tilt table test (HUT). If symptoms did not force the tilt test to be aborted they remained in the tilted position for at least 10 min. RR-intervals and blood pressure were measured continuously from one precordial ECG-lead and by photopleysmography (CNAP-500 monitor CNS 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 presence of orthostatic symptoms in the absence of orthostatic hypotension and a sustained heart rate increase of >= 30 min⁻¹ (in adults), >= 40 min⁻¹ (in adolescents), or to levels >= 120 min⁻¹ at all ages during a 10 minute head-up tilt table test [23].

**Statistical analysis**

Data are given as mean values and standard deviations. Comparisons between groups were made with the Students t-test for unpaired data. Correlations are given by Pearson’s correlation coefficient r. All calculations were made in IBM SPSS statistics version 19. A two sided significance level of 0.05 was used.

**Results and Discussion**

**Results**

The study included 39 girls/women aged 22.9 ± 7.2years (mean±sd) (range 13-39) at time of examination. Body weight and height were 63.8±14.5 kg and 171.0 ±5.3 cm, respectively, resulting in a BMI of 21.8±4.7kg/m². In the resting supine position, heart rate was 79.7 ±15.5 min⁻¹ with systolic and diastolic blood pressures of 126±11 mmHg and 84±10mmHg, respectively.

Twenty of the patients (51%) fulfilled the criteria for a diagnosis of POTS. Thirty-four (87%) and 35(90%) of the patients fulfilled the Canadian and IOM criteria for CFS/ME, respectively. POTS were diagnosed in 56% and 55% of patients diagnosed according to the Canadian and the IOM criteria, respectively.

The total weighted COMPASS 31 score was 53.1±13.6 which is comparable to that found in patients diagnosed with autonomic failure [22-24]. The score did not differ significantly between those with or without POTS (55.6±14.4 versus 49.8±12.1) (p= 0.253) but was significantly higher in patients fulfilling the Canadian and IOM diagnostic criteria for ME/CFS (Canadian: 56.2±11.4 and IOM: 60.0±10.0) compared to those who did not (Canadian 33.1 ±8.5; p=0.001 and -IOM 32.0±7.4; p<0.0005).

**Discussion**

This is a retrospective analysis based on 39 patients referred to our unit with symptoms of orthostatic intolerance and generalized dysautonomia as a suspected side effect to vaccination against human papilloma virus. We have demonstrated that most of the patients seem to fulfill the diagnostic criteria for CFS/ME and that this diagnosis encompasses a greater share of the patients than the POTS diagnosis - and gives a better reflection of their symptom burden related to autonomic dysfunction [25].

Our study was not designed to establish whether or not a diagnosis of CFS/ME would lead to a correct classification of patients with suspected side effects. However, we suspected from our clinical experience that the CFS/ME diagnosis would encompass most of the symptoms seen and this was confirmed by the systematic analysis. It is important to get an appropriate diagnosis and reach an agreement on this subject in order to provide a more firm basis for pharmacovigilance and thus in the evaluation of the probability and prevalence of suspected side effects to the Q-HPV vaccine. We need to discuss how we approach the pharmacovigilance process when dealing with patients with unclear and diffuse symptoms as suspected side effects. How do we handle a situation where we may suspect that patients with the same complex of symptoms get different - or no - diagnoses dependent on country and/or medical specialty? We suggest that future research should aim at elucidating which diagnosis we should be looking for when assessing the suspected side effects to the Q-HPV-vaccine on a global scale.

It is also important to agree on the diagnostic criteria if a systematic approach to the study of these patients should be attained. We need futures studies aimed at elucidating the disease processes disabling these patients and hopefully thereby enable better and targeted treatment options.

We do recognize several limitations to our study. Firstly, the results may be regarded as a mere confirmation by circular reasoning as our clinical impression was tested systematically in the same group of patients and secondly, the CSF/ME diagnosis should be used only when possible somatic and psychiatric differential diagnosis have been thoroughly evaluated, which was not done on a systematic basis in our study. The suggestion of using the CSF/ME/SEID diagnosis for the possible side effect should be considered a first methodical approach to reach consensus as to how these patients are classified.

Although we recognize that our studies do not establish whether or not the Q-HPV vaccine is a cause of the symptoms seen in our patients we are also aware that vaccines have the potential of eliciting side effects and that the rare side effects are only seen when the vaccines are used in a much larger cohort than that used in the registration studies. Genetic susceptibility perhaps coupled with environmental triggers could likely cause new onset symptoms or a flare in a pre existing condition. Because of the concerns expressed worldwide with regard to the HPV-vaccine, we find that there is an urgent need for a systematic approach to the patients and for solid, scientific studies of the possible relations between the vaccine and their symptoms.

**Conclusion**

We have demonstrated that the diagnosis chronic fatigue syndrome/myalgic encephalomyelitis may be suitable in patients with suspected side effects to the Q-HPV vaccine. For the time being we can neither confirm nor dismiss a causal link between the vaccine and the disabling symptoms but a consensus on the classification of the patients is needed in order to attain a more systematic clinical and scientific approach to this challenge. This could hopefully result in a specific treatment protocol, maintained public confidence in the vaccine and thereby strengthen the worldwide program to combat cancers caused by human papilloma virus.

**Conflict of Interest**

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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