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THERAPEUTIC ASPECTS IN AUTOIMMUNITY

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Postural tachycardia syndrome (POTS) with anti-NMDA receptor antibodies after human papillomavirus vaccination

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Abstract We describe a young woman who developed POTS with positive serum anti-NMDA receptor antibodies and no evidence of encephalitis after vaccination with HPV vaccine, Cervarix. Her symptoms improved significantly with immunomodulatory therapy and re-occurred after immunomodulatory therapy was stopped, suggesting an autoimmune etiology of POTS after vaccination.

Keywords Human papillomavirus vaccination · Postural tachycardia syndrome · Anti-NMDA receptor antibodies · Orthostatic intolerance · Plasmapheresis

Introduction

Postural tachycardia syndrome (POTS) is a disorder of the autonomic nervous system characterized by a rise in heart rate of at least 30 bpm from supine to standing position and various orthostatic and non-orthostatic symptoms, such as fatigue, palpitations, lightheadedness, dizziness, gastrointestinal disturbance, headaches and neuropathic pain [1]. Anti-NMDA receptor antibodies (anti-NMDAR-Ab) are most commonly associated with autoimmune encephalitis, which typically presents with acute neurological and psychiatric symptoms, such as seizures, psychosis, autonomic instability, hypoventilation, movement disorders and decreased levels of consciousness [2]. We report a patient who developed POTS and positive serum anti-NMDAR Ab, without evidence of encephalitis, after vaccination with a bivalent human papillomavirus (HPV) vaccine, Cervarix.

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Case presentation

A previously healthy 18-year-old woman developed fatigue, pre-syncope, dizziness and nausea 48 h after vaccination with HPV vaccine, Cervarix. The symptoms were initially mild and were not attributed to vaccination. She subsequently received a second HPV vaccine 6 weeks after the first injection. Her symptoms immediately intensified, and she became bed-bound with pre-syncope, dizziness, nausea, sore throat, difficulty falling asleep, frequent awakenings during the night, visual disturbance, transient episodes of confusion and difficulty concentrating. She was unable to attend school and after seeing numerous specialists was diagnosed with chronic fatigue syndrome. Over the following 3 years, she received no specific treatment, and her symptoms fluctuated in severity with some periods when she was able to attend school part-time. Eventually, a tilt table test was performed demonstrating an increase in heart rate from 54 bpm supine to 108 bpm within 10 min of standing, without changes in blood pressure (supine blood pressure 96/54; 10 min after the tilt, blood pressure 110/68), consistent with a diagnosis of POTS. Deep breathing test and Valsalva maneuver were unremarkable, and QSART showed no evidence of small fiber neuropathy. A gastric emptying test demonstrated mildly delayed gastric emptying. MRI of the brain, MRI of the cervical and

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thoracic spine, EEG, EMG and visual evoked potentials were all unremarkable. Ophthalmology evaluation for complaints of recurrent visual distortion, recurrent visual depth perception abnormalities and blurry vision showed no evidence of optic neuritis or visual field defect. Autoimmune markers were negative for antinuclear antibodies (ANA), anti-SSA and anti-SSB antibodies, anti-TPO antibodies, anti-thyroglobulin antibodies, anti-phosholipid antibodies and anti-DS DNA antibodies, but positive for low level of anti-NMDAR Ab (performed by Oxford University Hospital Laboratory, UK; normal range: no antibodies detected). Further testing demonstrated positive beta 2 adrenergic and M2 muscarinic receptor antibodies (Berlin Cures, Germany). A paraneoplastic panel, including ganglionic AchR antibody, was negative. Serum anti-NMDA Ab were repeated 2 months later and were once again mildly elevated. To rule out a paraneoplastic syndrome with positive anti-NMDA Ab, a pelvic ultrasound was obtained and did not reveal any ovarian or pelvic masses. Subsequently, a full body FDG-PET scan was performed and was also unremarkable. CSF analysis was negative for anti-NMDA Ab and other neuronal antibodies and showed normal cell count, glucose and protein. The patient received 5 treatments with plasmapheresis followed by a daily dose of prednisone, and her symptoms improved significantly for about 7 weeks after the treatment. When plasmapheresis was stopped and prednisone was tapered, the symptoms recurred. Following plasmapheresis and prednisone treatment, a repeat serum anti-NMDAR Ab were negative.

Discussion

De novo POTS after vaccination with quadrivalent HPV vaccine, Gardasil, has been originally described in 6 patients [3]. Subsequently, a case series of 53 patients with autonomic dysfunction after HPV vaccine has been reported in Denmark, 28 of whom had POTS [4]. In recent years, evidence has been mounting that in a subset of patients, POTS may have an autoimmune basis after several autoantibodies have been identified in patients with POTS, such as ganglionic N-type acetylcholine receptor antibodies, alpha 1 adrenergic receptor antibodies, beta 1/beta 2 adrenergic receptors antibodies and M1/M2 muscarinic receptors antibodies [1, 5–7]. Our patient also tested positive for beta 2 adrenergic and M2 muscarinic receptors antibodies, similar to another recently reported patient who developed POTS and complex regional pain syndrome following immunization with quadrivalent HPV vaccine, Gardasil [8]. In that case report, as in our patient, significant symptomatic improvement was achieved with immunomodulatory therapy, including plasmapheresis [8].

POTS patients have a higher prevalence of positive ANA, other autoimmune markers and comorbid autoimmune disorders than the general population [9], but anti-NMDAR Ab have never been described in a patient with POTS. Additionally, positive anti-NMDAR Ab after vaccination with HPV vaccine have not been previously reported, and to our knowledge, this is the first case describing such an occurrence.

Anti-NMDA receptor encephalitis, an autoimmune disorder mediated by antibodies to the NR 1 subunit of the N-methyl-D-aspartate receptor, presents with acute neurologic, psychiatric and autonomic manifestations [2]. Our patient did not have evidence of encephalitis, based on her clinical features, unremarkable MRI of the brain and normal CSF analysis, which was negative for CSF anti-NMDAR Ab. It is unclear whether in our patient, serum anti-NMDAR Ab had any correlation with POTS or whether it occurred by coincidence. We believe that, based on the temporal association between vaccination with Cervarix and the onset of symptoms, coupled with evidence of re-challenge, whereas symptoms worsened after the second dose of the vaccine, both POTS and anti-NMDAR Ab were most likely precipitated by vaccination. A literature search revealed one case report of anti-NMDA receptor encephalitis after TdaP-IPV booster vaccination [10].

POTS is a heterogeneous disorder of the autonomic nervous system, and although anti-NMDAR encephalitis can manifest with autonomic symptoms, POTS is not associated with acute encephalitis and is not considered in the spectrum of the anti-NMDAR Ab clinical phenotypes. The intriguing and unique aspects of this case are the finding of anti-NMDAR Ab in a patient with POTS following vaccination with HPV vaccine, subsequent symptomatic improvement with immunomodulatory therapy, and recurrence of symptoms once immunomodulatory therapy was discontinued. These facts suggest an autoimmune etiology of POTS in our patient. Whether the presence of anti-NMDAR Ab is coincidental or causative in this patient is unknown. Testing a cohort of patients with POTS for anti-NMDAR Ab may help determine whether POTS can be associated with anti-NMDAR Ab or whether our patient represents an isolated case.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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