


Autoimmunity, Autonomic Neuropathy, and the HPV Vaccination: A Vulnerable Subpopulation

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Case Report

An 11-year-old girl received her first dose of the Gardasil vaccine at a well-child visit. She had been healthy aside from sinus surgery and frequent infections. Prior immunology evaluation was negative, but there was a family history of autoimmune disease. Two days postvaccination, she developed headache and vomiting thought due to a viral illness. Her symptoms were progressive, however, and by 5 to 6 weeks postvaccination, there was abdominal pain, frequent vomiting, severe fatigue, pallor, daily syncope, chest pain, dyspnea, low-grade fevers, arthralgias, daily headache, memory loss, tinnitus, hearing loss, vertigo, unsteady gait, leg weakness, muscle twitches, paresthesias, and insomnia. By 7 weeks postvaccination, she had become bed-bound. She also developed moderate alopecia, Raynaud's phenomenon, recurrent oral ulcers, and nasal scabbing, suggesting the possibility of systemic autoimmunity. Eight months postvaccination, she was diagnosed with postural tachycardia syndrome (POTS) and neurocardiogenic syncope (NCS) by tilt table testing and autonomic reflex testing revealed abnormal blood pressure response to Valsalva and reduced baroreflex adrenergic sensitivity.

Nonautoimmune causes for her symptoms were excluded with laboratory testing, echocardiogram, cardiac monitoring and brain magnetic resonance imaging. The autoimmune dysautonomia panel antibodies, NMDA (*N*-methyl-D-aspartate) receptor antibodies, thyroid antibodies, and celiac antibodies were all negative. Testing for Sjogren's syndrome (including the early Sjogren's antibodies), antiphospholipid syndrome (with primary and secondary antibodies) and lupus was also negative. However, autoantibodies against adrenergic and muscarinic receptors were detected as shown in Table 1.

The patient did improve with conservative therapy, but she remained moderate to severely disabled by her illness. Small fiber neuropathy was suspected due to her cardiovascular and presumed gastrointestinal autonomic dysfunction as well as the presence of muscle twitches and paresthesias, and a skin biopsy was performed (from the

lower legs as normative data are available) to evaluate for this possibility. These results are shown in Table 2. The sensory results were compared with controls aged 20 to 29 years and the autonomic results were compared with healthy adults not stratified by age. Healthy children have significantly higher nerve fiber density compared to healthy adults. Thus, given the patient's young age (13 years at the time of the biopsy), these results were consistent with a very severe autonomic neuropathy and likely a mild to moderate small fiber sensory neuropathy. Given evidence for autoimmune autonomic neuropathy, a trial of intravenous immunoglobulin therapy was initiated.

After four months of therapy at a dose of 1 gm/kg monthly, the patient continues to gradually improve. Her COMPASS-31 score has improved from 46 to 29 and her estimated level of functioning has improved from 20% (mostly bedridden) to 60% (more good days than bad days). The earliest signs of improvement came after the second week of treatment. Her recurrent syncope and paresthesias have resolved. Her epigastric pain, migraines, insomnia, anxiety, fatigue, and cognitive ability have all moderately improved and she has been able to stop her biweekly saline infusions. She continues on monthly intravenous immunoglobulin.

Discussion

International recommendation for human papillomavirus (HPV) vaccination for girls aged 11 to 12 years using 3 doses of the quadrivalent Gardasil vaccine began in 2006. The bivalent vaccine Cervix was introduced in 2009. More recently, HPV vaccination has also been recommended for boys and it is being administered to children as young as 9 years. The first reported association of

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Table 1. Patient Test Results for Antiadrenergic and Muscarinic Receptor Antibodies by Enzyme-Linked Immunosorbent Assay Testing.^a

Antibody Type	Cutoff	Units/mL
Anti- β -1 adrenergic receptor antibodies	<15.0 units/mL: negative >15.0 units/mL: positive	21.7 (positive)
Anti- β -2 adrenergic receptor antibodies	<8.0 units/mL: negative 8.0-14.0 units/mL: indeterminate >14.0 units/mL: positive	11.4 (indeterminate)
Anti-muscarinic cholinergic receptor-3 antibodies	<6.0 units/mL: negative 6.0-10.0 units/mL: indeterminate >10.0 units/mL: positive	13.5 (positive)
Anti-muscarinic cholinergic receptor-4 antibodies	<5.0 units/mL: negative 5.0-7.0 units/mL: indeterminate >7.0 units/mL: positive	24.9 (positive)

^aAnalysis was performed by enzyme-linked immunosorbent assays performed by CellTrend GmbH in Berlin, Germany and CellTrend GmbH, Luckenwalde, Germany.

Table 2. Skin Biopsy Results.^a

Biopsy Site ^b	Epidermal Nerve Fiber Density (Sensory)	Sweat Gland Nerve Fiber Density (Autonomic)
Left lower leg	8.1 (normal >8.0/mm)	16.7 (normal >38.2%)
Right lower leg	8.6 (normal >8.0/mm)	27.5 (normal >38.2%)

^aAnalysis was performed by Corinthian Reference Laboratory, Lubeck, Texas, USA.

^bNormative data are available from the lower legs.

autonomic dysfunction and HPV vaccination was a case report of a patient with POTS in 2010.¹ This was followed by at least 15 case series from different countries describing cardiovascular and gastrointestinal autonomic disturbance as well as complex regional pain syndrome. From these reports, a consistent clinical phenotype has emerged with evidence for sensory and autonomic dysregulation and often severe disability. This has come to be called the “HPV vaccination syndrome.”² The most commonly reported symptoms of this syndrome are similar to those in the present case report. The onset of progressive symptoms begins within days to weeks of vaccination. The HPV vaccine is one of the few given as a series. In the present case, the link between symptom onset and vaccination was apparent and she did not receive more doses of the vaccine. Several of the published case series, however, make note of a clear worsening of symptoms after subsequent doses, often many months later, further suggesting a causal link between the neurological illness and the HPV vaccine. Although temporality of symptoms to vaccine administration does not prove causality, further evidence suggesting the HPV vaccine may lead to immune-mediated neurological injury comes from the recently described Gardasil mouse model.³ In this study, wild-type C57B6 mice were injected with the quadrivalent HPV vaccine at 6 months of age. These mice developed anti-HPV

antibodies that cross reacted with protein and phospholipid extracts from brain as well as evidence for neurological impairment.

We believe this is the first reported case of biopsy-proven autonomic neuropathy developing within days of HPV vaccination. There have been 2 prior cases of biopsy-proven small fiber sensory neuropathy in patients with suspected HPV vaccination syndrome^{4,5} and 3 other patients with the suspected syndrome with presumed small fiber neuropathy based on abnormal quantitative sudomotor testing.⁶ Given these reports and the nature of the symptoms observed in cases without biopsy data, small fiber neuropathy—sensory and/or autonomic—is suspected to be involved in the pathogenesis of the HPV vaccination syndrome.²

Small fiber neurons greatly outnumber large fiber neurons and include both sensory and autonomic nerves. Small fiber sensory nerves transmit pain, itch, and temperature sense. Pain in small fiber neuropathy may be non-length dependent, may occur anywhere in the body and may be migratory; pruritis, paresthesias, and unusual sensations may also occur, for example, a sensation of cold or hot water being poured on the patient’s leg. The autonomic small fiber neurons transmit complex signals from the autonomic ganglia to all blood vessels and internal organs to maintain homeostasis of many domains. For this reason, dysautonomia results in widespread effects, including cardiovascular dysautonomia—which may manifest clinically as POTS, NCS, labile hypertension and/or orthostatic hypotension, gastrointestinal dysautonomia, neurogenic bladder, temperature and/or sweating dysregulation. Importantly, there is also impairment of the stress response which results in intolerance of even minimal stressors. Skin biopsy is emerging as the gold standard to diagnose small fiber

sensory and autonomic neuropathy with an estimated sensitivity and specificity of up to 90%.⁷ While the specimen processing and analysis is complex, commercial laboratories provide testing kits that facilitate processing of outside samples.

There is not presently a well-established laboratory or antibody signature in patients with the HPV vaccination syndrome. Antiphospholipid antibodies,^{5,8,9} antinuclear antibodies,^{5,8,9} adrenergic and muscarinic receptor antibodies,^{6,10} thyroid antibodies,⁹ ganglionic AChR antibodies, and NMDA receptor antibodies¹⁰ have been reported in some affected patients. These antibodies are similar to those that have been reported in patients presenting with autoimmune dysautonomia without preceding HPV vaccination, suggesting that different environmental triggers may lead to the same clinical phenotype. The clinical manifestations reported in the HPV vaccination syndrome are virtually identical to those we described in a case series of patients with biopsy-proven autonomic neuropathy in the antiphospholipid syndrome⁸ and in a case series of patients with “unexplained juvenile-onset small fiber polyneuropathy.”⁷ Most of the patients in the latter study were found to have serological evidence suggestive of immune dysregulation and 80% responded to immune modulatory therapy. It is well recognized that immune modulatory therapy is efficacious in the treatment of immune-mediated neuropathies as well as most other immune-mediated neurological disorders. There are 2 case reports demonstrating clinical benefit of immune modulatory therapy in the HPV vaccination syndrome^{10,11} as well as case series demonstrating benefit in presumed or proven autoimmune autonomic disorders.^{7,12,13} In addition, it is clear that many patients with the HPV vaccination syndrome do not spontaneously recover, and patients severely affected for up to 9 years postvaccination have been reported.⁹ Thus, we propose that immune modulatory therapy should be considered in patients with severe suspected HPV vaccination syndrome who remain disabled despite conservative treatments.

The severe disability seen in many patients with the HPV vaccination syndrome, including several deaths, led the Japanese Ministry of Health to suspend its recommendation for HPV vaccination. Investigation into the HPV vaccine has also been initiated in Europe and many parents are choosing to forgo vaccination of their children given the numerous reports that have surfaced on social media. It is clear, however, that only a vulnerable subset of the population is at risk for the HPV vaccination syndrome. A reasonable alternative to complete avoidance would be to consider forgoing this vaccine in select patients with a personal or family history of autoimmune disease and/or autonomic disorders. Additionally, increased awareness of the

potential for neurological complications is important, particularly for primary care providers, since multiple case reports have documented clinical worsening with subsequent HPV vaccine doses. It would seem prudent for patients who develop new persistent headaches, fatigue, presyncope, tachycardia, gastrointestinal symptoms, and/or limb pain or weakness after the first vaccination to avoid subsequent doses. Further studies aimed at defining the at-risk phenotype and/or genotype are warranted, given the devastating clinical outcome of severe, long-term disability and even death of some affected by the HPV vaccination syndrome.

Author Contributions

JRS wrote the first draft of the manuscript. JEH made important contributions during the revision process.

Declaration of Conflicting Interests

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References

1. Blitshteyn S. Postural tachycardia syndrome after vaccination with Gardasil [letter to the editor]. *Eur J Neurol*. 2010;17:e52.
2. Martínez-Lavín M. Hypothesis. Human papillomavirus vaccination syndrome—small fiber neuropathy and dysautonomia could be its underlying pathogenesis. *Clin Rheumatol*. 2015;34:1165-1169.
3. Inbar R, Weiss R, Tomljenovic L, et al. Behavioral abnormalities in female mice following administration of aluminum adjuvants and the human papillomavirus (HPV) vaccine Gardasil. *Immunol Res*. 2017;65:136-149.
4. Kafaie J, Kim M, Krause E. Small fiber neuropathy following vaccination. *J Clin Neuromusc Dis*. 2016;18:37-40.
5. Kinoshita T, Abe RT, Hineno A, Tsunekawa K, Nakane S, Ikeda S. Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine. *Intern Med*. 2014;53:2185-2200.
6. Blitshteyn S. Postural tachycardia syndrome following human papillomavirus vaccination. *Eur J Neurol*. 2014;21:135-139.
7. Oaklander AL, Klein MM. Evidence of small-fiber polyneuropathy in unexplained, juvenile-onset, widespread pain syndromes. *Pediatrics*. 2013;131:e1091-e1100.
8. Schofield JR. Autonomic neuropathy—in its many guises—as the initial manifestation of the antiphospholipid syndrome. *Immunol Res*. 2017;65:532-542.

9. Palmieri B, Poddighe D, Vadalà M, Laurino C, Carnovale C, Clementi E. Severe somatoform and dysautonomic syndromes after HPV vaccination: case series and review of the literature. *Immunol Res.* 2017;65:117-119.
10. Blitshteyn S, Brook J. Postural tachycardia syndrome (POTS) with anti-NMDA receptor antibodies after human papillomavirus vaccination. *Immunol Res.* 2017;65:282-284.
11. Hendrickson JE, Tormey CA. Human papilloma virus vaccine and dysautonomia: considerations for autoantibody evaluation and HLA typing. *Vaccine.* 2016;34:4468.
12. Flanagan EP, Saito YA, Lennon VA, et al. Immunotherapy trial as diagnostic test in evaluating patients with presumed autoimmune gastrointestinal dysmotility. *Neurogastroenterol Motil.* 2014;26:1285-1297.
13. Goodman BP. Immuno-responsive autonomic neuropathy in Sjogren syndrome—case series and literature review [published online March 31, 2017]. *Am J Ther.* doi:10.1097/MJT.0000000000000583.