Annals of Arthritis and Clinical Rheumatology

Research Article
Published: 10 Sep, 2019

Autoantibodies against Autonomic Nerve Receptors in Adolescent Japanese Girls after Immunization with Human Papillomavirus Vaccine

Akiyo Hineno[1,2], Shu-ichi Ikeda[1], Carmen Scheibenbogen[3,4], Harald Heidecke[5], Kai Schulze-Forster[5], Juliane Junker[5], Gabriela Riemekasten[6], Ralf Dechend[8], Duska Dragun[9] and Yehuda Shoenfeld[10]*

[1]Intractable Disease Care Center, Shinshu University Hospital, Japan

[2]Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Japan

[3]Department of Medicine, Institute for Medical Immunology, Germany

[4]Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Germany

[5]Cell Trend GmbH, Germany

[6]Department of Rheumatology, Universitätsklinikum Schleswig-Holstein, Germany

[7]Experimental and Clinical Research Center, Charité-Universitätsmedizin Berlin Germany

[8]Department of Cardiology and Nephrology, HELIOS-Klinikum, Germany

[9]Department of Nephrology and Intensive Care Medicine, Charité-Universitätsmedizin Berlin, Germany

[10]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Israel

Abstract

In Japan a significant number of adolescent girls complain of unusual symptoms after human papillomavirus (HPV) vaccination, and these symptoms, composed of orthostatic dysregulation, chronic regional pain syndrome (CRPS) and cognitive dysfunction are considered adverse effects of HPV vaccination. However, a causal link between HPV vaccination and these adverse effects has not been demonstrated. In the present study, we investigated autoantibodies against diverse G-protein coupled receptors in the serum of girls who complained of possible adverse effects after HPV vaccination. Fifty five girls with HPV vaccination and 57 girls without HPV immunization were enrolled in the study. The serum levels of autoantibodies against the adrenergic receptors α1, α2, β1and β2, muscarinic acetylcholine receptors 1, 2, 3, 4, 5; and endothelin receptor A was significantly elevated in girls with HPV vaccination, compared with those in the controls. The serum levels of these autoantibodies tended to decrease with the time course of the illness, but there was no statistically meaningful association between the clinical symptoms and elevated serum levels of these autoantibodies. This preliminary study provides evidence that post-vaccination abnormal autoimmunity plays an important role in the development of unique symptoms after HPV vaccination.

Keywords: Autonomic nerve dysfunction; Autoantibody; Autoimmune disorder; Chronic regional pain syndrome; HPV; Human papillomavirus; Chronic regional pain syndrome

OPEN ACCESS

Correspondence:
Shu-ichi Ikeda, Intractable Disease Care Center, Shinshu University Hospital, Matsumoto 390-0802, Japan, Tel; 81-263-37 -3148; Fax: 81-263-34-6589;
E-mail: ikedasi@shinshu-u.ac.jp

Received Date: *14 Aug 2019*
Accepted Date: *06 Sep 2019*
Published Date: *10 Sep 2019*

Citation:
Hineno A, Shu-ichi Ikeda, Scheibenbogen C, Heidecke H, Schulze-Forster K, Junker, et al. Autoantibodies against Autonomic Nerve Receptors in Adolescent Japanese Girls after Immunization with Human Papillomavirus Vaccine. Ann Arthritis Clin Rheumatol. 2019; 2(2): 1014.

Introduction

Human papillomavirus (HPV) infection promotesr uterine and cervical cancers [1], and thus, in 2010, HPV vaccines were introduced worldwide [2,3]. Since then case series of suspected adverse effects after HPV vaccination have been reported from several countries and the symptoms described by independent researchers are similar [4-9].

Previously, we described the clinical characteristics of 40 Japanese girls with possible HPV vaccine-related adverse effects in 2014 [10], and the common symptoms were chronic headache, general fatigue, limb pain and weakness. All these symptoms can be attributed to a combination of orthostatic dysregulation and chronic regional pain syndrome (CRPS); additionally, peripheral sympathetic nerve dysfunction was surmised to be responsible for the occurrence of both orthostatic dysregulation and CRPS [11]. Cognitive dysfunction has also been reported as a possible adverse effect, manifesting late after HPV vaccination: it appears mainly as memory impairment, decreased calculation ability, and transient prosopagnosia-like symptoms, and

calculation ability, and transient prosopagnosia-like symptoms, and therefore, affected patients experienced difficulties in performing their schoolwork, with some being absent from school for long periods [12,13,14]. It has been supposed that long-term orthostatic dysregulation and CRPS might secondarily induce myalgic encephalomyelitis/chronic fatigue syndrome in affected patients [11].

The temporal relationship between HPV vaccination and the occurrence of these unique symptoms strongly suggests a causal link of both events [12], but the exact pathogenesis of orthostatic dysregulation and CRPS after HPV vaccination remains unclear. Recent evidence has shown that autoantibodies against adrenergic and cholinergic receptor play an important role in the development of both orthostatic dysregulation [15, 16] and CRPS [17,18]. Thus, we investigated autoantibodies against diverse G-protein coupled receptors (GPCRs) including adrenergic and muscarinic acetylcholine receptors in the serum of girls who complained possible adverse effects after HPV vaccination and the results were compared with those obtained from non-vaccinated girls.

Materials and Methods

Subjects and human blood samples

From June 2013 to September 2016, 55 girls were hospitalized in our institute, complaining of several symptoms after HPV vaccination, including 44 patients with a history of vaccination with Cervarix®, 10 with Gardasil®, and one with unknown. Using self-reported answers to printed questionnaires from out institute and medical records from other institutes where available, we obtained a detailed history of the patients' symptoms to determine the duration between vaccination and the development of the first symptom suspected to be related to the vaccination. All patients underwent complete physical and neurological examinations. If a patient exhibited hypotension or coldness of the limbs, or both, Schellong test and/or digital plethysmography were performed. The latter was recorded in the right second finger and right first toe, while checking the patient's skin temperature [10]. The controls were age-matched 57 healthy girls, from Nagano prefecture and Kanto area including Tokyo, without a history of immunization with HPV vaccine. Serum was collected from each of the girls after obtaining informed consent.

Ethics approval

The study protocol was approved by the Institutional Review Board (approval nos. 4128 & 4150) of Shinshu University School of Medicine, Matsumoto, Japan.

Quantification of autoantibodies by enzyme-linked immunosorbent assay (ELISA)

GPCRs-related receptors including adrenergic receptors α1,2 and β1,2; muscarinic acetylcholine receptors M1,2,3,4,5; angiotensin receptor 1 (AT1R) and endothelin receptor (ETAR) were targeted, and the methods to measure these autoantibodies have been previously described [19]. Briefly, the serum level of these autoantibodies was assessed using commercially available solid-phase sandwich ELISA kits according to the manufacturer's instructions (CellTrend GmbH, Luckewalde, Germany). The concentrations of autoantibodies were calculated as arbitrary units (U) by extrapolation from a standard curve of five standards of concentrations ranging from 2.5 to 120 U/ml. The ELISAs were validated according to the Food and Drug Administration's Guidance for industry: Bioanalytical Method Validation. Samples from patients and controls were analyzed in the same assay plate, and these samples were analyzed blinded to group allocation.

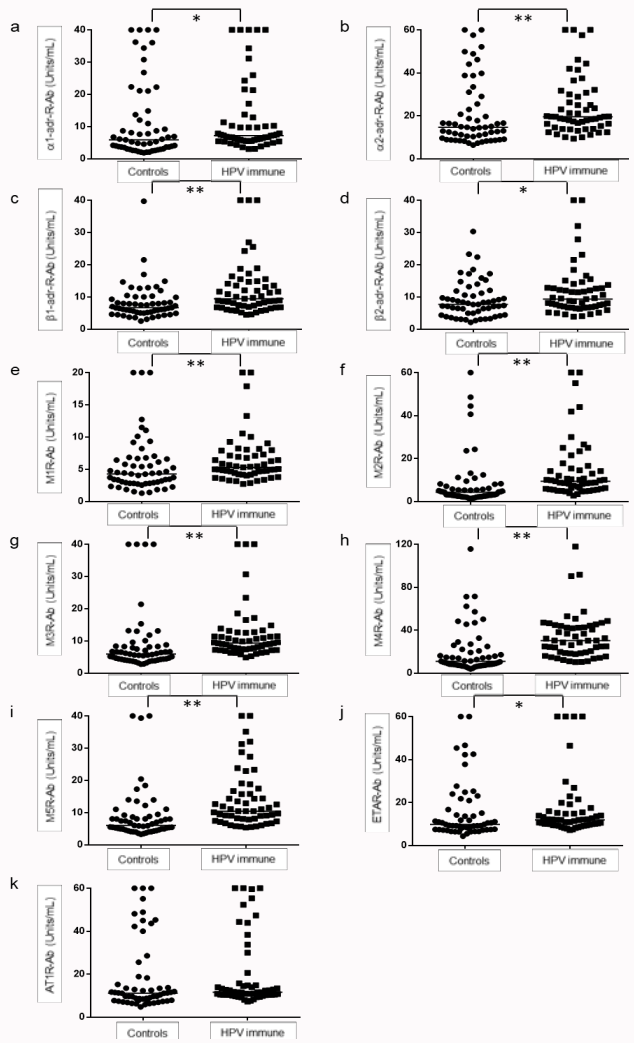

Figure 1: Comparison of serum levels of autoantibodies between girls with HPV immunization and those without immunization (controls). *p<0.05, **p<0.01. a: antibodies against α1 adrenergic receptor (α1-adr-R-ab), -: median, Mann-Whitney test p=0.0359; b: antibodies against α2 adrenergic receptor (α2-adr-R-ab), -: median, Mann-Whitney test p=0.005; c:antibodies against β1-adrenergic receptor (β1-adr-R-ab), -: median, Mann-Whitney test p=0.0002; d: antibodies against β2-adrenergic receptor antibody (β2-adr-R-ab), -: median, Mann-Whitney test p=0.0424; e: antibodies against muscarinic 1 acetylcholine receptor (M1R-Ab), -:median, Mann-Whitney test p=0.0075; f: antibodies against muscarinic 2 acetylcholine receptor (M2R-Ab), -: median, Mann-Whitney test p<0.0001; g: antibodies against muscarinic 3 acetylcholine receptor (M3R-Ab), -: median, Mann-Whitney test p<0.0001; h: antibodies against muscarinic 4 acetylcholine receptor (M4R-Ab), -: median, Mann-Whitney test p<0.0001; i: antibodies against muscarinic 5 acetylcholine receptor (M5R-Ab), -: median, Mann-Whitney test p<0.0001; j: antibodies against endothelin receptor (ETAR), -: median, Mann-Whitney test p=0.032; k: antibodies against angiotensin receptor 1 (AT1R), -: median, Mann-Whitney test p = 0.0585.

Statistical analysis

Statistical data analyses were performed using the software's (GraphPad PRISM and BellCurve for Excel). Nonparametric statistical methods were used. Continuous variables were expressed as median and Interquartile Range (IQR). Univariate comparisons of two independent groups were performed using the Mann-Whitney-U test. The results with a two-tailed p-value of <0.05 were considered statistically significant. Contingency analysis was performed by

Table 1: Main clinical manifestations of 55 patients.

	No of cases	Frequency (%)
Prolonged general fatigue	38	69.1
Dysautonomic symptoms	37	67.3
Widespread pain	34	61.8
Chronic headache	33	60
Motor dysfunction	30	54.5
Learning impairment	29	52.7
Limb shaking	24	43.6
Sleep disturbance	23	41.8
Abnormal sensation	22	40
Menstrual abnormality	18	32.7

Dysautonomic symptoms contain orthostatic fainting or palpitation, severe headache after standing, difficulty in getting up and abnormal bowel movement with frequent diarrhea

Fisher's exact test. Comparisons between two dependent groups were performed using Wilcoxon matched-pairs signed-rank test. Correlation analysis was performed using nonparametric Spearman coefficient *r*.

Results

Clinical characteristics of vaccinated girls

The average age of the 55 vaccinated girls at an initial vaccination was 13.9 ± 2.7 years, and that at symptoms' onset and blood sampling was 14.7 ± 2.8 years and 16.6 ± 3.1 years, respectively. The time to blood sampling from the first vaccination ranged from 2 to 64 months and the time to blood sampling from the onset of symptoms ranged from 0 to 59 months.

Clinical summary of the 55 girls is presented in Table 1. Symptoms or signs frequently observed in these girls were prolonged general fatigue, chronic headache, widespread pain, limb shaking, dysautonomic symptoms, motor dysfunction, abnormal sensation, sleep disturbance, learning impairment, and menstrual abnormality. The average age at blood sampling of the 57 controls was 18.8 ± 2.7 years; the controls did not have any serious disorders.

Serum levels of GPCRs-related autoantibodies

The serum levels of antibodies against diverse GPCRs tested in the vaccinated girls and controls are shown in Figure 1. Significantly higher autoantibody levels against α1-adrenergic, α2- adrenergic, β1-adrenergic, β2- adrenergic, muscarinic 1 acetylcholine, muscarinic 2 acetylcholine, muscarinic 3 acetylcholine, muscarinic 4 acetylcholine, muscarinic 5 acetylcholine receptors, and ETAR were observed in the vaccinated girls than in the controls (Table 2). However, there was no significant difference in the serum levels of antibodies against AT1R between the vaccinated girls and controls.

Clinical manifestations, clinical course, and serum levels of autoantibodies

We compared the symptoms and serum levels of autoantibodies among the vaccinated girls; there was no significant association between the symptoms and serum levels of autoantibodies tested. A comparison of the duration after symptom and serum levels of autoantibodies showed the patients with symptoms for a short duration tended to have high serum levels of autoantibodies, whereas the patients with symptoms for a long duration tended to have low serum levels of autoantibodies (Figure 2). This tendency was more apparent in the serum level change ofanti-β1-adrenergic receptor and anti-β2-adrenergic receptor antibodies, muscarinic 2 acetylcholine receptor, muscarinic 3 acetylcholine receptor and muscarinic 5 acetylcholine receptor antibodies (Figure 2c, 2g, 2f and 2i).

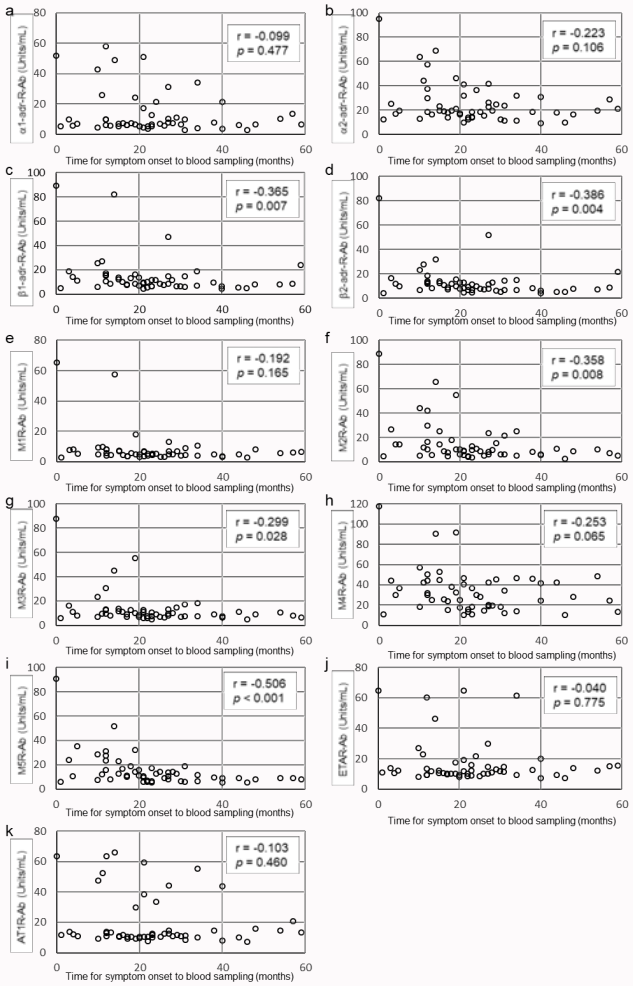

Figure 2: Correlation analysis of serum levels of autoantibodies and time from symptom onset to blood sampling. a: antibodies against α1 adrenergic receptor (α1-adr-R-ab); b: antibodies against α2 adrenergic receptor (α2-adr-R-ab); c:antibodies against β1-adrenergic receptor (β1-adr-R-ab); d: antibodies against β2-adrenergic receptor antibody (β2-adr-R-ab); e: antibodies against muscarinic 1 acetylcholine receptor (M1R-Ab); f: antibodies against muscarinic 2 acetylcholine receptor (M2R-Ab); g: antibodies against muscarinic 3 acetylcholine receptor (M3R-Ab); h: antibodies against muscarinic 4 acetylcholine receptor (M4R-Ab); i: antibodies against muscarinic 5 acetylcholine receptor (M5R-Ab); j: antibodies against endothelin receptor (ETAR-Ab); k: antibodies against angiotensin receptor 1 (AT1R-Ab).

Discussion

Significant numbers of girls developed a unique disorder after HPV vaccination worldwide: a comparative study of the symptomatic complex has shown that all manifestations were similar between affected Japanese and Danish young females after HPV vaccination [20]. This disorder can be explainable by a combination of orthostatic dysregulation, CRPS and brain cognitive dysfunction [11,21]. Furthermore, these three disorders seem to be causally related.

Autoimmunity and autoantibodies in orthostatic dysregulation, CRPS and chronic fatigue syndrome/ myalgic encephalomyelitis

Recently, it has been shown that autoimmunity and

Table 2: Comparison of area under the curve (AUC), cut off with specificity and sensitivity between girls with/without human papillomavirus vaccine immunization.

Antibody	No of girls with HPV immune	No of girls without HPV immune	Cut off (Units/ml)	AUC (%)	Sensitivity (%)	Specificity (%)
α1-adr-R-Ab	55	57	4.3	61.5	92.7	40.4
α2-adr-R-Ab	55	57	17	63.5	67.3	64.9
β1-adr-R-Ab	55	57	8.1	70.3	65.5	66.7
β2-adr-R-Ab	55	57	8.2	61.1	56.4	52.6
M1R-Ab	55	57	4.7	64.6	67.3	59.7
M2R-Ab	55	57	5.4	78.3	81.8	68.4
M3R-Ab	55	57	7.1	75.7	83.6	66.7
M4R-Ab	55	57	17.5	77	80	70.2
M5R-Ab	55	57	8.1	76.4	72.7	71.9
AT1R-Ab	55	57	9.1	60.4	92.7	36.8
ETAR-Ab	55	57	8	61.7	94.6	31.6

autoantibodies play an important role in a subset of patients with orthostatic dysregulation including postural orthostatic tachycardia syndrome (POTS) and CRPS [18,19]; orthostatic dysregulation is commonly associated with autonomic nerve dysfunctions, in which abnormal bowel movement with vague abdominal pain and bladder dysfunction are frequently observed [23]. Furthermore, POTS is intractable and usually manifests as several non-specific symptoms including migraine-like headache, chest pain, gastroparesis, chronic fatigue [24], and mental confusion (brain-fog) [16]. Autoantibodies against adrenergic receptors β1 and β2, and muscarinic acetylcholine receptors 2 and 3 have been detected in the serum of patients with orthostatic dysregulation [15]. Additionally an antibody towardα1 adrenergic receptor has been also detected in the serum of patients with POTS [16].

CRPS is clinically composed of pain, hyperalgesia, vasomotor and trophic changes in the affected limbs [25] and the appearance of these symptoms are influenced by dysfunctions of peripheral or central sympathetic nervous system [26]. Moreover, cortical reorganization processes are observed in the chronic stage of the patients [27]. CRPS is also considered to be an immune system-mediated disorder and it has been shown that autoantibodies against the adrenergic receptors α1 and β2, and muscarinic acetylcholine receptor 2 are associated with this condition [28]. In practice, immune system-modulating therapies including the administration of corticosteroids, intravenous immunoglobulin (IVIg), and rituximab, and plasma exchange seem to be effective for limb pain and other systemic symptoms in patients with CRPS [28,29].

All these findings suggest that some individuals, not all, might develop orthostatic dysregulation including POTS and CRPS on the basis of abnormal immune responses [28]. Furthermore, long-lasting fatigue and/or pain in patients with each disorder leads to chronic fatigue syndrome/myalgic encephalomyelitis (CSF) [11], and it has been reported that autoantibodies against the adrenergic receptor β2 and muscarinic acetylcholine receptor 3 and 4 were significantly elevated in the serum of patients with CFS [30]. It is, therefore, likely that orthostatic dysregulation, CRPS and CFS belong to the same clinical spectrum and that in a subset of patients these three disorders might be caused by some common autoimmune mechanisms, resulting in a variety of clinical manifestations [11].

Relationship between clinical symptomatology and autoantibodies in patients after HPV vaccination

In the present study, compared with those in controls, the serum levels of autoantibodies against adrenergic receptors α1, α2, β1, β2; muscarinic acetylcholine receptor 1, 2, 3, 4, and 5; and ETAR were significantly elevated in patients with HPV vaccination. In contrast, there was no significant difference of serum levels of autoantibody againstAT1R between both groups of individuals examined. The anti-AT1R and anti-ETAR antibodies are different from the autonomic nerve receptor related autoantibodies, and these two autoantibodies are known to be important biomarkers in transplantation [28].

We further evaluated the correlation between elevated levels of autoantibodies and various clinical manifestations. There was no significant association between the major symptoms including dysautonomic symptoms and serum levels of autoantibodies; in the present study the time of blood sampling after the first vaccination or after the onset of illness considerably varied among the patients examined. The time difference for the former was approximately 3 years and that for the latter was approximately 2 years on an average, indicating that very limited number of patients provided serum samples at the peak of clinical symptoms. Thus, it might be difficult to validate that some symptoms were statistically related to elevated serum levels of autoantibodies. On the contrary, it has been shown that the serum levels of autonomic nerve receptor related autoantibodies were high in the patients at the early stage of illness, and they probably tended to decrease with the time courses of illness, although we did not check the serial serum levels of these autoantibodies in the patients. Therefore, we considered that high serum levels of autonomic nerve receptor-related autoantibodies in the patients were up regulated by HPV vaccination.

The relationship between HPV vaccination and positive serum autoantibodies against autonomic nerve receptors were already described in the previous three case reports [31,32,33]; autoantibodies against adrenergic receptors β1, β2 and muscarinic acetylcholine receptors 2, 3, and 4 were associated with the development of a post-HPV vaccination disorder.

It is well known that autonomic nerve dysfunction including POTS and CRPS do develop in young girls without prior vaccination [34]. Recently, it has been reported that a significant number of non-vaccinated Japanese girls suffer from similar symptoms described as adverse effects after HPV vaccination [35]. In the present study, we found that healthy controls without HPV vaccination have some amount of autoantibodies against the adrenergic receptors α and β, and muscarinic acetylcholine receptors in the serum. It is not

clear whether or not there are some functional or conformational difference among these autoantibodies between healthy individuals and patients [36,37], but it is conceivable that low serum levels of these autoantibodies against autonomic nerve receptors can result in the occurrence of orthostatic dysregulation and/or CRPS in non-vaccinated individuals.

Pathogenesis in the induction of autoantibodies after HPV vaccination

A viral/bacterial infection and vaccination can occasionally trigger the development of POTS, CRPS and CFS [22]. Vaccination results in the iatrogenic production of useful antibodies in the human body, but it cannot be ruled out that the exposure to an external stimulus including adjuvants induces unexpected abnormal immune responses, such as a newly evoked situation with an autoimmune abnormality [38].

Regarding HPV vaccine, the primary sequence of the HPV major capsid L1s antigen, which is expressed in HPV strain 6, 11, 16 and 18, is similar to that of several human autonomic nerve receptors and their related proteins, including adrenergic receptors α1 and β1, β adrenergic receptor kinases 1 and 2 [39,40]. According to the publicly available epitope database (The Immune Epitope Data Base), these pentapeptides share their sequence with diverse autonomic nerve receptors and are surmised to be endowed with immunogenicity and antigenicity [41]. It has also been reported that patients produced autoantibodies against more than one autonomic nerve receptor. This is reasonably acceptable by the fact that there is a 40% to 70% sequence homology within the two β adrenergic receptors and within the five muscarinic acetylcholine receptors [30].

Our study had some limitations. First, the number of the study subjects was small. Second, blood sampling in some patients to evaluate serum autoantibodies was not carried out in time.

Conclusion

The exact pathogenesis of various symptoms after HPV vaccination remains unclear and therefore, affected individuals are diagnosed to have psychiatric illness. The symptoms developed after HPV vaccination cannot be clearly categorized into any traditional well-defined conditions. This might be because that a vulnerable subset of the population is at a risk of developing post-HPV vaccination symptoms. To clarify the associated molecular backgrounds, a wide range of approaches are required. The present preliminary study provides that some of the symptoms after HPV vaccination can be attributed to the abnormal autoimmune response after HPV vaccination. Therefore, immune modulatory therapies, which remove these pathologic autoantibodies and/or suppress their production in serum, can be used for the patients with post-HPV vaccination symptoms.

Acknowledgment

We thank Mrs. Misuzu Kurashina for her many helps in this study.

Funding

This study was supported by a grant from a Health and Labour Science Research Grant on Emerging and Re-emerging Infectious Diseases (Establishment of Treatments and Providing Information on Symptoms after HPV vaccination, H28-001) to S.I. from the Ministry of Public Health, Labour and Welfare, Japan. This study was also supported by grant from Shinshu Intractable Research Foundation, and Research Grant from Okaya Municipal Hospital to A.H.

References

1. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12-9.
2. FUTURE II study group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356(19):1915-7.
3. Jeurissen S, Makar A. Epidemiological and economic impact of human papillomavirus vaccines. Int J Gynecol Cancer. 2009;19(4):761-71.
4. Blitshteyn S. Postural tachycardia syndrome following human papillomavirus vaccination. Eur J Neurol. 2014;21(1):135-9.
5. Brinth L, Theibel AC, Pors K, Mehlsen J. Suspected side effects to the quadrivalent human papillomavirus vaccine. Dan Med J. 2015:62(4):A5064.
6. Brinth LS, Pors K, Theibel AC, Mehlsen J. Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papillomavirus. Vaccine. 2015;33(22):2602-5.
7. Palmieri B, Poddighe D, Vadala M, Laurino C, Carnovale C, Clementi E. Severe somatoform and dysautonomic syndromes after HPV vaccination: case series and review of literature. Immunol Res. 2017;65(1):106-16.
8. Martínez-Lavín M. Fibromyalgia-like illness in 2 girls after human papillomavirus vaccination. J Clin Rheum. 2014;20(7):392-3.
9. Pompilio Martinez. Motor and sensory clinical findings in girls vaccinated against the human papillomavirus from Carmen de Bolivar, Colombia. 2016.
10. Kinoshita T, Abe R, 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(19):2185-200.
11. Blitshetyn S, Brinth L, Hendrickson J, Martinez-Lavin M. Autonomic dysfunction and HPV immunization: an overview. Immunol Res.2018;66(6):744-54.
12. Ozawa K, Hineno A, Kinoshita T, Ishihara S, Ikeda S. Suspected adverse effects after human papillomavirus vaccination: a temporal relationship between vaccine administration and the appearance of symptoms in Japan. Drug Saf. 2017;40(12):1219-29.
13. Carnovale C, Damavandi PT, Gentili M, Pozzi M, Antoniazzi S, Radice S, et al. On the association between human papillomavirus vaccine and sleep disorder: evaluation based on vaccine adverse reporting systems. J Neurol Sci. 2017;373:179-81.
14. Hirai T, Kuroiwa Y, Hayashi T, Uchiyama M, Nakamura I, Yokota S, et al. Adverse effects of human papillomavirus virus vaccination on central nervous system: neuro-endocrinological disorders of hypothalamo-pituitary axis. J Auton Nerv Syst. 2016;201:49-74.
15. Yub X, Stavrakis S, Hill MA, Huang S, Reim S, Lin H, et al. Autoantibody activation of beta-adrenergic and muscarinic receptors contributes to an "autoimmune" orthostatic hypotension. J Am Sco Hypertens. 2012;6(1):40-7.
16. Ruzieh M, Batizy L, Dasa O, Oostra C, Grubb B. The role of autoantibodies in the syndromes of orthostatic intolerance: a systemic review. Scand Cardiovasc. 2017;51(5):243-7.
17. Kohr D, Singh P, Tschernatsch M, Kaps M, Pouokam E, Diener M, et al. Autoimmunity against the ß2 adrenergic receptor and muscarinic-2 receptor in complex regional pain syndrome. Pain. 2011;152(12):2690-700.
18. Dubuis E, Thompson V, Leite MI, Blaes F, Maihofner C, Greensmith D, et al. Longstanding complex regional pain syndrome is associated

with activating autoantibodies against alpha-1a adrenoreceptors. Pain. 2014;155(11):2408-17.

19. Cabral-Marques O, Marques A, Giil LM, De Vito R, Rademacher J, Günther J, et al. GPCR-specific autoantibody signatures are associated with physiological and pathological immune homeostasis. Nat Commun. 2018;9(1):5224.
20. Kuroiwa Y, Yokota S, Nakamura I, Nakajima T, Nishioka K. Human papilloma virus vaccination (HPVV)-associated neuro-immunopathic syndrome (HANS): a comparative study of the symptomatic complex occurring in Japanese and Danish young females after HPVV. Auton Nerv Syst. 2018;55(1):21-30.
21. Matsudaira T, Takahashi Y, Matsuda K, Ikeda H, Usui K, Obi T, et al. Cognitive dysfunction and regional cerebral blood flow changes in Japanese females after human papillomavirus vaccination. Neurol Clin Neurosci. 2016;4(6):220-7.
22. Dahan S, Tomljenovic L, Shoenfeld Y. Postural orthostatic tachycardia syndrome (POTS) – a novel member of the autoimmune family. Lupus. 2016;25(4):339-42.
23. Mosnaim AD, Abiola R, Wolf ME, Permuter LC. Etiology and risk factors for developing orthostatic hypotension. Am J Ther. 2010;17(1):86-91.
24. Thieben MJ, Sandroni P, Sletten DM, Benrud-Larson LM, Fealey RD, Vernino S, et al. Postural orthostatic tachycardia syndrome: The Mayo Clinic experience. Mayo Clin Proc. 2007;82(3):308-13.
25. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med. 2007;8(4):326-31.
26. Kurvers HA, Jacobs MJ, Beuk RJ, Van den Wildenberg FA, Kitslaar PJ, Slaaf DW, et al. Reflex sympathetic dystrophy: evaluation of microcirculatory disturbance in time. Pain. 1995;60(3):333-40.
27. Wasner G, Schattschneider J, Heckmann K, Maier C, Baron R. Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanism and diagnostic value. Brain. 2001;124(Pt 3):587-99.
28. Meyer C, Heidecke H. Antibodies against GPCR. Front Biosci (Landmark Ed). 2018;23:2177-2194.
29. Hendrickson JE, Hendrickson ET, Gehrie EA, Sidhe D, Wallukat G, Schimke I, et al. Complex regional pain syndrome and dysautonomia in a 14-year-old girl responsive to therapeutic plasma exchange. J Clin Apher. 2016;31(4):368-74.
30. Loebel M, Grabowski P, Heidecke H, Bauer S, Hanitsch LG, Wittke K, et al. Antibodies to ß adrenergic and muscarinic cholinergic receptors in patients with chronic fatigue syndrome. Brain Behav Immun. 2016;52:32-9.
31. Blitshteyn S, Brook J. Postural tachycardia syndrome (POTS) with anti-NMDA receptor antibodies after human papillomavirus vaccination. Immunol Res. 2017;65(1):282-4.
32. Hendrickson JE, Tormey CA. Human papilloma virus vaccination and dysautonomia: consideration for autoantibody evaluation and HLA typing. Vaccine. 2016;34(38):4468.
33. Schofield JR, Hendrickson JE. Autoimmunity, autonomic neuropathy, and the HPV vaccination: a vulnerable subpopulation. Clin Pediatr(Phila). 2018;57(5):603-6.
34. Tanaka H, Fujita Y, Takenaka Y, Kajiwara S, Masutani S, Ishizaki Y, et al. Task Force of Clinical Guidelines for Child Orthostatic Dysregulation, Japanese Society of Psychosomatic Pediatrics. Japanese clinical guidelines for juvenile orthostatic dysregulation version 1. Pediatr Int. 2009;51(1):169-79.
35. Suzuki S, Hosono A. No association between HPV vaccine and reported post-vaccination symptoms in Japanese young women: results of the Nagoya study. Papillomavirus Res. 2018;5:96-103.
36. Bornholtz B, Weidtkamp-Peters S, Schitmeier S, Seidel CA, Herda LR, Felix SB, et al. Impact of human autoantibodies on ß1-adrenergic receptor conformation, activity, and internalization. Cardiovasc Res. 2013;97(3):472-80.
37. Bornholtz B, Roggenbuck D, Jahns R, Boege F. Diagnostic and therapeutic aspects of ß1-adrenergic receptor autoantibodies in human heart disease. Autoimmun Rev. 2014;13(9):954-62.
38. Shoenfeld Y, Agmon-Levin N. 'ASIA'-Autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun. 2011;36(1):4-8.
39. Kanduc D. Quantifying the possible cross-reactivity risk of an HPV16 vaccine. J Exp Ther Oncol. 2009;8(1):65-76.
40. Kanduc D. Potential cross-reactivity between HPV16 L1 protein and sudden death-associated antigens. J Exp Ther Oncol. 2011;9(2):159-65.
41. Ryabkova VA, Shubik YV, Erman MV, Churilov LP, Kanduc D, Shoenfeld Y. Lethal immunoglobulins: autoantibodies and sudden cardiac death. Autoimmun Rev. 2019;18(4):415-25.