

Case Report

Hemorrhagic Myelitis after Papilloma Virus (HPV) Vaccination

Badarny S^{1,2*}, Badarny Y³, Goldfeld M⁴ and Wakid H¹

¹Department of Neurology, Galilee Medical Center, Israel

²Azrieli Faculty of Medicine, Bar Ilan University, Israel

³Neurosurgery Department, Rambam Medical Center, Israel

⁴MRI Unit, Department of Radiology, Galilee Medical Center, Nahariya, Israel

*Corresponding author: Samih Badarny, Department of Neurology, Galilee Mseal Center, PO-BOX 21, Nahariya, 2210001, Israel

Received: November 26, 2020; Accepted: December 10, 2020; Published: December 17, 2020

Background

Vaccine for HPV was approved in 2006 and within a few years, it was introduced in many countries around the world to prevent cervical cancer in women. The WHO has recommended worldwide HPV vaccination and about 30 countries have included it in their immunization schedules [1]. Cervical cancer is the second most common cancer in women, with associated morbidity in young adolescent women [2]. Chronic infection of the cervix transmitted by sexual contact with some oncogenic subtypes 16 and 18 of Human Papilloma Virus (HPV) can cause cancer. HPV is a DNA virus from the papilloma viridae family, encompasses a group of more than 100 viruses, of which at least 13 are high-risk types, responsible for cervical and other anogenital cancers. Vaccination against this infection before the first sexual experience may reduce morbidity by approximately seventy percent [3]. It's well known that Acute Disseminated Encephalomyelitis (ADEM), myelitis, optic neuritis, neuromyelitis optica, multiple sclerosis and GBS can appear after vaccination, however a small number of them after HPV vaccination [4,5]. In most cases, symptoms begin a few days after vaccination but can at times appear even several months after vaccination.

Case Report

A 26-year old female with no past medical history was admitted to hospital for eight days of low back pain mainly on her left side, which radiated to both legs and with numbness of left leg, urinary retention and general weakness. A few days earlier, she had been examined twice in the emergency room of another medical center and was released on suspicion of kidney stones. She had no any preceding viral infection or infective symptoms in the month leading up to the actual illness. She had received the third dose of papilloma vaccine (Gardasil) one month earlier; the first and second vaccination doses had been administered five and seven month prior. Neurological examination revealed -4/5 strength of left proximal muscles by MRC scale and 4/5 of distal muscles and 4/5 in proximal and distal muscles on right leg, spastic gait and difficulty in walking, as well as hyperreflexia, positive Babinski sign both sides, absence of left middle and lower abdominal

Abstract

We present a young woman with weakness and tingling in the lower extremities, urinary retention, pyramidal signs and sensory level at D9, one month after the third dose of Papilloma Virus (HPV) vaccine. MRI showed myelitis with intramedullary hemorrhages. According to what we know this is, the first reported case with hemorrhagic myelitis described as post HPV vaccination.

Keywords: Papilloma virus vaccination; Hemorrhagic myelitis; Autoimmune disease



Figure 1: Sagittal T1-weighted MRI showing long segment of high intensity signal in the medulla. Corresponds to intramedullary hemorrhages.



Figure 2: Sagittal T2-weighted MRI showing long segment, intramedullary hyperintense signal and several very hypointense dots corresponding to myelitis and intramedullary hemorrhages.

reflexes, sensory level at D10 and 1500 urine residue, which was seen by catheter insertion into the bladder. Lumbar puncture revealed 7 cells, 86% monocytes, with CSF glucose 97 mg/dl and protein 23.1 mg/dl (normal values), Vitamin B12 is 194 pg/ml (160-948) and chest X-ray is normal.



Figure 3: Axial T2-weighted MRI showing the central location of the disease, involving both halves, sparing the periphery.



Figures 4 and 5: T1 (Figure 4) and T2 (Figure 5) the high intensity signal on the cord resolved completely and only a residual tiny dot of blood is seen.

Sagittal T1-weighted MRI showed long segment of high intensity signal in the medulla, corresponding to intramedullary hemorrhages (Figure 1). Sagittal T2-weighted thoracic MRI showing long segment, intramedullary hyper-intense signal and several very hypo-intense dots corresponding to myelitis and intramedullary hemorrhages (Figure 2) Axial T2-weighted MRI showed the central location of the disease involving both halves, sparing the periphery (Figure 3), MRI of Head and cervical spine were normal, anti MOG, aquaporin 4 and OCB were negative. HV 1, 2 and 6, VZV, CMV, EBV, hepatitis B and C, corona virus, HIV, TPHA, LAC, Anticardiolipin antibody were negative. Protein S, antithrombin 3, anti-beta 2-glycoprotein antibody are normal. Protein C was 214 (mildly increased) Anti DS-DNA is 20 (slightly increased), ANA, ENA profile, RF, CCP were normal.

Clinical and MRI findings suggested acute hemorrhagic transverse myelitis. The patient was treated with IV methylprednisolone 1000mg for three days and 500mg for another 3 days, followed by tablet prednisone 60mg with tapering according to protocol. There was a clinical improvement in her condition, she began walking without help, the sensory level almost disappeared but the pyramidal signs remained in the lower extremities.

The patient was released for further rehabilitative treatment and was re-examined by a neurologist two months later, who reported a marked improvement in gait and almost complete disappearance of the pyramidal signs, with thoracic spine MRI of T1 and T2 modality (Figures 4 and 5) showed that the high intensity signal on the cord resolved completely and only a residual tiny dot of blood is seen.

Discussion

The ability of vaccination to induce autoimmune illness has been debated in the literature for decades and is often surrounded by controversy, it has been postulated that vaccination might induce autoimmunity similar to those induced by infection [6]. Several cases of young females presenting with CNS demyelination two to four weeks following HPV vaccine have been reported, but some of the patients had symptoms at the time of vaccination, raising the possibility that this vaccine may accelerate the transition from subclinical to clinical disease [7-9]. Acute disseminating encephalomyelitis was described by several authors following HPV vaccinations, Sekiguchi et al., published two young girls presenting with clinical and radiological findings suitable for ADEM disease after HPV vaccination and clinical relapse was not observed over a two-year follow-up period in both cases [10-12].

Vaccinations have been incriminated as triggers of the onset of MS in susceptible individuals. Some studies indicated a significant risk for CIS or conversion to clinically definite MS whereas other investigators did not confirm this observation [13,14]. A recent extensive review published by an Italian group of physicians did not find sufficient evidence to support a causal relationship between the onset of MS and HPV vaccination [15]. However, immune-mediated myelitis may be idiopathic as isolated or as a part of ADEM, MS or NMO due to post-infection or post-vaccination [15]. Fernandez-Fournier et al., published 14-year-old girl with bilateral diminished sensation below C5 level; muscle weakness of left arm and leg, hyperreflexia bilaterally with clonus and a left extensor plantar response with positive OCB, three days after HPV vaccination. Brain and cervical spine MRI revealed an isolated C1-C2 hyper-intense lesion in T2-weighted images, she was diagnosed with transverse myelitis, IV methylprednisolone was given for 5 days and clinical improvement ensued, 6 months later only mild left hand hypoesthesia and lower extremity hyperreflexia persisted, brain and spinal MRI follow-up revealed an improvement in the cervical lesion without development of new lesions [16].

Our case was also a young female, one month after the third dose of the HPV vaccine with numbness and weakness of both legs, moderate weakness of both legs more on left, spastic gait, hyperreflexia, Babinski sign of both legs with sensory level at D10 and 1500-urine residue. MRI of spine hemorrhagic myelitis at level of T9-10. The treatment and course of the disease was similar to Fernandez's case as described above.

It is true that hemorrhagic myelitis is high-grade of myelitis but as far as we know hemorrhagic myelitis, was not previously described related to HPV vaccination. Wu et al., however, did describe hemorrhagic myelitis after seasonal influenza vaccination, though it is worth noting that OCB, aquaporin 4 and anti MOG were negative [17].

In conclusion, hemorrhagic myelitis has not been described in the literature after HPV vaccination, to the best of our knowledge, although there is no complete agreement that vaccines themselves cause hemorrhagic myelitis and other demyelinating diseases, but anyway it is worth remembering that these complications can exist.

References

1. WHO. Human Papilloma Virus (HPV) and cervical cancer. World Health Organization.
2. Human papillomavirus vaccines. WHO position paper. Wkly Epidemiol Rec. 2009; 84: 118-131.
3. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med.* 2003; 348: 518-527.
4. Langer-Gould A, Qian L, Tartof SY, Brara SM, Jacobsen SJ, Beaber BE, et al. Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases. *JAMA Neurol.* 2014; 71: 1506-1513.
5. Karussis D, Petrou P. The spectrum of post-vaccination inflammatory CNS demyelinating syndromes. *Autoimmun Rev.* 2014; 13: 215-224.
6. Molina V, Shoenfeld Y. Infection, vaccines and other environmental triggers of autoimmunity. *Autoimmunity.* 2005; 38: 235-245.
7. Sutton I, Lahoria R, Tan I, Clouston P, Barnett M. CNS demyelination and quadrivalent HPV vaccination. *Mult Scler.* 2009; 15: 116-119.
8. Wildemann B, Jarius S, Hartmann M, Regula JU, Hametner C. Acute disseminated encephalomyelitis following vaccination against human papilloma virus. *Neurology.* 2009; 72: 2132-2133.
9. Langer-Gould A, Qian L, Tartof S, Brara S, Jacobsen S, Beaber B, et al. Vaccines and the Risk of Multiple Sclerosis and Other Central Nervous System Demyelinating Diseases. *JAMA Neurol.* 2014; 71: 1506-1513.
10. Wildemann B, Jarius S, Hartmann M, Regula JU, Hametner C. Acute disseminated encephalomyelitis following vaccination against human papilloma virus. *Neurology.* 2009; 72: 2132-2133.
11. Bompreszi R, Wildemann B. Acute disseminated encephalomyelitis following vaccination against human papilloma virus. *Neurology.* 2010; 74: 864-865.
12. Sekiguchi K, Yasui N, Kowa H, Kanda F, Toda T. Two Cases of Acute Disseminated Encephalomyelitis Following Vaccination against Human Papilloma Virus. *Intern Med.* 2016; 55: 3181-3184.
13. Salemi S, D'Amelio R. Could autoimmunity be induced by vaccination? *Int Rev Immunol Jun.* 2010; 29:247-269.
14. Hocine MN, Farrington CP, Touze E, Whitaker HJ, Fourrier A, Moreau T, et al. Hepatitis B vaccination and first central nervous system demyelinating events: reanalysis of a case-control study using the self-controlled case series method. *Vaccine.* 2007; 25: 5938-5943.
15. Meggiolaro A, Migliara G, La Torre G. Association between Human Papilloma Virus (HPV) vaccination and risk of Multiple Sclerosis: A systematic review human vaccines and immunotherapeutics 2018; 14: 1266-1274.
16. Fernandez-Fournier M, Diaz de Teran j, Tallon Barranco A, Puertas I. Early cervical myelitis after human papilloma virus vaccination. *Neurol Neuroimmunol Neuroinflammation.* 2014; 1: e31.
17. Wu C, Riangwiwat T, Nakamoto K. Hemorrhagic longitudinally extensive transverse myelitis. *Case Reports in Neurological Medicine* Volume 2016, Article ID 1596864, 3 pages.