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CNS demyelination and quadrivalent HPV vaccination

I Sutton[1,2], R Lahoria[3], IL Tan[1], P Clouston[4] and MH Barnett[2,3]

Vaccination is generally considered safe in patients with multiple sclerosis (MS). We report five patients who presented with multifocal or atypical demyelinating syndromes within 21 days of immunization with the quadrivalent human papilloma virus (HPV) vaccine, Gardasil®. Although the target population for vaccination, young females, has an inherently high risk for MS, the temporal association with demyelinating events in these cases may be explained by the potent immuno-stimulatory properties of HPV virus-like particles which comprise the vaccine. A prospective case–control study of patients with MS or clinically isolated demyelinating syndromes receiving the Gardasil® vaccine may provide relevant safety data in this population. *Multiple Sclerosis* 2009; **15:** 116–119. http://msj.sagepub.com

Key words: demyelination; multiple sclerosis; human papillomavirus; vaccination

Introduction

Vaccination in patients with multiple sclerosis (MS) is generally considered to be safe, based on accumulated clinical experience and, in the case of influenza, a double-blind prospective study [1]. However, many case reports of acute disseminated encephalomyelitis (ADEM) or MS exacerbation following vaccination with a variety of agents exist in the literature. A moderately increased risk CNS demyelination was suggested by a case–control study of 402 patients with a first demyelinating event following hepatitis B vaccination [2]. Recent studies have failed to corroborate this association and indicate that hepatitis B immunization does not significantly increase the risk of a first episode of MS in childhood [3] or the risk of conversion of a clinically isolated syndrome (CIS) to MS [4]. In general, therefore, the risk-benefit analysis favors vaccination in patients with previous CIS, MS and in the broader community.

Gardasil® is a non-infectious quadrivalent vaccine comprising virus-like particles (VLPs) of the major capsid L1 protein of human papilloma virus (HPV) types 6, 11, 16, and 18 and has proven efficacy in the prevention of cervical, vulval, and vaginal dysplasia; genital warts; and cervical cancer. A safety evaluation during phase II and III clinical trials, using a vaccination report card–aided surveillance for 14 days after each of three Gardasil® injections, reported no events that could be attributed to CNS inflammation in 5088 Gardasil®-treated girls and women aged 9–26 or 3790 placebo-treated individuals. (Gardasil® Product Information, Merck & Co, Inc. 2006) [5]. Following approval from the Therapeutics Goods Administration (Australia) in June 2006, a nationwide voluntary immunization program targeting 12 to 26-year-old females was commenced in April 2007, and by March 2008, 2.2 million doses of Gardasil® had been distributed in Australia (and close to 20 million doses worldwide) [6]. Since commencement of this program, five individuals aged 16–25 years have presented to the Multiple Sclerosis Clinics at the University of Sydney and St Vincent's Hospital with a CNS inflammatory disorder occurring within 28 days of a Gardasil® immunization. We consider that these cases are noteworthy not only because of their temporal association with immunization but also because of the atypical or multifocal nature of the presentations.

Patients

All five cases have been referred from within the metropolitan Sydney region to two neurologists (IS

[1]Department of Neurology, St Vincent's Hospital, Darlinghurst, New South Wales, Australia
[2]The Brain and Mind Research Institute, The University of Sydney, New South Wales, Australia
[3]St George Hospital, Kogarah, New South Wales, Australia
[4]Westmead Hospital, Westmead, New South Wales, Australia
Correspondence to: Dr Michael H Barnett, The Brain and Mind Research Institute, University of Sydney, Level 4, 94 Mallet Street, Camperdown, NSW 2050, Australia. Email: mbarnett@mail.usyd.edu.au
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and MHB) with a specific interest in MS. The demographic and clinical characteristics of the cases are summarized in Table 1. The five cases range in age from 16 to 26 years old and presentations occurred 1–21 days following the 2nd ($n = 3$) or 3rd ($n = 2$) doses of Gardasil®. Three patients had previously experienced clinically isolated episodes of neurological dysfunction and were diagnosed with clinically definite MS (CDMS) at presentation. Two patients were diagnosed with a first demyelinating event or CIS, of which one has subsequently developed CDMS. The three patients with monosymptomatic presentations were notable for unusual aspects to their presentation: one patient presented with pseudoathetosis of the right arm and had multifocal spinal cord disease with a longitudinally extensive cervical cord lesion in addition to rare multifocal deep white matter lesions of the cerebral hemispheres (Figures 1A–C); one patient presented with global headache 2 days post immunization, before developing an incomplete transverse myelitis; and one patient presented with an acute hemiparesis (Figures 1D–F). Two individuals developed polysymptomatic or multifocal disease following immunization; one presented with incomplete cervical transverse myelitis 24 h post-immunization and subsequently developed left optic neuritis 7 days later (Figure 1H–J); a second patient presented with an incomplete thoracic transverse myelitis 4 days post-immunization, followed by a brainstem syndrome 24 days later. Complete or near-complete clinical recovery was observed in all patients, either spontaneously ($n = 1$) or following the administration of intravenous methylprednisolone ($n = 4$).

Discussion

Vaccination has been implicated in the pathogenesis of a number of inflammatory disorders affecting the nervous system including ADEM, post-vaccination encephalitis, brachial neuritis, and Guillain Barre Syndrome. However, the risk of developing these disorders following vaccination is extremely low, in the order of 0.1–0.2 per million immunizations [7]. Although there are many case reports of acute CNS demyelination complicating vaccination, less than 5% of cases of ADEM are preceded by vaccination. In these cases, molecular mimicry between vaccine antigen and myelin proteins or the presence of toxic materials in vaccine components have been invoked as potential causative factors.

Although vaccination in general does not substantially influence the risk of developing a CIS or MS relapse, it should not be overlooked that several epidemiological studies indicate that viral infection is associated with a threefold increase in the risk of an MS relapse [8]; and risks associated with individual vaccines may vary according to the nature of the immunogen. HPV VLPs bind strongly to dendritic cells (DC) and induce a maturation response characterized by the expression of co-stimulatory molecules and production of the cytokines IL-12, TNF-α, and IL-6 [9], which have been implicated in the development of CNS inflammatory responses associated with demyelination and axonal injury.

In the present study, we report five cases of CNS inflammatory demyelination that fall within the "clinically isolated syndrome/multiple sclerosis" diagnostic spectrum and occurred within 21 days of Gardasil® vaccination. No definitive conclusions can be made regarding the risk of an MS relapse or presentation with a CIS based on this report, particularly since the target population has an inherently higher risk of developing MS than the general population; a recent study indicates that the incidence of 6.27/100,000 amongst women aged 20–29 is almost double the incidence observed in the overall Australian female population [10]. However, the multifocal and atypical nature of these presentations suggests that the immuno-stimulatory properties of the Gardasil® vaccine may influence the nature and severity of CNS inflammation. Although the efficacy of the Gardasil® vaccine in preventing female genital tract cancers clearly favors vaccination in the

Table 1 Demographics and clinic characteristics

Case	Age	Gardasil® dose	Symptom onset: days post dose	Main clinical feature	MR brain lesions	MR cord lesions	Diagnosis at presentation
1	16	3	21 (monosymptomatic)	Upper limb pseudo-athetosis	Scant subcortical	C2–C5, C6/7, T10	CIS
2	25	2	16 (monosymptomatic)	Acute hemiparesis	Left parietal cortical/ subcortical	Normal	CIS
3	21	2	1 (multifocal)	Incomplete Transverse Myelitis (TM), left Optic Neuritis (ON)	Multiple: typical MS distribution	C3/4	CDMS
4	26	3	4 (monosymptomatic)	Headache, incomplete TM	Multiple: typical MS distribution	C2, T7/8, T9/10	CDMS
5	16	2	4 (multifocal)	Incomplete TM, brainstem	Multiple: typical MS distribution	C5, C7/T1	CDMS

MR, magnetic resonance; CIS, clinically isolated syndrome; MS, multiple sclerosis; CDMS, clinically definite MS.

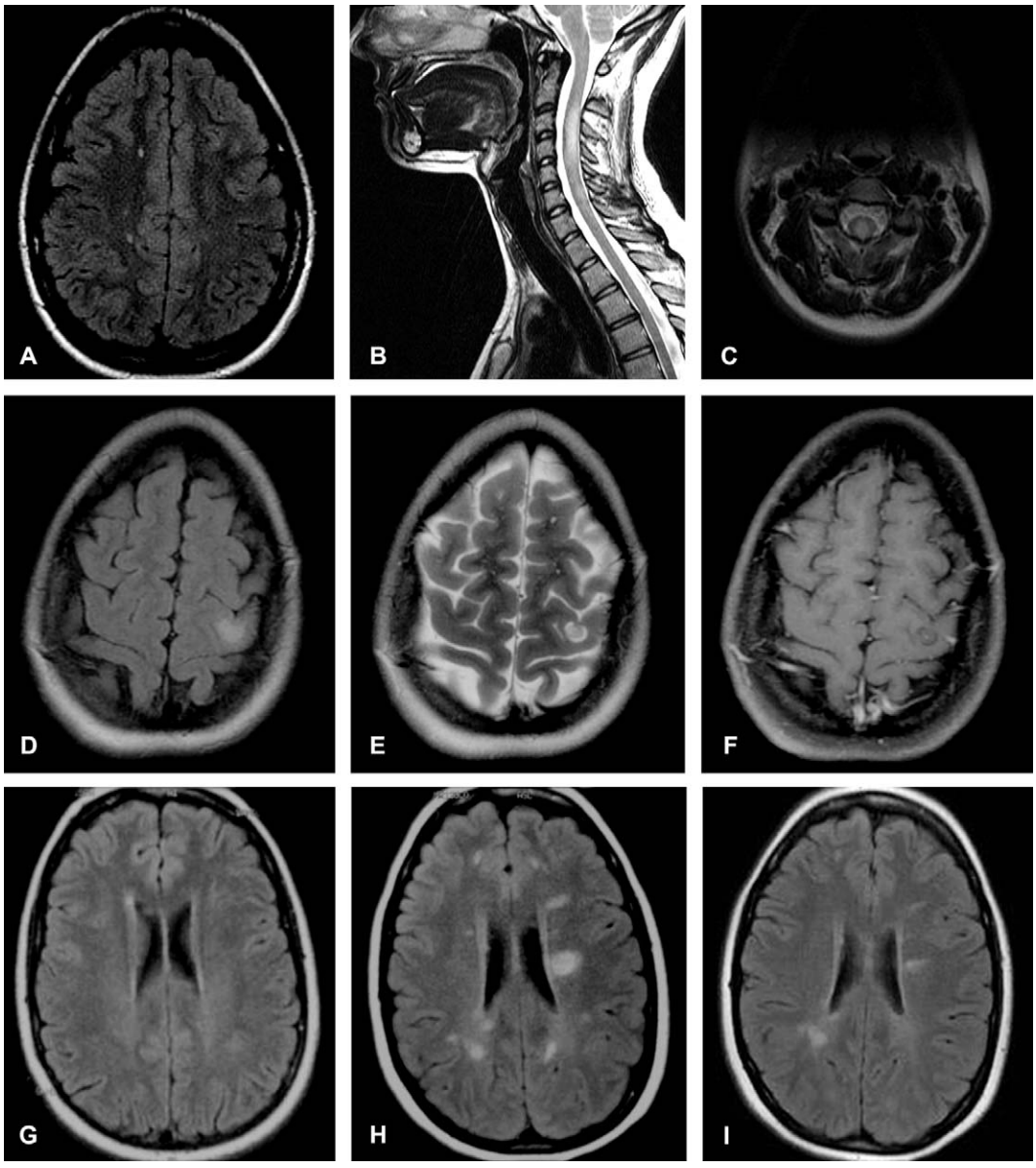

Figure 1 Case 1 (A–C). Twenty one days after the third immunization with Gardasil® this 16-year old developed progressive clumsiness of the dominant right hand evolving over 2 weeks. Examination disclosed marked pseudoathetosis of the right hand, but no other abnormality. MRI of the brain (A) showed four small non-specific right hemispheric lesions, none of which exhibited contrast enhancement or restricted diffusion. MR imaging of the spine showed a high T2-signal lesion (B) expanding the cervical cord and extending over three vertebral segments. On axial sections the lesion involved the posterior columns and central cord (C). Repeat imaging at 4 months after initial presentation showed no change in the cerebral imaging and partial resolution of the cervical cord lesion. Case 2 (D–F). Sixteen days after the second immunization with Gardasil®, this 25-year old awoke with right hemiplegia and dysarthria. Her symptoms began to resolve within 4 h; residual impairment of right hand fine motor skills persisted for 8 weeks. Axial FLAIR MRI (D) of the brain 2 days after presentation reported a lesion in the left parietal cortex in which a central blood vessel was surrounded by concentric rings of cytotoxic and vasogenic edema (E,F). The CSF contained nine mononuclear cells per milliliter and CSF-specific oligoclonal bands. Four months after initial presentation, the patient developed right leg paraesthesiae and a progress MRI brain study showed a new periventricular lesion. Repeated CSF analysis showed persistence of CSF-specific oligoclonal bands. Case 3 (G–I). This 21-year old presented with a mild left optic neuritis in June 2007 and an MRI brain showed one juxtacortical and three periventricular lesions (G). In November 2007, 1 day after immunization with Gardasil®, the patient developed symptoms of an incomplete transverse myelitis and 8 days later experienced recurrent left optic neuritis. A non-contrast MRI study 16 days post-immunization showed a dramatic increase in burden of cerebral disease (H) and a plaque at C3/4. A progress MRI study in May 2008 showed a marked decrease in overall burden of disease (I).

general population, there is presently insufficient data to justify making firm recommendations regarding treatment of patients with known MS. A prospective clinical and MRI-based case–control study of patients with CDMS or CIS receiving the Gardasil® vaccine may provide more meaningful safety data in this population.

References

1. Miller, AE, Morgante, LA, Buchwald, LY, *et al*. A multicenter, randomized double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. *Neurology* 1997; **48**: 312–314.
2. Touzé, E, Fourrier, A, Rue-Fenouche, C, *et al*. Hepatitis B vaccination and first central nervous system demyelinating event: a case-control study. *Neuroepidemiology* 2002; **21**: 180–186.
3. Mikaeloff, Y, Caridade, G, Rossier, M, *et al*. Hepatitis B vaccination and the risk of childhood-onset multiple sclerosis. *Arch Pediatr Adolesc Med* 2007; **161**: 1176–1182.
4. Hocine, MN, Farrington, CP, Touze, E, Whitaker, HJ, Fourrier, A, Moreau, T, Tobert-Bitter, P. 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.
5. Gardasil Product Information. Merck & Co, Inc. 2006. Web Link: http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf. Issued December 2007. Accessed 18 August 2008.
6. Therapeutic Goods Administration. Australia. Web Link: http://www.tga.gov.au/alerts/medicines/gardasil.htm. Updated 4 July 2008. Accessed 18 August 2008.
7. Nakayama, T, Onoda, K. Vaccine adverse events reported in post-marketing study of the Kitasato Institute from 1994 to 2004. *Vaccine* 2007; **25**: 570–576.
8. Sibley, WA, Bamford, CR, Clark, K. Clinical viral infections and multiple sclerosis. *Lancet* 1985; **1**: 1313–1315.
9. Lenz, P, Day, PM, Pang, YS, *et al*. Papillomavirus-like particles induce acute activation of dendritic cells. *J Immunol* 2001; **166**: 5346–5355.
10. Barnett, MH, Williams, DB, Day, S, Macaskill, P, McLeod, JG. Progressive increase in incidence and prevalence of multiple sclerosis in Newcastle, Australia: a 35 year study. *J Neurol Sci* 2003; **213**: 1–6.