HENOCH-SCHÖNLEIN PURPURA NEPHRITIS FOLLOWING INFLUENZA VACCINATION: A CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract. We reported a 16-year-old boy who developed Henoch-Schönlein purpura (HSP) 15 days after receiving a seasonal influenza vaccine. His symptoms improved temporally with treatment but he developed HSP nephritis (HSPN) that relapsed multiple times over the following three years. This case of Henoch-Schönlein purpura may have been due to the seasonal influenza vaccine. The mechanism for this association is unclear. Practitioners should be aware of this possible complication.

Keywords: Henoch-Schönlein purpura, influenza vaccine, vasculitis

INTRODUCTION

Henoch-Schönlein purpura (HSP) is a systemic disease that includes a purplish rash on the lower extremities and buttocks because of inflammation and bleeding in the small blood vessels of the skin, joints, intestines and kidneys (Tahmassebi and Paterson, 2007). HSP is the most common vasculitis among children (Roberts *et al*, 2007) and the incidence of HSP among children is about 20.4 per 100,000 children per year (Gardner-Medwin *et al*, 2002). HSP usually occurs following an infection, such as of the upper respiratory tract infection (Trapani *et al*, 2005), but the etiology of HSP is unknown (Calvino *et al*, 2001). Numerous factors, such as bacterial and viral infections, drugs, and autoimmune mechanisms have been proposed as the cause of HSP (Tizard and Hamilton-Ayres, 2008). Vaccines may sometimes cause adverse reactions, and increased vaccine coverage inevitably results in larger numbers of vaccine-associated adverse events following immunization (AEFI) (Li *et al*, 2011a,b). HSP after vaccination has been reported although the cause has not been identified (Cervera, 2011). In this report, we present a 16-year old boy, who developed urinary abnormalities and cutaneous purpura 15 days after receiving seasonal influenza vaccination in Xuhui District, Shanghai, China, in 2010.

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CASE REPORT

A 16-year-old boy received one dose of pandemic influenza H1N1 vaccine (Batch No.: 200909005, Shanghai Institute of Biological Products, China) on November 16, 2009 and another seasonal influenza vaccine (Batch No.: 200909024,

Shanghai Institute of Biological Products, China) on January 13, 2010. The patient developed cutaneous purpura on his lower legs 15 days after the second vaccine and was treated as an outpatient at Affiliated Huashan Hospital, Fudan University, Shanghai, China one month later. He gave no history of gastrointestinal or joint symptoms. Physical examination revealed palpable purpura on his lower and upper limbs, bright erythematous skin swelling that did not blanch when compressed with symmetric distribution of the purpura. Laboratory tests revealed a white blood cell (WBC) count of 8.36×10^9 cells/l, a hemoglobin (HGB) level of 152 g/l, a red blood cell (RBC) count of 5.16×10^{12} cells/l, 13.0% monocytes, and a platelet (PLT) count of 182×10^9/l. Urinary tests showed 3+ protein (PRO), 2+ occult blood (BLD) and urinary RBC of 236.4/μl. The patient was diagnosed with having HSP according to the EULAR/PRINTO/PRES criteria (Ozen *et al*, 2010). The boy was hospitalized on February 25, 2010 with HSPN at the Shanghai Eighth People Hospital.

Further investigation showed a negative fecal occult blood test; a 24 hour urine protein level of 0.15 gram. The coagulation testing revealed a thrombin time (TT) of 20.2 seconds (normal value, 10~20 seconds), a prothrombin time (PT) of 12.1 seconds with an international normalized ratio (INR) of 1.01, a fibrinogen level (FIB) of 2.44 g/l and an activated partial prothrombin time (APTT) of 28.8 seconds. Liver and kidney function tests were normal. Humoral immunity, complement, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) results were all within normal limits, except immunoglobulin E (IgE) was 298 g/l (normal value, 0~100 g/l). One week after symptomatic treatment, which included antihistaminics and renal protection, the purpura symptoms disappeared and the patient was discharged home on March 6, 2010. The urinary protein level was monitored occasionally during the following 4 months and fluctuated around 1+ to 2+ on the urine dipstick. Finally the patient was started on prednisone (5 mg tid, orally) on July 15, 2010 to manage the renal involvement.

On May 24, 2011, the patient was admitted again to the Shanghai Sixth People Hospital because of fever (38.3°C), headache, nausea, and pink urine. Laboratory tests showed the 24 hour urine protein level was 0.40 g and the urine dipstick for protein was 4+. Renal biopsy was then performed. Pathology showed 42 glomeruli, among them, there were 7 cellular crescents. No significant abnormalities were found in the stroma but the basement membrane showed significant multiplication. Immunofluorescence histology showed positive IgA but negative IgG, IgM and C3. The patient was again diagnosed with having HSP nephritis (HSPN) and treated with Solu-Medrol 320 mg tid and Methotrexate 1 g daily (stoss therapy) twice. The patient was then discharged but later admitted again to the hospital on March 7, 2012, September 7, 2012, and December 7, 2012 for stoss therapy for HSPN. During that time the urinary protein levels were negative or trace levels. On December 2, 2013, the patient was seen for an upper respiratory tract infection and laboratory examination showed 2+ occult blood in the urine and 1+ protein. Traditional Chinese medication was given. In this case, we cannot exclude the possibility the influenza vaccine was a triggering factor for HSP. Consent was obtained from the patient and guardians to write this report.

Table 1
Reported cases of HSP following influenza vaccination.

Age (years)	Gender	Type of vaccine	Onset of HSP in relation to vaccination	Organ involvement	Outcome	Past history	Reference
16	M	Seasonal	15	Purpura, abdominal pain, HSPN	Chronic HSPN	NA	This report
52	M	Pandemic	1	Purpura, arthralgia	Recovery	NA	(Huang, 2012)
7	F	Seasonal	2	Purpura, abdominal pain, HSPN	Recovery	Drug eruption	(Watanabe, 2011)
4	F	Seasonal	15/1	Purpura, arthralgia	Recovery	Soba allergy	(Watanabe, 2011)
6	M	Seasonal Pandemic	22/5	Purpura, arthralgia	Recovery	NA	(Watanabe, 2011)
5	F	Seasonal	16/1	Purpura, arthralgia	Recovery	NA	(Watanabe, 2011)
39	F	Pandemic	1	Purpura, abdominal pain, arthralgia	No description	NA	(Pimentel *et al*, 2011)
2	F	Seasonal	1	Purpura, arthralgia, HSPN	Recovery	Overdose adult vaccine	(Lu and Xu, 2010)
7	M	Seasonal	1	Purpura, arthralgia	Recovery	Varicella infection before vaccination	(Chen, 2008)
8	M	Seasonal	1	Purpura, arthralgia	Recovery	Varicella infection before vaccination	(Zeng *et al*, 2005)
5	F	Seasonal	5	Purpura, abdominal pain, arthralgia	Recovery	NA	(Mormile *et al*, 2004)
9	F	Seasonal	2	Purpura, abdominal pain, HSPN	Recovery	NA	(Sun *et al*, 2004)
13	F	Seasonal	1	Purpura, abdominal pain, arthralgia	Recovery	Drug eruption	(Guo *et al*, 2004)
5	M	Seasonal	1	Purpura, abdominal pain, arthralgia	Recovery	HSP	(Watanabe and Onda, 2001)
77	M	Seasonal	10	Purpura, abdominal pain, arthralgia, HSPN	Recovery	NA	(Patel *et al*, 1988)
87	M	Seasonal	11	Purpura, arthralgia	Recovery	HSP	(Blumberg *et al*, 1980)
23	M	Seasonal	21	Purpura, abdominal pain, arthralgia	Chronic renal failure	HSPN	(Damjanov and Amato, 1979)

NA, not available.

DISCUSSION

HSP is more common among children especially those under 10 years old and the mean age of patients is 6 years (Saulsbury, 1999; Trapani *et al*, 2005). In adults the incidence of HSP is about 3.4~14.3 per million population (Watts *et al*, 1998; Garcia-Porrua and Gonzalez-Gay, 1999). HSP is most commonly seen from the autumn to the spring. Globally, Afro-Caribbeans have the least incidence while Asians have the highest incidence (Watts and Scott, 2004) . From 2007 to 2009, the average incidence of HSP in 6 districts in China was reported to be 8.82 per 100,000 population (Li *et al*, 2011a). HSP is generally benign and self-limited in children but more severe in adults. Adults with HSP have more renal morbidity than young children and a poorer prognosis (Garcia-Porrua *et al*, 2002). Our reported patient was aged 16 years. He developed HSP following influenza vaccination but the correlation between HSP and influenza vaccination is unclear.

HSP following vaccination has been described in case reports and the Adverse Events Following Immunization (AEFI) surveillance (Courtney *et al*, 2001; Chave *et al*, 2003; Lambert *et al*, 2003, Li *et al*, 2011b; Shu *et al*, 2011; Watanabe, 2011; Melo Gomes *et al*, 2013). Seventeen cases of HSP after influenza vaccination had been reported in the literature at the time of writing this paper, including the patient we reported (Table 1). Of these 17 cases, 9 were male and the average age was 21 years (2~87 years). Two of these cases had varicella infection prior to vaccination and in one case of 2-year old child received an adult dose of an influenza vaccine. The National AEFI Information System was established in China in March 2005 to monitor vaccine safety (Liu *et al*, 2007). A study found the incidence of HSP after receiving the pandemic influenza H1N1 vaccine was estimated to be 1.03 per million doses in China during 2009~2010 (Li *et al*, 2011b).

It is hypothesized HSP occurs due to vasculitis which results from an immunological response to an infectious antigen or the components of the vaccine (such as gelatin, ovalbumin, or phosphate buffers), but a causal relationship has not been established (Lohse *et al*, 1999, Zafrir *et al*, 2009). Patja *et al* (2001) found a case of HSP after measles, mumps, and rubella vaccination had egg-specific IgE on immunospot examination. Although the mechanism behind the development of HSP among those who had received influenza vaccination is unknown, a possible link between influenza vaccination and autoimmunity has been suggested (Watanabe, 2011). A possible association between vaccines and autoimmunity may be mediated through several mechanisms, including immune-mediated responses to the infectious antigen or other components of vaccine, such as gelatin, ovalbumin or phosphate buffers (Watanabe, 2011).

We report here a case of HSP that appeared after influenza vaccination. However, influenza vaccination should not be limited because of no proven association and the low incidence of HSP. This case shows physicians need to be aware of the potential association between HSP and influenza vaccination. Caution may be required for vaccine use in children with immunologically mediated diseases, such as HSP, drug eruptions or possibly food allergies. It has been suggested patients with a history of vaccine-induced vasculitis should not be revaccinated (Watanabe, 2011). Larger studies are needed to evolve the association between influenza

vaccination and HSP. To do this, large post-marketing studies are needed due to the rarity of this possible association (Goodman *et al*, 2010).

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