

Original Article

# H1N1 Vaccination may Transient Increased Seizure Frequency in Epileptic Children

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Most children tolerated well the H1N1 vaccine and adverse post-vaccination neurological effects are unusual. We report two case-series of transient unexpected neurological events (UNE) that occurred in two groups of children after they had been given an H1N1 vaccination. The second group consisted of 53 children with epilepsy, 28 of whom had been vaccinated, who were being regularly followed-up. Seizure frequencies were significantly higher in the vaccinated group ( $P = 0.008$ ). All patients totally recovered without consequences. We concluded that some children manifest transient unexpected neurological events (UNE) after vaccination, particularly in epileptic children.

**Key words:** H1N1 vaccination, epilepsy, children

## Introduction

The H1N1 influenza epidemic in 2009 and 2010 prompted most countries to schedule H1N1 vaccinations: they were offered to all residents of Taiwan and to those living in many other countries. The vaccine was generally well tolerated by adults. Common side effects, similar to those caused by vaccines for seasonal influenza, are pain in the local administration site, which generally persists for less than 2 days, and fever, fatigue, and myalgia, which become apparent 6 to 12 hours after the vaccination and generally disappear within 1 to 2 days.<sup>1-3</sup> Allergic reactions to the vaccine, to egg protein in the vaccine, and to delayed local

reactions to thimerosal in the vaccine are rare in adults<sup>[1,2,4,5]</sup>. Other vaccine-associated adverse effects include vasculitis, allergic alveolitis, and ulcerative colitis<sup>[5-8]</sup>. However, adverse post-vaccination neurological effects are unusual.

To date, there is no definitive body of evidence that associates the H1N1 virus vaccine with a disproportionate amount of neurologic illness<sup>[9]</sup>. However, fear of the adverse effects of H1N1 vaccine can cause parents to decline the vaccinations of their children. One of the most serious adverse effects is neurological complications caused by the influenza vaccine, including Guillain-Barré syndrome (GBS), a form of peripheral neuropathy. However, mild transient unexpected neurological events (UNE) has rarely been reported, particularly in the era of pandemic H1N1 infection.

We report two case-series of transient unexpected neurological events (UNE) that occurred in two groups of children after they had been given an H1N1 vaccination. The first group consisted of 6 previously healthy children who had visited the pediatric neurology outpatient clinic because of UNE after the H1N1 vaccination, and

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the second group consisted of 53 children with epilepsy, 28 of whom had been vaccinated, who were being regularly followed-up.

## Patients and methods

### Study design

This was a single center, 2 case-series study. The study hospital, Chung Shan Medical University Hospital, is a medical center and a main referral hospital that serves an area with 2 million inhabitants in the middle of Taiwan. Beginning on November 1, 2009, Taiwan began administering the H1N1 vaccine sequentially according to a priority list, and eventually to all inhabitants in Taiwan.<sup>10</sup>

### Patients

Over a two month period from December 2009 through January 2010, we recruited, from the pediatric neurology clinic of Chung Shan Medical University Hospital, 6 children with UNE that had visited our pediatric clinics because of UNE after vaccination. UNE were defined as obvious neurological dysfunctions that negatively affected the daily life activity of children. The clinical course was detailed and we also recorded changes before and after the vaccination in the frequencies of seizures in the 53 children with epilepsy being regularly followed-up in our clinic. We divided the 53 children into vaccinated and non-vaccinated groups. The seizure frequencies were provided by the parents, who recorded and reported seizure frequency changes within 4 weeks after the vaccination. We used this information to determine the effect of an H1N1 vaccination on seizure frequency.

### Statistical analysis

The differences in the ratios and the distribution of the outcomes between groups were assessed using Fisher's exact test. Significance was set at  $p < 0.05$ , and p-values were all continuity-corrected. The statistical differences between different groups were analyzed using an independent t-test (SPSS 14.0; SPSS Institute, Chicago, IL). If the sample distribution was non-parametric, a Mann-Whitney U test was used.

## Results

### Unexpected neurological events after an H1N1 vaccination

Of the 6 previously healthy children with UNE after an H1N1 vaccination, 4 were seen in our outpatient clinic, and 2 were admitted via the Emergency Department (ED) because of their severe symptoms: one had consciousness disturbance and the other was unable to stand up due to muscle weakness.

### Case Histories

**Case 1.** This 14-year-old girl had a normal developmental and growth history. She had no history of adverse reactions to other vaccinations. Twenty minutes after her H1N1 vaccination, however, she complained of dizziness and being too weak to stand. Because the symptoms were persistent, she was transferred by ambulance to our Emergency Department and admitted. Her physical examination 54 hours after the vaccination showed that both her eyes had peripheral movement limitations that affected her peripheral vision (disconjugate eye movements) (Figure 1). By that time, her dizziness had disappeared and her facial expression was normal. She was able to smile, but her mood was unstable and her mother reported that she did not want to communicate with others. She also mistook her nurse for her mother, and did not recognize her mother during the morning of her admission. Her muscles were at full strength during the neurological examination. She was depressed and emotionally unstable. A lumbar tap showed unremarkable findings. She was given one day of intravenous hydrocortisone (5 mg per kilogram of body weight), and she recovered after 3 days. Electroencephalography, visual evoked potentials, and audiometric brainstem responses were normal, as were NCV

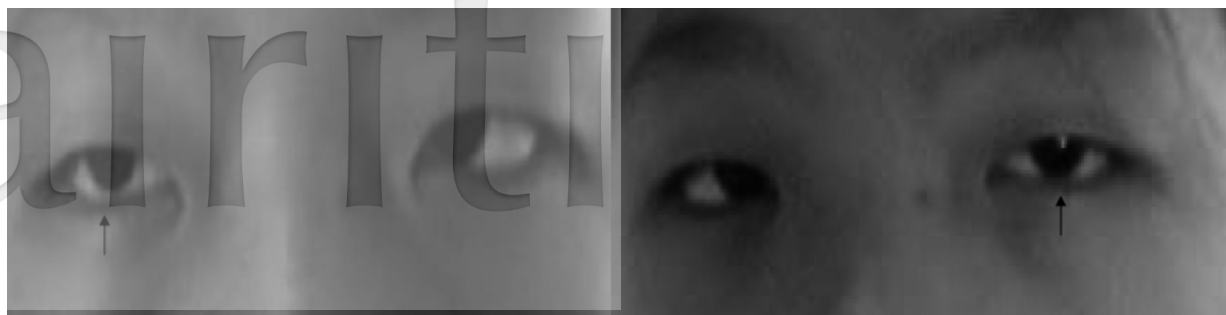


Figure 1. Both of this 14-year-old girl's eyes had peripheral movement limitations (disconjugate eye movements) that affected her peripheral vision (upper, right and left, arrows). She recovered 24 days after the onset of symptoms (lower, right and left, triangular arrows).

studies of her arms and legs. An examination of her spinal fluid showed a normal white cell count and total protein of 30.2 mg/dL. A protein electrophoresis of her spinal fluid and blood showed an IgG index of 39% (reference range: 30-60%), and an MRI of her brain was also normal. Her unstable gait improved on post-admission day 3. She was discharged after 7 days.

Twenty-four days after the vaccination, she was admitted to a pediatric intensive care unit in another hospital because she had been comatose for 4 hours. After being transferred to our hospital, she was conscious but

still felt weak and could not stand. A neurological examination showed that her eye movement had significantly improved, and that her cranial nerves and muscular strength were normal. She was discharged, without any noticeable neurological abnormality, after 6 days.

**Case 2.** This 13-year-old girl had been in unremarkable health, except for a 40-dB hearing impairment in her right ear. After her H1N1 vaccination, she complained of weakness in her left but not her right leg. She had felt pain in her left leg 7 hours after the vaccination. Eleven hours after the vaccination, a neurological examination showed

**Table 1.** Clinical presentations summarized in 5 children with unexplained neurological events after an H1N1 vaccination.

Case number	Age (years)	Gender	Time of symptom onset after vaccination	Time of symptoms were obviously remitted	Core symptoms	Outcome
1	14	F	20 minutes	7 days	Lower leg weakness, consciousness disturbance, bilateral external ophthalmoplegia	Relapse 21 days after vaccination, recovery one month after vaccination
2	13	F	7 hours	1 day	Left leg pain, muscle weakness, and claudication particularly in lower legs, decreased muscle power, deep tendon reflex	Complete recovery
3	10	M	1 day	11 days	Right leg numbness	Complete recovery
4	9	M	14 days	21 days	Left paresthesia	Complete recovery
5	2	M	1 days	5 days	Right leg claudication	Complete recovery
6	14	F	3 days	7 days	Left facial palsy	Complete recovery

F indicates female; M, male.

significantly decreased muscle strength in her legs, an inability to pass an antigravity test (proximal: 2; distal: 3), and a decreased deep-tendon reflex (knee and ankle joints). The next day, a test showed that her muscle strength had recovered but that her left leg was relatively weak. She refused a lumbar tap. However, 1 month after the vaccination, she still complained of pain in her left leg.

- Case 3.** This 11-year-old boy was excessively sleepy and uncommunicative, and he had no feeling in his right leg 1 day after the H1N1 vaccination. He could walk normally but complained that his right leg was numb. The symptoms remitted 11 days after the vaccination.
- Case 4.** This 9-year-and-2-month-old boy complained of left-side paresthesia 14 days after an H1N1 vaccination. His neurological examination results in our clinic were essentially normal on that day. His symptoms remitted 3 weeks after the vaccination.
- Case 5.** This 2-year-old boy showed claudicating of his right leg (not the vaccinated arm), and an unstable gait after the vaccination. His neurological exam was essentially normal, but his symptoms were persistent. He recovered completely 7 days after the vaccination.
- Case 6.** The 14-year-old girl ever had left facial palsy when she was 8 years old. This

time, 3 days after H1N1 vaccination, she suffered left facial palsy again. Then, intravenous hydrocortisone sodium succinate (5 mg per kilogram of body weight) was given for one day, and followed up with oral prednisolone. At 7 days after vaccination, she then completely recovered.

### Seizure frequencies in epileptic children after an H1N1 vaccination

Fifty-three children (age range: 9 months to 19 years old) with epilepsy were divided into vaccinated ( $n = 28$ ) and non-vaccinated ( $n = 25$ ) groups (Table 2). Increased seizure frequencies during the first two weeks after they had been vaccinated were found in 6 (21.43%) of 28 in the vaccinated group (see Table 3 for clinical data), and in none in the non-vaccinated group. The difference was significant ( $p = 0.008$ ). Seizure frequencies in the unvaccinated group did not change during those two weeks. One 14-year-old child with symptomatic occipital lobe epilepsy had more frequent seizures with more clusters of visual flashes after the vaccination. One week after the vaccination, however, he recovered. Of the other children, 3 with rolandic epilepsy had 1 to 2 more seizures in the first 2 weeks after the vaccination; 1 with symptomatic temporal lobe epilepsy, caused by temporal lobe dysplasia, went from a monthly seizure before the vaccination to a daily seizure after the vaccination; and an 8-year-old boy with cryptogenic frontal lobe epilepsy went from weekly general tonic-clonic and atypical absence seizures

**Table 2.** Comparison of seizure frequency between vaccinated and non-vaccinated groups.

	Vaccinated	Non-vaccinated	P-value
Number of cases	28	25	
Age (year)	10.53 (3.54)	10.99 (6.13)	N.S.
Gender (M/F)	18 M/10 F	18 M/7 F	N.S.
Seizure frequencies before Vaccination			
Day	1	0	N.S.
Week	2	4	
Month	3	7	
Year	12	9	
Seizure-free more than 1 year	10	5	
Unexpected seizures in the 2 weeks after the H1N1 vaccination	6 (21.43%)	0 (0%)	0.008

N.S., non-significant.

**Table 3.** Clinical courses are shown in 6 childhood epileptic patients, in whom, increased seizure frequencies were noted within two week following H1N1 vaccination.

Age (Y)	Sex	MRI	Epileptic syndrome	Antiepileptic drugs	Mentality	Seizure semiology	Seizure frequency	
							Pre-vaccination	Post-vaccination
14	F	Old left Occipital lesion	Symptomatic OLE	VPA, GBP, OXC	Normal	General tonic, myoclonic, visual hallucination, flash	Every month	More flash in following days
6	M	Normal	BCET	OXC, TOP	Normal	Drooling, hemiconvulsion	Free for 6 months	Seizure attack once after vaccination
8	M	Normal	Cryptogenic FLE	VGB, TOP, OXC	Normal, Hyperactive behavior	General tonic-clonic seizure, atypical absence	Every week	Daily seizure
8	M	Normal	BCET	OXC	Normal	Hemiconvulsion, nocturnal onset	Every half year	First dose, one seizure in following g week; second dose, 4 more seizures in the Following weeks
1.4	M	Left temporal lobe dysplasia	Symptomatic TLE	TOP, VGB	Delayed development	Epileptic spasm	Every month	Daily
5	M	Normal	BCET	OXC, TOP	Normal	Hemiconvulsion, drooling	Every two months	Two seizures in following 2 weeks

Y indicates year; F, female; M, male; MRI, magnetic resonance image; VPA, valproic acid; CBZ, carbamazepine; PHT, phenytoin; OXC, oxcarbazepine; TOP, topiramate; VGB, vigabatrin; GBP, gabapentin; BCET, benign childhood epilepsy with centrotemporal spikes; TLE, temporal lobe epilepsy; FLE, frontal lobe epilepsy; OLE, occipital lobe epilepsy.

to daily seizures after the vaccination.

## Discussion

We have collected two-case series in over a two month period and reported the transient unexpected neurological events (UNE) that occurred in two groups of children after they had been given an H1N1 vaccination. The mechanisms of UNE after an H1N1 vaccination are unknown. Possible explanations include a post-vaccination immune-mediated mechanism, direct pyrogenic effect of influenza antigen, or adjuvant vaccine material<sup>[11]</sup>, which can cause rapid-onset neuropathy more quickly than immune-mediated neuropathy, such as post-vaccination Guillain-Barré syndrome<sup>[12,13]</sup>. Increased post-vaccination seizure frequencies

in children with epilepsy indicated that the vaccination probably lowered seizure thresholds because of a vaccine-induced local or systemic inflammation. The UNE in our 6 previously healthy pediatric patients were not associated with gender. One possible mechanism of UNE includes an underlying disorder, as in case 1, in which the patient had an unusual bilateral abducens nerve palsy that was noticed only after the H1N1 vaccination. There are no published reports of cranial nerve VI palsy after an H1N1 vaccination, but there are after mumps, rubella, and annual influenza immunizations<sup>[14,15]</sup>. A mass psychogenic illness cannot explain widespread UNE despite the fact that it might explain some cases of adolescents with post-vaccination dizziness or headache<sup>[16]</sup>. Our 2-year-old, however, was far too young to be a

victim of mass psychogenic illness.

We chose epileptic children and investigated the seizure frequencies after H1N1 vaccination because increased seizure frequencies have been also noticed after diphtheria-tetanus-pertussis (DPT) vaccination, however, the seizure frequencies after H1N1 vaccination is not known. The finding of transient UNE in children after they had been given an H1N1 vaccination was that seizure frequencies were significantly higher in about 21.43% of 53 children with epilepsy, irrespective of their specific epileptic syndrome. A post-vaccination pseudo-seizure (nonepileptic seizure) for those with seizure-like movement after a vaccination can lead to a debate about it possibly being a psychogenic illness. For our pediatric patients with epilepsy, however, the stereotype seizure semiologies were the same as those in their previous seizures: three patients with benign childhood epilepsy with centrotemporal spikes still had hemiconvulsions and oral drooling, which rules out pseudo-seizures. In addition, the epileptic syndromes, benign and symptomatic, manifested by those patients varied.

Influenza vaccines cause mild but common reactions. About one in three people get a sore arm from the shot, some with a little redness or even swelling. Some 10% to 15% of people feel tired or get a headache and some may even run a low fever. Although it has been reported<sup>[17,18]</sup> that common vaccinations, including those for influenza, apparently do not increase the risk of relapse in patients with multiple sclerosis. Four cases of new onset or relapsing anti-neutrophil cytoplasmic-antibody-associated vasculitis in response to influenza vaccinations have been reported<sup>[7]</sup>. Lymphadenitis was reported in a 23-year-old man 1 week after an H1N1 vaccination<sup>[19]</sup>. Approved vaccines, including the 2009 H1N1 vaccine, are calculated to be much less risky than the diseases they are intended to prevent. For example, out of every million people given a flu shot, one or two will have a serious neurological reaction called Guillain-Barré syndrome; however, the flu itself causes more than twice as many serious problems, including Guillain-Barré syndrome. And because a large proportion of the population will get swine flu, the vaccine itself is far less risky than the

disease.

The seizure frequency changes in epileptic children were reported by their parents, and a memory bias is possible. However, we recorded seizure frequency changes within 4 weeks after the H1N1 vaccination, and that will reduce the bias. Questions will arise regarding which symptoms may have been accidental or not vaccine-related. However, in our experience with outpatient clinics, 6 patients having transient UNE after vaccination in a short 2-month period was unusual. Therefore, more studies of larger populations are required.

## Conclusion

We conclude that H1N1 vaccine can cause transient UNE, most of which are mild and can be recovered from, as in our series. Seizure frequencies increased in more than 20% of our vaccinated patients with epilepsy in the two weeks after their H1N1 vaccination. Vaccine-associated seizure in epileptic children should be given attention.

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### Declaration of Conflicting Interests

The authors declare that they have no conflicts of interest with respect to the authorship or publication of this article.

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# 正常兒童與癲癇病人流感（H1N1）疫苗注射後的未預期突發事件

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大多數兒童對H1N1流感疫苗無特別反應，只有少數兒童接種疫苗後會出現未預期的神經反應（unexpected neurological events）。在此，對53個癲癇兒童調查，發現在施打疫苗的兒童，在接種疫苗後二個禮拜內抽搐有增加的情形（ $P = 0.008$ ），之後所有的病人均完全復原。結論為臨床醫師應注意在一些癲癇兒童，在施打H1N1流感疫苗後，可能會增加抽搐頻率。

**關鍵詞：**H1N1疫苗、癲癇、兒童

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