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Clinical manifestations and outcomes of Guillain-Barré syndrome after diphtheria and tetanus vaccine (dT) during a diphtheria outbreak in Thailand: A Case series

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Abstract

Four cases of Guillain-Barré syndrome (GBS) after diphtheria and tetanus vaccine (dT) during diphtheria outbreak in Thailand are reported. Three cases had an age over 60 years, and developed GBS after the second dose of dT vaccine. Two cases received intravenous immunoglobulin and had improvement after treatment. The autoantibodies or anti-ganglioside antibodies are believed to be the possible explanation of GBS associated with vaccination. Data regarding post-dT vaccine GBS are limited in Asian populations particularly on clinical presentation and outcomes.

INTRODUCTION

Diphtheria, caused by *Corynebacterium diphtheriae*, has a clinical syndrome with a white patch on the tonsils or uvula. In severe diphtheria cases, bronchial obstruction, myocarditis, heart failure, or respiratory failure may occur. Routes of transmission of diphtheria are respiratory droplets, direct contact with utensils, or sexual intercourse. Asymptomatic carriers are the main spreading source in the community.[1]

The first diphtheria outbreak in Thailand was in 1977 resulting in diphtheria vaccination in Thailand. The recent outbreak was between June 2012 and January 2013 in the northeastern and southern parts of Thailand[1], first in the Loei province. In total, there were 42 definite cases, 6 possible cases, and 102 carriers. Of those, six patients died. A diphtheria vaccination campaign was promoted by using dT vaccine, a combination of diphtheria and tetanus toxoids.

Vaccine-associated adverse events (VAEs) from dT vaccine are reported to be approximately 40 events per million net doses.[2] VAEs include injection site reactions such as redness, pain, fever, and pruritus. Serious neurological complications such as encephalitis, meningitis, paralytic syndromes, seizures, cranial nerve disorders, or Guillain-Barré syndrome (GBS) may occur but rarely.[2-6]

The dT vaccine is comprised of two vaccines; diphtheria and tetanus. Tetanus toxoid causing GBS is very rare in literature.[7] The combination with other vaccines such as diphtheria, pertussis, or anti-venum has not shown an increased risk of GBS development.[3,8] Risks of GBS from tetanus toxoid containing vaccines were not different between adults and children and extremely rare.[7] Here, a case series of four cases of GBS after dT vaccination during the diphtheria outbreak in Thailand are reported. All patients lived in the Northeastern Thailand. There are limited data on GBS and dT vaccine use in Thai or Asian populations.

RESULTS

During the outbreak period, a total of 2,213,530 dT vaccine doses were distributed in 5 provinces of the upper Northeastern, Thailand. The vaccine used was a combination of purified diphtheria toxoid and purified tetanus toxoid and given 0.5 ml intramuscularly for two separate doses (0 and 4 weeks). There were four patients in two provinces who developed dT vaccine associated GBS. The rate of GBS occurrence was 0.29/100,000 vaccine doses. Clinical features and outcomes of all four cases are summarized in Table 1 and are as follows:

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Patient 1

This 61-year-old Thai male developed muscle pain in both of his thighs, glove and stocking sensation loss in both lower limbs five weeks after the second dose of dT vaccine (Lot no 024L1016b, Serum Institute of India Ltd.). Two days later, he developed facial palsy on left side with numbness. On physical examination, he had bilateral facial diplegia, limitation of extraocular movement in all directions except lateral gaze of left eye, loss of pinprick sensation on his left face, and absent reflexes. Cerebrospinal fluid (CSF) showed albuminocytologic dissociation with a protein level of 146 mg/dL (normal < 40 mg/dL). Electromyography (EMG) demonstrated sensorimotor polyradiculoneuropathy. He had unremarkable findings on magnetic resonance imaging (MRI) of the brain and spine.

Patient 2

A Thai male, 65 years old had severe pain at the dT injection site that lasted for a week. Four months after first dose of dT vaccine (Lot no 024L1013c, Serum Institute of India Ltd.), he developed weakness in both thighs and legs for four days. He reported no paresthesia, bowel bladder involvement, or dysphagia. On physical examination, he had absent reflexes without cranial nerve abnormalities. Laboratory investigations showed albuminocytologic dissociation of CSF (CSF protein 46 mg/dL), sensorimotor polyneuropathy (demyelinating process) on EMG, and normal CT scan of the brain.

Patient 3.

A 41 –year-old Thai male had numbness at both feet with weakness of both lower extremities and myalgia 4 weeks after the second dose of dT vaccine (Lot. no 0412012, PT Biopharma, Indonesia). He noted that he had fever for two days after the first dose of dT vaccine. Physical examination revealed an absence of reflexes. His symptoms improved gradually after two weeks. No further investigation was done.

Patient 4

A 72-year-old Thai female developed numbness in both legs and hands four weeks after the second dose of dT vaccine (Lot no 024L9011b, Serum Institute of India Ltd.). She also had progressive motor weakness in both legs and was unable to walk. Physical examination also showed decreased reflexes. Laboratory results were normal CSF examination (CSF protein 28 mg/dL), and sensorimotor polyneuropathy (axonopathy) on EMG.

A summary of EMG findings are shown in Table 2. Two patients received intravenous immunoglobulin and had clinical improvement (Table 1).

DISCUSSION

The evidence of vaccine associated GBS has been known since 1979 after the national swine flu vaccination program.[9] Similarly, diphtheria toxoid and acellular pertussis vaccine (Tdap) or dT vaccine have shown several neurological complications.[3] Among those complications, GBS is found at the lowest rate. It has been reported to have occurred in 4 patients out of 660,245 administered doses (0.61/100,000 doses). In this study, the rate of dT vaccine associated GBS was somewhat lower at 0.29/100,000 doses. Reports of diphtheria tetanus vaccine associated with GBS are summarized in Table 3.

This case series was comprised of four patients who developed GBS after dT vaccine. The earliest incubation period was 4 weeks in 2 patients and the longest one was 4 months. Generally, GBS usually occurs within 6 weeks after dT vaccination[10] but may develop as long as one year later.[3] Patient 2 had quite a long incubation period of 4 months. Clinical features, however, were mostly compatible with vaccination associated with GBS. No other obvious causes of GBS were identified in this patient. Patient 1 had the most severe disease with facial diplegia and bulbar involvement. All four patients had motor weakness and absent reflexes, which were typical symptoms for GBS. Two patients had albuminocytologic dissociation in the CSF analysis (Patient 1 & 2).

The EMGs of Patients 1, 2, and 4 were compatible with the diagnosis of GBS. Patient 4 had axonal involvement, and the clinical manifestations was compatible with GBS. EMG findings was indicative of polyneuropathy. It was therefore believed that this patient had GBS with axonal involvement. Patient 3 and 4 came to the University Hospital after symptomatic treatment at their primary hospital. They therefore did not receive immunoglobulin therapy. Three of four patients (Patient 1, 3, and 4) had improvement of their motor weakness. Note that three out of four patients had an age over 60 years. The oldest patient had the most severe neurological sequelae (Patient 4). Three patients developed GBS after the completion of two doses of dT vaccine.

Table 1: Clinical characteristics and outcomes of dT vaccine associated with Guillain-Barré syndrome (GBS)

No.	Age	Sex	Onset	Dose	Motor weakness	Sensation	Reflexes	CSF protein (mg/dL)	Pre-treatment status	Treatment	Post-treatment status
1	61	Male	5 weeks	Second	Both thighs with facial diplegia	Glove and stocking	Absent	146	Unable to walk	Intravenous Ig, physical therapy	Improved, able to walk with gait aids (2 weeks), residual facial weakness and limit gaze of left eye
2	65	Male	4 months	First	All extremities	Normal	Absent	46	Difficult to walk	Intravenous Ig, physical therapy	Improved, able to walk with gait aids (2 weeks)
3	41	Male	4 weeks	Second	All extremities	Glove and stocking	Absent	Not done	Difficult to walk	Symptomatic, physical therapy	Improved, able to walk with gait aids (2 weeks)
4	72	Female	4 weeks	Second	Both thighs and legs	Glove and stocking	Decreased	28	Unable to walk	Symptomatic, physical therapy	Slightly improved but still unable to walk (2 months)

Note. Onset: onset of GBS after dT vaccination; Dose: indicated dT dose before occurrence of GBS; CSF: cerebrospinal fluid; Ig: immunoglobulin; all patients received 0.5 ml of dT vaccine.

Table 3: Reports of diphtheria tetanus vaccine associated with Guillain-Barré syndrome (GBS)

Study	Year	Type of vaccine	Findings
Nelson *et al.*[18]	2013	DTaP-IPV-Hib	No case of GBS in DTaP-IPV-Hib vaccine recipients (149,337 doses)
Chang *et al.*[19]	2013	Tdap	GBS 10/2090 doses (0.48% or 478.47/100,000 doses)
Ammar[6]	2011	Tdap; Boostrix	One case report
Yih *et al.*[3]	2009	Tdap	GBS 0.12–0.83 cases/100,000 observations
Tuttle[7]	1997	tetanus-toxoid-containing vaccines	GBS 0.3 cases/1,000,000 person-week
Newton *et al.*[15]	1997	tetanus-diphtheria toxoid	One case report

Note. DTaP-IPV-Hib:a pentavalent combination diphtheria and tetanus toxoids and acellular pertussis adsorbed (DTaP), inactivated poliovirus (IPV), and *Haemophilus influenzae* type b (Hib) conjugate vaccine; Tdap: diphtheria toxoid and acellular pertussis vaccine; Tdap; Boostrix: A tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine

Table 2: Summary of electromyographic findings of three patients with Guillain-Barré syndrome after diphtheria and tetanus vaccine (dT)

Motor NCS	Patient 1			Patient 2			Patient 4		
Nerve	distal latencies ms	CMAP mV	velocities m/s	distal latencies ms	CMAP mV	velocities m/s	distal latencies ms	CMAP mV	velocities m/s
Motor Median Left									
Wrist - APB	3.49	**3.6**		3.63	6.0		NR	NR	
Elbow-Wrist	8.71	**3.0**	**47.9**	7.38	5.5	53.3			
Motor Median Right									
Wrist - APB				3.95	4.2		**5.1**	**1.3**	
Elbow-Wrist				7.61	4.0	57.4	9.7	**1.3**	40
Motor Peroneal Left									
EDB- Ankle	**5.38**	**1.25**		4.03	3.5		NR	NR	
Fibular head-Ankle	16.8	**0.24**	**28.0**	10.3	**2.5**	45.5			
Motor Peroneal Right									
EDB- Ankle	**8.55**	**1.59**		3.89	4.5		NR	NR	
Fibular head-Ankle	17.4	**0.47**	**34.5**	10.2	**3.7**	42.0			
Motor Tibial Left									
Ankle - Abductor hallucis	4.77	**3.6**		4.11	5.8		NR	NR	
Knee-Ankle	17.5	**0.62**	**26.7**	12.2	**3.5**	40.2			
Motor Tibial Right									
Ankle - Abductor hallucis	**6.59**	**0.85**		3.93	8.7		NR	NR	
Knee-Ankle	18.5	**0.14**	**28.5**	11.7	**4.0**	43.1			
Motor Ulnar Left									
Wrist - ADM	**4.71**	**3.4**		2.88	5.7		**3.6**	**0.8**	
Bl. elbow-Wrist	10.5	**2.3**	**40.2**	6.10	5.7	68.3	7.5	**0.7**	47
Motor Ulnar Right									
Wrist - ADM				2.58	7.9		**3.6**	5.2	
Bl. elbow-Wrist				5.85	7.3	64.2	7.4	4.8	45

Sensory NCS		Patient 1			Patient 2			Patient 4	
Nerve	**distal latencies**	**SNAPs**	**velocities**	**distal latencies**	**SNAPs**	**velocities**	**distal latencies**	**SNAPs**	**velocities**
	ms	**mV**	**m/s**	**ms**	**mV**	**m/s**	**ms**	**mV**	**m/s**
Sensory Median (Segment) Left									
Wrist – Digit	**4.99**	10.5		**3.92**	7.7		NR	NR	
Elbow - Digit	10.0	8.0	**46.9**	7.50	4.6	53.1			
Sensory Median (Segment) Right									
Wrist – Digit				3.44	5.4		NR	NR	
Elbow – Digit				7.33	2.9	51.4			
Sensory Sural Left									
Mid lower leg - Lateral Malleolus	**3.54**	10.1		NR			NR	NR	
Sensory Sural Right									
Mid lower leg – Lateral Malleolus	3.37	4.7		NR			NR	NR	
Sensory Ulnar (Segment) Left									
Wrist – Digit	**4.01**	6.7		3.06	5.8		NR	NR	
Below elbow – Digit	9.42	10.0	**43.4**	6.48	5.4	57.9			
Sensory Ulnar (Segment) Right									
Wrist – Digit				3.16	9.3		**4.2**	15	
Below elbow - Digit				6.98	4.3	52.4	8.3	13	**46**
F-Wave Studies							**Min F Latency**	**% of F-wave**	
Ulnar.Left							27.0	60.0	
Ulnar.Right							29.8	50.0	
Median.Right							0	0.0	

Note. ADM: abductor digiti minimi, APB: abductor pollicis brevis, CMAP: Compound muscle action potential, EDB: Extensor digitorum brevis, ms: milliseconds, m/s: meter per second, mv: millivolts, NCS: nerve conduction studies, NCV: nerve conduction velocities, NR: not reponse, SNAP: sensory nerve action potentials; bold indicated abnormal values.

GBS usually occurs after infection, particularly with *Campylobacter jejuni*, Cytomegalovirus, Ebstein-Barr virus, Varicella-zoster virus, *Mycoplasma pneumoniae*, and Influenza virus.[11,12] The main mechanism of this syndrome is an immune-mediated process resulting in peripheral nerve destruction from autoantibodies. Vaccination is believed to stimulate the immune system and cause autoantibodies against peripheral nerves.[13] Post-vaccination GBS has been reported in other vaccines including tetanus toxoid[14,15] and influenza vaccine.[16] However, there is no previous reports from seasonal influenza vaccine.

Regarding dT vaccine associated with GBS, Bakshi and Grave reported a case of GBS occurring four days after dT vaccination.[5] The Tdap vaccine may have a higher relative risk of GBS development than dT vaccine (1.6 times) but overall adverse events were not different.[3] The World Health Organization (WHO) recommends to use cell culture vaccines instead of brain-derived vaccine which may have ganglioside contamination. Anti-ganglioside antibodies were related to GBS in animal models.[17]

In conclusion, GBS associated with dT vaccine is rare and may not be severe. Three out of four of our patients who developed GBS from dT vaccine had age over 60 years. Due to low prevalence of dT vaccine complications, dT vaccination during the outbreak of diphtheria is beneficial and recommended.

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DISCLOSURE

Conflict of interests: None

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