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Guillain-Barre syndrome after generalized tetanus infection

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Guillain-Barre syndrome (GBS) is an auto-immune disease of peripheral nerve system. It occurs mainly after preceding infection such as upper respiratory or gastrointestinal infection and other antecedent events as tetanus vaccinations. However, any case of GBS after tetanus infection has not been reported. Recently, when analyzed the clinical aspects of 13 tetanus patients including ours, 2 GBS occurred after tetanus infection. We report the neurological and electrophysiologic findings of two cases of Guillain-Barre Syndrome after generalized tetanus.

Key words: Autoimmune diseases; Guillain-Barre syndrome; Tetanus

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Guillain-Barre syndrome (GBS) is an autoimmune disease resulting in peripheral nerve destruction from autoantibodies and rapidly evolving polyneuropathy, typically presenting with limb muscle weakness, paresthesia, and areflexia.[1,2] It occurs mainly after a preceding infection, such as an upper respiratory or gastrointestinal infection.[1] Other antecedent events are known, including vaccination, acute hepatitis A and B, pegylated interferon treatment for chronic hepatitis C, human immunodeficiency virus infection, and non-infectious conditions such as lymphoma, surgery, and cerebral infarction.[1-6]

GBS cases after tetanus vaccinations have been previously been reported and were associated with autoantibodies.[2-6] However, GBS after tetanus infection has not been reported. Recently, when we analyzed the clinical aspects of 13 tetanus patients who had been admitted to Wonkwang University Hospital between 2000 and 2015 including ours, two GBS cases were detected after tetanus infection.[7] Herein, we report the neurological and electrophysiologic findings of these two cases.

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CASE

Case 1

A 78-year-old female presented with persistent posterior neck pain, neck rigidity, and dysphagia. Retrocollis was shown, and her neck flexion and rotation were limited due to severe rigidity. Her medication history was unremarkable. In a general physical examination, we found a recent abrasion wound on her anterior neck, which had resulted from hooking a metal necklace. Severe nuchal rigidity was noticed, but other neurologic examinations were normal. Her vital signs showed 150/90 mmHg blood pressure, a 70/minute pulse rate, and a 17/minute respiratory rate. Laboratory findings revealed only mild elevation of serum creatine kinase (423 IU/L) and myoglobin (266 ng/mL), suggesting mild generalized muscular injury. On tentative diagnosis of tetanus, 3,000 IU of tetanus immune globulin (TIG) was administered in a single injection. However, the patient still complained of worsening neck stiffness, trismus due to lockjaw, generalized myalgia, and muscle spasm. She was intubated due to asphyxia with respiratory muscle spasm and showed aggravated general pain, muscle spasm, and fluctuating blood pressure and heart rate. With close monitoring and intensive care, her generalized symptoms improved over the course of days.

Even though accurate examination on motor grades had been difficult due to frequent use of sedative agents such as benzodiazepine, her limbs moved against the gravity with adequate withdrawal and localization to pain stimulation until the twenty-second day after the onset of tetanus. But, on the twenty-third day, she showed quadriparesis (Medical Research Council [MRC] grade 2) and diminished deep tendon reflexes, which had been normoactive at first. She could not lift her arms and legs up and only showed minimal flexion response with painful response. A nerve conduction study (NCS) of right extremity revealed prolongation of upper motor action potential latencies, reduced motor conduction velocities, and reduced amplitudes. In addition, prolonged latency and reduced amplitudes were noted in phrenic nerve. Peroneal and posterior tibial nerve motor action potentials were absent. F-waves were not detected in either upper or lower limbs (Table 1). These findings indicated a main demyelinating disorder with secondary axonopathy. On diagnosis of concurrent GBS, even though we did not performed cerebrospinal fluid (CSF) study, intravenous immunoglobulin (IVIG; 24 g [0.4 g/kg/day]) therapy was applied for five days with continuous general support. After treatment with IVIG, limb weakness and respiratory symptoms gradually improved. With rehabilitation, motor improved to MRC grade 4, and she was able to walk with some help. A repeated NCS revealed results within the normal range except for reduced amplitudes in the ulnar nerve (Table 1).

Case 2

A 71-year-old male presented with fever, neck pain, and dysphagia due to trismus, which had started the previous day. He had multiple abrasion wounds on his right hand and left foot, which had resulted from falling down in the street two weeks before. He had been on regular medication for diabetes mellitus for several years, but otherwise had a nonspecific past medication history. On physical examination, neck stiffness, trismus, and generalized myalgia with muscle spasm were noted. Neurologic examination was normal with normoactive deep tendon reflexes. On suspicion of generalized tetanus, 3,000 IU of TIG was administered in a single injection with regular intravenous injections of metronidazole. He also complained of severe general pain and autonomic symptoms such as fluctuations in heart rate and blood pressure (heart rate: 70-114 times/minute; blood pressure: 194/74-120/70 mmHg). His respiratory rate was 15-18 times/minute.

For control of generalized pain with muscle spasm and irritability, continuous intravenous sedative agent and muscle relexant (midazolam and vecuronium) were injected to the patient. On eighth day after the onset of tetanus, general pain and muscle spasms showed mild improvements in frequency and severity. So, intravenous injection of midazolam and vecuronium was discontinued. However, after his mentality had recovered from sedative state, he exhibited diminished motor power in both upper (MRC grade 3) and lower extremities (MRC grade 1). Areflexia was noted in all joints, which had been intact before use of sedative agent. An NCS revealed prolongation of upper and lower motor action potential latencies, reduced motor conduction velocities, and reduced amplitudes, indicating a demyelinating pattern with secondary axonal injury. F-waves in the right median, ulnar, and peroneal nerves were not detected (Table 1). And temporal dispersion-like abnormality was noted on

tibial nerve. On diagnosis of GBS, even though we did not performed CSF study, IVIG (25 g/day) therapy was administered over five days. Motor strength showed gradually improved. Motor grade was MRC grade 4 in all limbs after IVIG treatment.

DISCUSSION

According to previous reports, there have been many cases of post-vaccination GBS, following administration of not only the tetanus vaccine but also oral poliovirus vaccine, hepatitis

Table 1. Nerve conduction studies of the right upper and lower extremities

	Patient 1 (23rd day after onset of tetanus /60th day after onset of tetanus)			Patient 2 (8th day after onset of tetanus)		
	Latency (ms)	Amp (μV)	NCV (m/s)	Latency (ms)	Amp (μV)	NCV (m/s)
Motor NCS						
Median nerve						
Wrist	5.7/3.3	0.7/10.2		5.9	5.9	
Elbow		0.7/9.9	37.1/51.3		5.8	49.2
Axilla		0.6/9.6	38.9/58.8		5.6	48.7
F-latency			-/25.6			-
Ulner nerve						
Wrist	4.3/2.8	1.7/5.7		6.0	1.0	
Below elbow		1.2/5.6	41.5/65.2		0.7	50.0
Above elbow		0.9/5.5	62.5/62.5		0.4	41.0
Axilla		0.9/5.2	50.0/62.5		0.4	43.5
F-latency			-/25.7			-
Phrenic nerve	11.4/8.0	1.2/2.0				
Peroneal nerve						
Ankle	-/4.1	-/5.4		8.8	0.2	
Below knee		-/5.6	-/41.7		0.1	26.6
Above knee		-/5.4	- /45.8		0.1	28.6
F-latency			-/40.0			-
Tibial nerve						
Ankle	-/4.5	-/5.8		8.8	2.5	
Knee		-/5.7	-/42.7		2.2	33.0
F-latency		-	-/49.9			60.8
Sensory NCS						
Median nerve						
Finger-wrist		17.1/26.4	39.3/50.0		3.3	39.6
Wrist-elbow		40.8/31.8	45.9/54.5		19.2	51.0
Elbow-axilla		112.9/98.2	62.5/52.6		84.6	48.9
Ulnar nerve						
Finger-wrist		14.9/17.8	51.9/56.3		2.2	39.7
Wrist-elbow		43.4/26.8	50.0/56.8		9.0	58.3
Elbow-axilla		34.3/72.9	52.2/58.8		10.5	47.8
Sural nerve						
Calf		13.1/7.8	33.3/36.8		4.1	32.5

Amp, amplitude; NCV, nerve conduction velocity; NCS, nerve conduction study.

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B vaccine, rabies vaccine, and others.[5,6] However, our cases involved generalized tetanus complicated by GBS, which had not been previously reported.[7]

GBS is an autoimmune disorder, and ganglioside is the target of the autoimmune reaction, with T cells playing a role in disease development.[8] Ganglioside-specific T cell reactivity is an important cause of damage to nerves through several mechanisms, including direct axonal or schwann cell cytotoxicity and secretion of proinflammatory cytokines, which induce damage directly and indirectly by recruitment and activation of macrophages.[9] The terminal part of the carboxyl group in the heavy chain of the tetanus toxin (tetanospasmin) is a strong inducer of T cell activity and has an affinity for ganglioside in peripheral nerves.[10] Therefore, the suspected mechanism of GBS after tetanus infection in our cases is that the tetanus toxin induced T cell attacks on ganglioside.[9]

However, in our patients, the tetanus was treated with TIG, which precluded our ability to determine whether GBS development was due to the tetanus infection itself or the TIG. This limitation of our study requires further research on the pathophysiology of GBS that occurs after tetanus infection. Furthermore, accurate differential diagnosis between GBS and critical illness polyneuropathy and myopathy (CIPNM) after tetanus is difficult. But, mainly demyelinating pattern with secondary axonopathy including prolongation of conduction, preceding infections and clinical improvement after treatment of IVIG in our patients are suggesting GBS rather than CIPNM.[11]

In conclusion, we suggest that careful and close neurologic observation in tetanus patients is important when there is suspicion of superimposed peripheral nerve diseases such as GBS because the generalized symptoms of tetanus can ask motor and sensory symptoms.

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