Point of view

Is testosterone a potential agent for patients with delayed recovery from Guillain-Barre Syndrome?

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Abstract

Background: Management of some of the patients with Guillain-Barre syndrome is challenging, requiring weeks to months of intensive care and prolonged institutional care.

Case report: We report a 32-year-old male with acute inflammatory demyelinating polyneuropathy (AIDP) with markedly delayed recovery. He was ventilator dependent and multiple therapeutic interventions were attempted.

Other possible contributing factors for delayed recovery were looked into. Co-existing critical illness myopathy and polyneuropathy with low level of serum testosterone were detected. Following replacement of testosterone, he was weaned off from the ventilator within a short period of time after eleven weeks of ventilator dependency and slow recovery of neurological weakness had been achieved resulting in total independency and normal working capacity.

Conclusion: Delayed recovery in GBS could be multifactorial. The effects of neuroendocrine changes in a critical illness could alter the expected recovery process. Thus, the role of testosterone in recovery from peripheral nerve injury, as well as in critical illness myopathy needs to be looked into.

Key words: Guillain-Barre syndrome, delayed recovery, critical illness myopathy, testosterone

Case report

A 32-year-old male presented with bilateral upper and lower limb numbness followed by progressive ascending type weakness and a preceding history of recent diarrheal illness.

On examination there was bilateral symmetrical proximal predominant weakness with areflexia. His vital capacity (VC) declined from the 4th day of weakness and his blood pressure fluctuated with intermittent high values. On the 6th day of weakness, he was intubated.

The nerve conduction study showed an acute inflammatory demyelinating polyneuropathy (AIDP) pattern and the CSF showed cyto-protein dissociation compatible with Guillain-Barre syndrome. He was treated with IV immunoglobulin 0.4 g/kg for 5 days.

The recovery was very slow, and he underwent tracheostomy following prolonged intubation on the 12th day. He received a second cycle of IV immunoglobulin on 15th day of weakness. Due to poor recovery and dependency on a ventilator, in the absence of an alternative treatment strategy and with limited evidence in literature, therapeutic plasma exchange (PEX) was commenced on the 31st day of the illness. Only four out of five cycles could be performed as he developed gram negative septicemia. However, there was no clinical improvement. As he had a very long intensive care unit (ICU) stay with poor recovery, a second course of plasma exchange was commenced on the Day 51. In fact, his recovery was poor and was ventilator dependent.

The long illness was complicated with syndrome of inappropriate ADH release leading to hyponatremia (SIADH) which was managed successfully with fluid restriction. He suffered from a few episodes of febrile illnesses while in the ICU where there was culture positivity with gram negative bacteria on two occasions which were managed successfully with antibiotics. Repeat nerve conduction study on Day 71 showed absent sensory motor responses in the limbs indicating advanced secondary axonal loss following acute neuropathy. The Electromyogram (EMG) showed mixed neurogenic and myopathic changes suggestive of additional myopathic dysfunction secondary to prolonged critical illness. At the same time his serum testosterone level was low, although the serum dehydroepiandrosterone (DHEA) level was normal.

On anecdotal evidence it was decided to give him intra muscular testosterone 300 microgram weekly for three weeks, which was started on day 74 and completed on day 87. Within the first week, there was a marked increase in the vital capacity, and he was weaned off from the ventilator by day 83. The improvement of limb power was gradual and did not show such a dramatic response.

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Repeat nerve conduction study and electromyography was done on day 101 and showed recovering neurogenic changes and absence of myopathic changes previously noted on day 71. Furthermore, sensory and motor responses were not yet evocable in the lower and upper limbs. This suggests established axonal degeneration following acute neuropathy. By day 180 the patient showed significant clinical recovery as he could walk without support and went back to his profession as a doctor by day 250 of the illness.

Investigations

CSF – Protein 190 g/L, cells L- 5, RBC – 8 Polymorphs – nil, Glucose 5.4 mol/l, RBS – 9.3 mol/L

First nerve conduction study on day 3

Nerve	Segment	Amplitude	Conduction Velocity [normal range]
Motor nerve conduction			
Right ulnar	Wrist Wrist-elbow	3.17 mV 2.99 mV (5.5 ± 2.0 (2.7))	50.8 m/S [58.7 ± 5.1 (49)]
Left ulnar	ADM	1.95 mV	
	Wrist-elbow	1.88 mV (5.5 ± 2.0 (2.7))	45.2 m/S [58.7 ± 5.1 (49)]
Left ulnar	FDI	2.54 mV	
	Wrist-elbow	1.33 mV Conduction Block	46.4 m/S [58.7 ± 5.1 (49)]
Right peroneal	Ankle	720 µV	
	Ankle-fibula	720 µV [5.1 ± 2.3 (2.5)]	38.3 m/S [48.3 ± 3.9 (40)]
Right tibial	Ankle	2.55 mV [5.8 ± 1.9 (2.9)]	
Left peroneal	Ankle	850 µV (5.1 ± 2.3 (2.5))	
	Head of fibula	739 µV	40.3 m/S [48.3 ± 3.9 (40)]
Left tibial	Ankle	5.42 mV (5.8 ± 1.9 (2.9))	
Sensory nerve conduction			
Right ulnar	Wrist	3 µV (35.0 ± 14.7 (18))	
Left ulnar	Wrist	3.5 µV (35.0 ± 14.7 (18))	
Right sural	Sural	35.3 µV (20.9 ± 8.0)	
Left sural	Sural	38.8 µV (20.9 ± 8.0)	
EMG – Neurogenic changes only			

Second nerve conduction study on day 71

Motor nerve conduction			
Right Median	Wrist	NR	
	Wrist-elbow		
	Elbow-axilla		
Right Ulnar	Wrist	NR	
	Wrist-elbow		
Right Peroneal	Ankle Head of fibula	 NR	
Sensory nerve conduction			
Right Ulnar		NR	
Right Sural		NR	
Right Radial		NR	
EMG – Mixed neurogenic and myopathic changes			
Left Biceps	Poor activation, small polyphasic unstable units		
Right Biceps	Poor activation and small units		
Right rectus femoris	No MUP activity		
Right Extensor Digitorum	Fibrillation		
	Positive Sharp Waves Occasional small MUP		

Third nerve conduction study on day 102

Motor nerve conduction			
Right Median		NR	
Right Ulnar		NR	
Right Peroneal		NR	
Sensory nerve conduction			
Right Ulnar		NR	
Right Sural		NR	
Right Radial		3 μV	
EMG			
Right Rectus Femoris	Poor activation Bursts of large MUPs		
Right Biceps	Large MUPs Reduced interference		
Previously noted myopathic changes are not seen and only recovering neurogenic changes are noted			

Other investigations

Day of illness	6	59	87	94
Hemoglobin – g/dl	14.8	12	11	13.7
S. Protein – g/L	80	52	61	
S. Albumin – g/L	36	30	30	
CRP	12	95	48	13
Testosterone		144	302	
S. DHEA		5.8	5.9	

Normal values – S. DHEA – 3.8-13.1 µmol/L, Serum testosterone – 241-827 ng/dL

Clinical progression of the disease with muscle power in MRC grading

Day of illness	VC/ Cc	Neck power	UL Proximal	UL distal	LL proximal	LL distal
8	1000	2	2	3	2	2
15 - 2nd cycle of IV IG		2	0	0	0	0
27		2	0	0	0	0
31 - PEX commenced						
51 - Second round of PEX						
58		3	1	0	0	0
70		3	2	1	0	0
74 (1st dose of Testosterone IM 300 mg	350	3	2	1	0	0
76	850	4	2	1	0	0
78	1200					
80	1100					
83 off ventilator		4	2	2	2	0
85		4	2	2	2	0
87		4	3	2	3	0
91		4+	4	4-	3	3
107	1700	5	4	4	3	3
Patient was transferred to ward						

Therapeutic plasma exchange (PEX), Intra venous immunoglobulin (IV IG)

Discussion

This case highlights the management challenges in a patient with poor recovery in GBS on the background of limited evidence based treatment options. In fact, this has become a challenging situation worldwide, where some patients with poor recovery are kept in intensive care units for many months due to ventilator dependency, often being bed bound with a tracheostomy tube and permanent disability. About 50-70% recover without symptoms or with minor deficits that does not affect their day to day activities[1]. This patient did not show signs of recovery up to 8 weeks into the illness and he was ventilator dependent with remote expectations of recovery facing complications related to ICU stay.

Factors affecting delayed recovery in GBS

There are several factors affecting delayed recovery in GBS. Old age, history of diarrhea preceding the weakness, and a low medical research council sum score (MRC-SS) at the time of hospital admission and after 1 week, were associated with inability to walk in the next few weeks to 6 months[2].

A significant proportion of GBS patients require intensive care support. Neuroendocrine changes during a long-lasting critical illness are different from changes during the acute phase. In the acute phase, the anterior pituitary actively secretes and there is peripheral inactivation of anabolic hormones. Whereas, prolonged critical illness is characterized by diminished neuroendocrine stimulation of the pituitary. Therefore, acute and prolonged critical illness are likely to be two different neuroendocrine paradigms. In acute stress, turning off the anabolic effects of adrenal androgens may be an appropriate response in order to redirect the utilization of energy. But, when a severe stressful condition last for a long time, hypogonadotropism can result[3].

This patient, who was a healthy young adult who was a father of a 5 months old child, was found to have a low level of serum testosterone (144 ng/dL) in the 8th week of illness. The normal range for his age is 241-827 ng/dL. His clinical course drastically changed following replacement of testosterone.

Role of testosterone in nervous system

Testosterone act on several sites of the nervous system by several mechanisms. It could affect, the myelin sheath, the axons and the myocytes. In this patient, following the acute inflammatory demyelinating peripheral neuropathy, there was secondary axonal degeneration and coexisting critical illness myopathy. However, following therapy with testosterone his respiratory functions improved rapidly with slow recovery of limb power. Objectively the EMG study following therapy showed marked improvement of the myopathy with recovering neurogenic changes. However, on the nerve conduction study, the neurons were still not evocable as neurophysiological recovery lags markedly behind the clinical recovery.

The effects of testosterone on myelin had been demonstrated by several groups experimentally. Rashad Hussain et al demonstrated that treatment with testosterone could efficiently stimulate the formation of new myelin and could reverse the myelin damage in chronic demyelinating brain lesions caused by a toxin, cuprizone, which is toxic for oligodendrocytes. They also have identified the androgen receptor as a novel therapeutic target for myelin recovery[4]. This was reinforced by several other in vitro studies[5,6].

In peripheral nervous system, Schwan cell is responsible for myelination and Melcangi RC et al brings out experimental evidence of effects of testosterone and other sex steroids on gene expression on two peripheral myelin proteins, the glycoprotein Po and peripheral myelin protein 22 (PMP22) which play a vital role in the rebuilding of myelin. There is growing evidence of importance of androgen receptor with regard to its role in peripheral nervous system disorders and as a potential target for therapeutic intervention in demyelinating disorders of peripheral nervous system[7,8].

The role of testosterone in axonal regeneration of motor neurons and dendrites had been recognised. It plays an important role in the development of central nervous system. Androgens alter the morphology, survival and axonal regeneration of motor neurons. Androgen treatment enhances the ability of motor-neurons to recover from regressive changes and regenerate both axons and dendrites, restoring normal neuromuscular function through a variety of molecular pathways[9,10]. There are many important effects of testosterone on myocytes. Enhanced contractile protein synthesis is an important mechanism by which testosterone can enhance the size of muscle fibers. Testosterone induces the hypertrophy of both type I and type II muscle fibers. By several mechanisms it stimulates precursor cell proliferation and myogenic lineage in order to regenerate muscle cells[11,12].

On the other hand, when considering the effect of androgen deprivation, for instance in patients with prostate carcinoma, who were treated with androgen deprivation therapy (ADT), several neuromuscular effects could be observed. Those include decreased neuromuscular performance due to reduced motor unit recruitment, reduced fiber innervation and reduced acetylcholine release. Reduced androgens in serum also inhibit the motor growth and repair in muscle and cause atrophy of muscles[13]. All these suggest an important role for androgens and androgen receptor on nervous system.

Conclusion

Delayed recovery in Guillain-Barre syndrome could be multifactorial. The unnoticeable neuroendocrine changes that take place in critical illness could alter the expected recovery process. Testosterone as an androgen has a wide spectrum of action on central and peripheral nervous system. There was significant objective improvement following replacement of testosterone in this patient. The therapeutic role of testosterone and the androgen receptor in recovery from nerve injury and critical illness myopathy need to be looked into.

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