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UNVEILING THE HIDDEN CONNECTION: LEPTOSPIRA AS AN ANTECEDENT IN GUILLAIN-BARRÉ SYNDROME

Ishan Dasgupta* Resident Medical Officer, Department of Neurology, KINS Institute of Neurosciences (A unit of KINS Hospital), Siliguri. *Corresponding Author

Swayam Prakash Senior Consultant and HOD, Department of Neurology, KINS Institute of Neurosciences (A unit of KINS Hospital), Siliguri.

ABSTRACT Guillain-Barré Syndrome (GBS) is an immune-mediated acute polyneuropathy often triggered by infections. Although rare, leptospirosis, a zoonotic bacterial infection, can precede GBS, particularly in endemic regions. We report a case of GBS in a 32-year-old woman following leptospirosis. She presented with ascending lower motor neuron (LMN) quadriparesis, along with bulbar and respiratory involvement. Nerve conduction studies suggested the AMSAN variant of GBS. In addition to standard IVIg treatment for GBS, she was also treated with doxycycline due to positive Leptospira IgG and IgM results, indicating a recent leptospirosis infection. She showed a fairly good clinical recovery. The association of leptospirosis with GBS is not well-documented in previous literature. This case emphasizes the importance of recognizing leptospirosis as a potential antecedent in GBS, particularly in endemic regions, and highlights the role of early intervention in improving outcomes.

KEYWORDS : Antecedent infections, Intravenous immunoglobulin, Axonal sensorimotor neuropathy, Leptospirosis, Guillain-barré syndrome

INTRODUCTION

Guillain-Barré Syndrome (GBS) is an immune-mediated acute polyneuropathy that affects the nervous system, characterized by rapidly progressive muscle weakness in an ascending pattern and areflexia. It is the most common cause of acute flaccid paralysis worldwide, with an incidence rate of approximately 1 to 2 cases per 100,000 individuals annually, and tends to affect adults and the elderly more frequently [1,2]. The male population exhibits a slightly higher incidence of GBS compared to females [3]. The pathophysiology of GBS is complex and involves an aberrant immune response, often triggered by a preceding infection [4]. This immune response results in the destruction of the myelin sheath of axons within peripheral nerves, leading to muscle weakness, sensory disturbances, and, in severe cases, bulbar and respiratory dysfunction [5]. The exact mechanisms behind GBS remain under investigation, though molecular mimicry, where the immune system mistakenly targets neural components due to similarities with infectious agents, is widely considered a contributing factor [6].

Commonly associated infections that precede GBS include Campylobacter jejuni, cytomegalovirus, Epstein-Barr virus, and, more recently, emerging pathogens such as Zika and SARS-CoV-2 viruses. However, the list of potential antecedent infections continues to expand, with increasing recognition of rarer triggers like leptospirosis.

Leptospirosis is a zoonotic bacterial infection caused by spirochetes of the genus Leptospira. The bacteria are transmitted through contact with contaminated water or soil, and the infection is more prevalent in tropical and subtropical regions. The clinical spectrum of leptospirosis varies widely, ranging from mild flu-like symptoms to severe multisystem involvement, including liver and kidney dysfunction, meningitis, and pulmonary hemorrhage. The incidence of leptospirosis is notably higher in regions with poor sanitation, frequent flooding, and close human-animal interactions. Diagnosing leptospirosis can be challenging due to its broad clinical presentation and overlap with other febrile illnesses, making laboratory confirmation essential.

The association between leptospirosis and GBS, although rare, has gained attention in recent years. Cases have been reported where patients developed GBS following leptospiral infections, suggesting a potential link. The proposed mechanism involves immune-mediated cross-reactivity, where antibodies produced in response to Leptospira antigens may target nerve gangliosides, leading to the development of GBS [7].

In this context, the present case report details a 32-year-old female who developed Guillain-Barré Syndrome following leptospirosis, highlighting the importance of considering leptospirosis as a potential antecedent infection in GBS, particularly in endemic regions.

CASE PRESENTATION

A 32-year-old female presented with a 4-day history of rapidly progressing weakness in all four limbs, initially affecting her lower limbs and later extending to her upper limbs. She also reported tingling and numbness in all four limbs and the trunk.

Over the past 3 days, she experienced additional symptoms, including low-volume speech, effortful breathing, and difficulty swallowing. The patient mentioned a brief febrile illness 6-7 days before the onset of her neurological symptoms.

Upon admission, the patient's vital signs were stable, with a pulse rate of 76 beats per minute, blood pressure of 160/110 mmHg, respiratory rate of 28 breaths per minute, and oxygen saturation of 100% on 2 liters of oxygen per minute. Neurological examination revealed that the patient was conscious, alert, and oriented. Her speech was breathy, and she exhibited poor palatal arching and uvula visibility.

Muscle tone was decreased bilaterally, and muscle strength was notably reduced, with upper limb strength ranging from 3 to 4-/5, proximal lower limb strength at 1/5, and distal lower limb strength at 4-/5. Deep tendon reflexes were absent, and plantar reflexes were equivocal.

Sensory examination revealed paresthesia. Other systemic examinations were unremarkable.

Magnetic resonance imaging (MRI) of the brain and cervical spine did not show any significant abnormalities. Nerve conduction studies (NCS) revealed an axonal sensorimotor polyradiculoneuropathy pattern [Tables 1,2,3,4,5]. Cerebrospinal fluid (CSF) studies showed albuminocytologic dissociation (Protein: 110.3 mg/dL, Cells: 8 cells/cmm). Viral markers for neurotropic viruses were negative.

Nerve	R-Site	Stim Site	Lat 1 (ms)	Lat 2 (ms)	Dur (ms)	Amp (mV)	Area (mVms)	Segment	Dist. (mm)	Diff (ms)	Reference Range
Median-Lt	APB	Wrist	10.13	30.13	20.25	2.55	16.98	APB-Wrist	10.13	NR	Latency: 4.17 ms, CV: 55 m/s, Amp: 5 uV
Median-Lt	APB	Elbow	15.50	38.75	23.50	2.14	17.28	Wrist-Elbow	230	5.38	Latency: 4.17 ms, CV: 55 m/s, Amp: 5 uV
Median-Rt	APB	Wrist	9.63	29.88	20.25	2.29	15.50	APB-Wrist	9.63	NR	Latency: 4.17 ms, CV: 55 m/s, Amp: 5 uV
Median-Rt	APB	Elbow	14.63	41.00	26.38	2.14	18.19	Wrist-Elbow	230	5	Latency: 4.17 ms, CV: 55 m/s, Amp: 5 uV
Radial-Lt	Extensor Indicis	Elbow	15.00	23.75	16.25	2.71	16.06	Extensor Indicis-Elbow	7.25	NR	Latency: 2.5 ms, CV: 57 m/s, Amp: 6.5 uV
Radial-Lt	Extensor Indicis	Spiral Groove	13.50	28.50	19.75	2.49	16.34	Elbow-Spiral Groove	3.75	NR	Latency: 2.5 ms, CV: 57 m/s, Amp: 6.5 uV
Radial-Lt	Erb's	Shoulder	NR	NR	NR	NR	NR	Shoulder-Erb's	NR	NR	Latency: 2.5 ms, CV: 57 m/s, Amp: 6.5 uV
Radial-Rt	Extensor Indicis	Elbow	5.00	23.25	18.25	2.71	16.33	Extensor Indicis-Elbow	5	NR	Latency: 2.5 ms, CV: 57 m/s, Amp: 6.5 uV
Radial-Rt	Extensor Indicis	Spiral Groove	8.75	28.50	19.75	2.49	16.34	Elbow-Spiral Groove	3.75	NR	Latency: 2.5 ms, CV: 57 m/s, Amp: 6.5 uV
Radial-Rt	Erb's	Shoulder	NR	NR	NR	NR	NR	Shoulder-Erb's	NR	NR	Latency: 2.5 ms, CV: 57 m/s, Amp: 6.5 uV
Ulnar-Lt	ADM	Wrist	6.75	29.00	22.50	2.27	22.16	ADM-Wrist	6.75	NR	Latency: 3 ms, CV: 55 m/s, Amp: 6 uV
Ulnar-Lt	ADM	Elbow	8.50	32.00	23.50	2.50	20.00	Wrist-Elbow	230	6.00	Latency: 3 ms, CV: 55 m/s, Amp: 6 uV
Ulnar-Rt	ADM	Wrist	6.88	29.50	22.63	2.89	20.03	ADM-Wrist	6.88	NR	Latency: 3 ms, CV: 55 m/s, Amp: 6 uV
Ulnar-Rt	ADM	Elbow	8.75	33.25	24.50	2.75	18.75	Wrist-Elbow	230	6.50	Latency: 3 ms, CV: 55 m/s, Amp: 6 uV

TABLE 1 Motor Nerve Conduction Study of Upper Limbs

Nerve	R-Site	Stim Site	Lat 1 (ms)	Lat 2 (ms)	Dur (ms)	Amp (mV)	Area (mVms)	Segment	Dist. (mm)	Diff (ms)	Reference Range
Peroneal-Rt	EDB	Ankle	NR	NR	NR	NR	NR	EDB-Ankle	NR	NR	Latency: 4.56 ms, CV: 42 m/s, Amp: 2.7 uV
Peroneal-Rt	EDB	Knee	NR	NR	NR	NR	NR	Ankle-Knee	NR	NR	Latency: 4.56 ms, CV: 42 m/s, Amp: 2.7 uV
Peroneal-Lt	EDB	Ankle	NR	NR	NR	NR	NR	EDB-Ankle	NR	NR	Latency: 4.56 ms, CV: 42 m/s, Amp: 2.7 uV
Peroneal-Lt	EDB	Knee	NR	NR	NR	NR	NR	Ankle-Knee	NR	NR	Latency: 4.56 ms, CV: 42 m/s, Amp: 2.7 uV
Tibial-Rt	EHL	Ankle	NR	NR	NR	NR	NR	EHL-Ankle	NR	NR	Latency: 4.7 ms, CV: 44 m/s, Amp: 5 uV
Tibial-Rt	EHL	Popliteal	NR	NR	NR	NR	NR	Ankle-Popliteal	NR	NR	Latency: 4.7 ms, CV: 44 m/s, Amp: 5 uV
Tibial-Lt	EHL	Ankle	NR	NR	NR	NR	NR	EHL-Ankle	NR	NR	Latency: 4.7 ms, CV: 44 m/s, Amp: 5 uV
Tibial-Lt	EHL	Popliteal	NR	NR	NR	NR	NR	Ankle-Popliteal	NR	NR	Latency: 4.7 ms, CV: 44 m/s, Amp: 5 uV

TABLE 2 Motor Nerve Conduction (MNC) Study of Lower Limbs

Nerve	R-Site	Stim Site	Lat 1 (mS)	Lat 2 (mS)	Dur (mS)	Amp	Segment	Dist. (mm)	Reference Range
Median-Lt	Wrist	Dig2	NR	NR	NR	NR	Dig2-Wrist	NR	Latency: 3.5 ms, CV: 35 m/s, Amp: 5 μV
Median-Rt	Wrist	Dig2	NR	NR	NR	NR	Dig2-Wrist	NR	Latency: 3.5 ms, CV: 35 m/s, Amp: 5 μV
Radial-Lt	FDI	Forearm	NR	NR	NR	NR	FDI-Forearm	NR	Latency: 3.5 ms, CV: 52 m/s, Amp: 6.5 μV
Radial-Rt	FDI	Forearm	NR	NR	NR	NR	FDI-Forearm	NR	Latency: 3.5 ms, CV: 52 m/s, Amp: 6.5 μV
Ulnar-Lt	Wrist	Dig 5	NR	NR	NR	NR	Wrist-Dig5	NR	Latency: 3 ms, CV: 50 m/s, Amp: 5 μV
Ulnar-Rt	Wrist	Dig 5	NR	NR	NR	NR	Wrist-Dig5	NR	Latency: 3 ms, CV: 50 m/s, Amp: 5 μV
Sural-Lt	Ankle	Mid Calf	NR	NR	NR	NR	Ankle-Mid Calf	NR	Latency: 3.5 ms, CV: 45 m/s, Amp: 8 μV
Sural-Rt	Ankle	Mid Calf	NR	NR	NR	NR	Ankle-Mid Calf	NR	Latency: 3.5 ms, CV: 45 m/s, Amp: 8 μV

TABLE 3 Sensory Nerve Conduction (SNC) Study

Nerve	R-Site	M-Lat (m)	Fmin-Lat (ms)	Fmax-Lat (ms)	Fmean-Lat (ms)	(Fmean-M)-Lat (ms)	Reference Range
Median-Lt	APB	9.5	39.75	41.5	40.63	30.25	F-Latency: <32 ms
Median-Rt	APB	9.25	33.25	35.5	34.38	24	F-Latency: <32 ms
Peroneal-Lt	Extensor Digitorum Brevis	NR	NR	NR	NR	NR	F-Latency: <56 ms
Peroneal-Rt	Extensor Digitorum Brevis	NR	NR	NR	NR	NR	F-Latency: <56 ms
Tibial-Lt	Abductor Hallucis	NR	NR	NR	NR	NR	F-Latency: <56 ms
Tibial-Rt	Abductor Hallucis	NR	NR	NR	NR	NR	F-Latency: <56 ms

Ulnar-Lt	Abd Dig Quiniti	37.5	39.25	38.38	31.25	0	F-Latency: <32 ms
Ulnar-Rt	Abd Dig Quiniti	6.25	31.5	33	32.25	25.25	F-Latency: <32 ms
TABLE 4	F Wave Study						

Nerve	R-Site	M-Lat (m)	H-Lat (ms)	(H-M)-Lat	H-Ampi (Trace)	Reference Range
Tibial-Lt	Soleus Muscle	NR	NR	NR	NR	H-Reflex Latency: <30 ms
Tibial-Rt	Soleus Muscle	NR	NR	NR	NR	H-Reflex Latency: <30 ms
TABLE 5	H Reflex Study					

Given the patient's history of a preceding febrile illness, further tests were conducted. Malaria, dengue, and typhoid antigen tests were sent, all of which came back negative. Routine pathological examination showed leukocytosis. Liver and kidney function tests revealed abnormal results. Serology for Leptospira was sent, which revealed positive IgG and IgM antibodies, suggesting a recent leptospirosis infection. Other ancillary tests were negative [Table 6].

Parameter	Value	Normal Reference Range
Age	32 years	N/A
Sex	Female	N/A
Duration at Presentation	4 days	N/A
History of Antecedent Illness	Febrile illness 6-7 days prior to neurological symptoms	N/A
Clinical Presentation	Acute onset of ascending flaccid quadriparesis, bulbar involvement, effortful respiration, swallowing difficulty	N/A
CSF Routine	Protein: 110.3 mg/dL, Cells: 8 cells/cmm	Protein: 15-45 mg/dL, Cells: 0-5 cells/cmm
CSF Other Profiles	No microorganisms seen, negative for malignancy	N/A
MRI Brain + Spine	No significant abnormality	N/A
Leptospira Serology	Positive for IgG and IgM antibodies	N/A
Serum Sodium (Na+)	140.10 mEq/L	135-145 mEq/L
Serum Potassium (K+)	3.93 mEq/L	3.5-5.0 mEq/L
Serum Calcium (Ca++)	9.38 mg/dL	8.5-10.5 mg/dL
Total Bilirubin	3.05 * mg/dL	0.1-1.2 mg/dL
Direct Bilirubin	1.58 * mg/dL	0.0-0.3 mg/dL
Indirect Bilirubin	1.47 * mg/dL	0.1-1.0 mg/dL
SGOT (AST)	147.20 * U/L	10-40 U/L
SGPT (ALT)	380.70 * U/L	7-56 U/L
Total Protein	7.20 g/dL	6.4-8.3 g/dL
Albumin	4.09 g/dL	3.5-5.0 g/dL
Globulin	3.11 g/dL	2.0-3.5 g/dL
A/G Ratio	1.32	1.1-2.5
Alkaline Phosphatase	58.00 U/L	44-147 U/L
Urea	112.70 * mg/dL	7-20 mg/dL
Creatinine	0.60 mg/dL	0.6-1.2 mg/dL
Serum CPK MB	26 U/L	0-25 U/L
TABLE 6	Comprehensive Clinical Profile of the Patient	

In light of the above clinical, historical, electrophysiological, and pathological observations, the patient was diagnosed with Guillain-Barré Syndrome (AMSAN variant). She was started on a weight-calculated dose of intravenous immunoglobulin (IVIG) over five days and intravenous doxycycline due to positive Leptospira serology. Owing to impending respiratory failure, she required artificial ventilation. By days 4-5 of IVIG treatment, the patient began to show signs of improvement, including better neck control and increased limb strength. She was gradually weaned off the ventilator and successfully extubated. Given the positive Leptospira serology and the patient's clinical improvement after starting antibiotics for the infection, leptospirosis was considered a potential antecedent infection complicating GBS. The patient's laboratory parameters gradually improved, and she was eventually discharged in stable condition.

The patient was also advised to seek immediate medical attention if she experienced any worsening of limb strength, respiratory difficulty, or difficulty swallowing or speaking. During follow-up, the patient showed gradual recovery in strength and limb power over the next three months, with measurements of 5/5 in the upper limbs and 4+/5 in the lower limbs.

DISCUSSION

The association between Guillain-Barré Syndrome (GBS) and preceding infections is well-established, with the most common triggers being Campylobacter jejuni, cytomegalovirus (CMV), and Epstein-Barr virus (EBV). However, leptospirosis, a zoonotic infection caused by Leptospira spp., is an increasingly recognized antecedent infection in GBS, especially in tropical regions where the disease is endemic.

Leptospirosis is transmitted primarily through direct or indirect contact with contaminated water, soil, or animal tissues, leading to a wide spectrum of clinical manifestations. The pathogenesis of leptospirosis-associated GBS is not completely understood, but molecular mimicry, a mechanism where the immune system mistakenly targets neural tissues due to antigenic similarities with Leptospira, is thought to play a pivotal role. This hypothesis is supported by evidence of cross-reactivity between antibodies against Leptospira and nerve gangliosides, which could trigger an autoimmune response leading to nerve damage[8] . Although rare, the occurrence of GBS in leptospirosis cases has been documented in various studies, with an estimated incidence of 1-2% in leptospirosis patients[9] .

In the presented case, the patient developed the acute motor-sensory axonal neuropathy (AMSAN) variant of GBS following a febrile illness, with serological evidence pointing to a recent Leptospira infection. AMSAN is a severe form of GBS characterized by rapid progression and profound motor

and sensory deficits [10]. The patient's clinical presentation, including rapidly progressive limb weakness, low-volume speech, and respiratory distress, aligns with the typical features of AMSAN. Nerve conduction studies confirmed the diagnosis, revealing an axonal sensorimotor polyradiculoneuropathy pattern.

This case illustrates the critical importance of early diagnosis and intervention in GBS, particularly in the context of a preceding leptospiral infection. The patient's initial management with intravenous immunoglobulin (IVIG) was consistent with standard GBS treatment protocols, aimed at modulating the immune response and preventing further nerve damage. The decision to initiate doxycycline alongside IVIG, based on positive Leptospira serology, likely contributed to the patient's eventual improvement and recovery. This dual approach underscores the need for targeted therapy in cases where a specific antecedent infection is identified, as treating the underlying infection can mitigate complications and improve overall outcomes.

The role of serological testing in diagnosing leptospirosis cannot be overstated. In this case, the presence of both IgM and IgG antibodies against Leptospira provided strong evidence of a recent infection. While the microscopic agglutination test (MAT) remains the gold standard for leptospirosis diagnosis, enzyme-linked immunosorbent assay (ELISA) for IgM and IgG antibodies is more commonly used in clinical settings due to its accessibility and reliability, as in our case [11]. Polymerase chain reaction (PCR) testing can also aid in early diagnosis by detecting Leptospira DNA, particularly during the acute phase of the infection.

The association between leptospirosis and GBS presents several clinical challenges, particularly in regions where leptospirosis is endemic. In such settings, clinicians must maintain a high index of suspicion for leptospirosis in patients presenting with febrile illness, deranged liver and kidney function tests, and subsequent neurological symptoms. A thorough history, including details of potential exposure to contaminated water or animals, is essential in guiding diagnostic and therapeutic decisions.

This case also highlights the importance of ongoing research into the pathophysiology of leptospirosis-associated GBS and the development of evidence-based treatment protocols. While IVIG remains the cornerstone of GBS treatment, the addition of antibiotics in cases with confirmed leptospirosis may offer significant benefits, as demonstrated in this patient. However, more extensive studies are needed to validate this approach and determine the optimal management strategy for such cases.

CONCLUSION

Recognizing leptospirosis as a potential antecedent for Guillain-Barré Syndrome (GBS) is vital, particularly in endemic areas. Early diagnosis and targeted treatment, as demonstrated in this case, can significantly enhance outcomes and minimize complications.

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