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CHIKUNGUNYA VIRUS ASSOCIATED GUILLAIN-BARRE SYNDROME WITH VARIABLE PRESENTATION: A CASE SERIES.

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ABSTRACT

Chikungunya Virus Is A Mosquito-borne Alpha Virus Which Occasionally Causes Neurologic Complications Including Guillain-barre Syndrome, Myelitis, Myopathies And Encephalitis. Pakistan Experienced Its First Chikungunya Outbreak In The Metropolis Of Karachi Officially Confirmed By World Health Organization In December 2016. During This Outbreak, Over 30,000 People Have Been Reported To Be Infected In Different Parts Of Karachi. We Report Four Cases Of Chikungunya Virus Infection Associated Guillain-barre Syndrome Having An Atypical Clinical Presentation And Variable Outcome. Each Case Presented As A Different Variant Of Gbs Including Acute Inflammatory Demyelinating Polyneuropathy, Acute Motor And Sensory Axonal Neuropathy And Pharyngeal-cervical-brachial.

KEY WORDS

Guillain-barre Syndrome; Chikungunya Virus; Pharyngeal-cervical-brachial; Acute Motor And Sensory Axonal Neuropathy; Acute Inflammatory Demyelinating Polyneuropathy; Pakistan

INTRODUCTION: Chikungunya Is A Mosquito-borne Arbovirus Which Presents With Rapid Onset Of Fever, Fatigue, Myalgia, Arthralgias And Rash(1). Neurological Manifestations Are Less Commonly Reported And Include Meningoencephalitis, Acute Flaccid Paralysis, Guillain-barré Syndrome, Myelitis, Seizures And Cranial Nerve Palsies(2, 3).

Guillain-barré Syndrome (Gbs) Is The Most Common Acute Immune-mediated Polyradiculoneuropathy Typically Presenting With Sensory Symptoms And Weakness Over Several Days, Often Leading To Quadriplegia. In Two-thirds Of Patients, Gbs Occurs After An Infection And Is Generally Considered Secondary To Immune-mediated Response. The Most Commonly Associated Infection Is C. Jejuni, While Other Common Infections Include Cytomegalovirus, Epstein-barr Virus, Mycoplasma Pneumoniae, And Haemophilus Influenza(4). However, Only A Few Cases Of Gbs Have Been Reported After Infection With Chikungunya Virus.

Pakistan Recently Experienced Its First Outbreak Of Chikungunya Virus In The Metropolis Of Karachi(5). Here We Report Our Experience With Four Cases Of

Acute And Severe Gbs Associated With Chikungunya Virus Infection From Pakistan. Each Case Presented As A Different Variant Of Gbs Including Acute Inflammatory Demyelinating Polyneuropathy (Aidp), Acute Motor And Sensory Axonal Neuropathy (Amsan) And Pharyngeal-cervical-brachial (Pcb). Although Gbs Has Been Reported With Chikungunya Virus Infection, To The Best Of Our Knowledge There Has Been No Report On Variants Of Gbs Such As Amsan And Pcb After Chikungunya Virus Infection. The Atypical Neurological Presentation Has Been A Challenge For Early Diagnosis And Timely Management, Therefore We Discuss The Clinical Course And The Subsequent Variable Outcomes Observed In These Cases.

PATIENT 1:

A 42-year-old woman with no prior co-morbid was admitted with a ten-day history of intermittent high-grade fever, myalgia, and severe generalized joint pain. The patient was conservatively managed as viral fever with symptomatic medications. Patient's fever gradually resolved by the sixth day of symptoms but her

joint pain continued to restrict her mobility. On day seven, she experienced numbness on the left lower extremity followed by right lower extremity in the later course of the day. Next day the patient developed bilateral lower limb weakness without any bowel or bladder symptoms. The patient's weakness was progressive involving upper limbs and also the face bilaterally with lower motor neuron type weakness. During the hospital course, the patient developed respiratory distress and was put on non-invasive BIPAP (Bilevel Positive Airway Pressure) support. The initial neurological exam revealed a power of 2/5 in bilateral upper limbs proximally and distally and 1/5 in the lower limbs along with weak flexors of the neck. Reflexes were absent in bilateral knee and ankle and +1 in the bicep and triceps bilaterally with a patchy sensory loss. Electrophysiological studies were done which showed acute motor sensory axonal neuropathy (AMSAN) shown in table 1. She underwent five sessions of plasma exchange, with a volume of two liters in each session. Weakness improved to a power of 4/5 in upper limbs and 3/5 in lower limbs with improved breathing after completion of five sessions. The IgM chikungunya antibody was detected in serum while CSF PCR was negative. The CSF DR showed albuminocytological dissociation (table 2). She was discharged and had complete recovery of power at one month seen in clinic follow-up.

PATIENT 2:

A 61-year-old gentleman who was a known case of diabetes, hypertension and dyslipidemia. The patient presented with numbness of bilateral feet and gait difficulties. He had a recent febrile illness 4-5 day prior to admission. He presented to neurology with unsteady gait with a normal neurological exam except for bilaterally absent ankle reflexes. He underwent an electrophysiological study that was suggestive of acute inflammatory demyelinating polyneuropathy (AIDP) (table1). CSF analysis showed Protein 60 mg/dl, CSF TLC 14 (Poly 60%), CSF GLUCOSE 77 mg/dl with serum glucose 118 mg/dl. The blood workup for fever including dengue and chikungunya serology, malarial parasite and blood culture were sent and chikungunya IgM was detected.

The patient had progressive weakness involving all four limbs followed by severe respiratory distress and had to be intubated. There was no meaningful recovery requiring continuous respiratory support after five cycles of plasma exchange. He was later given 5 doses of IVIG which did not improve his condition. He had to undergo tracheostomy due to the prolonged ventilator support and after a month-long complicated hospital

course, he eventually died.

PATIENT 3:

A 43-year gentleman presented with progressive limb numbness and weakness with gait difficulty for 20 days. The limb numbness initially began in bilateral lower limbs slowly involving the upper limbs in a glove and stocking pattern. He had a history of viral fever two weeks prior to the current symptoms. The fever was high grade, continuous and associated with arthralgia and myalgia.

The initial neurological exam revealed a muscle strength of bilateral upper limb proximally 5/5 and distally 4/5 and in bilateral lower limb proximally and distally 4/5. Reflexes were absent at bilateral knee and ankle joints and were +1 in the bicep and triceps bilaterally. Sensory examination revealed decreased sensation in bilateral lower limbs up to the mid-thigh and upper limbs up to mid forearm. The nerve conduction study with needle electromyography was suggestive of acute inflammatory demyelinating polyneuropathy (AIDP). CSF analysis showed albuminocytological dissociation as described in table 2. The chikungunya IgM came out to be positive. He had five sessions of plasma exchange and significant clinical improvement.

PATIENT 4:

A 36-year old right-handed lady with no prior co-morbid presented with sudden onset of difficulty in swallowing for three days followed by left arm weakness for a day. She had a high-grade fever associated with arthralgia and myalgia, severe in intensity, 3 months prior to this weakness. The initial neurological examination revealed a hypernasal speech, Right facial weakness of lower motor neuron type with symmetrical bulbar weakness. Her motor exam revealed a muscle power of -4/5 proximally and +4/5 distally in the left upper extremity. The rest of the muscle groups in all other extremities were within normal limits. The left biceps and triceps reflexes were diminished (+1) with the rest of the reflexes being normal (+2).

She was initially suspected as a case of brainstem stroke and underwent MRI brain which turned out normal. Meanwhile, the weakness progressed involving the neck muscles with a power of 2/5 in the neck flexors and extensors. The left upper limb proximally was 2/5 and distally 3/5 with absent biceps and triceps reflexes and there was involvement of the right upper limb proximally the muscle strength was -4/5 and distally 3/5 with diminished biceps and triceps reflexes. The progressive bulbar, neck and asymmetric upper

limb weakness with areflexia strongly suggested the diagnosis of pharyngeal-cervical-brachial (PCB) variant of Guillain-Barré syndrome. Myasthenia Gravis was ruled out by performing repeated nerve stimulation. A test for botulinum toxin in stool or serum was not performed.

Electrophysiological showed a delayed blink reflex bilaterally with rapid firing units on needle electrode examination (table 1). CSF analysis was within normal limits (table 2). Considering the prior history of fever

associated with generalized body ache prior to this weakness, Chikungunya IgM serology was sent which came out to be positive. She was started on IVIG (0.4g/kg/day) but during the first day of treatment she progressively developed respiratory distress with type 2 respiratory failures and had to be intubated. By day 4 of IVIG, she had regained some neck muscle strength and was extubated. She was later discharged with residual bulbar and facial weakness, which had completely resolved at one month of follow up.

Table – 1

Table 1: Details of the Electrophysiological findings on electromyography

Patient	SNAP's (microvolt)	Motor Nerve Latencies(ms)	CMAPS (millivolt)	Conduction Blocks	NCV(m/sec)	F waves	H reflex	Blink Studies	EMG	Diagnosis
1.	Median, ulnar and sural were NR	Right median prolonged and left peroneal was NR.	Low median ulnar, tibial and peroneal nerves.	Not seen	Slowing in median, ulnar, peroneal and tibial nerves.	All were NR except left ulnar	Absent	Not done	RFR	AMSAN
2.	Median, ulnar, radial were low with sural sparing.	Prolonged median, ulnar, tibial and peroneal in demyelinating ranges.	Low in median, ulnar, tibial and left peroneal nerves	Block in left posterior tibial nerve	Slowing in median, ulnar, peroneal and tibial nerves.	Prolonged Median, ulnar and tibial . Peroneal were NR	Absent	Prolonged Ipsi R1 bilaterally	RFR No denervation	AIDP
3.	Median, ulnar and sural were NR	Prolonged median, ulnar, tibial and peroneal in demyelinating ranges.	Low in median, ulnar, tibial and peroneal nerves	Block in right peroneal nerve.	Slowing in median, ulnar, peroneal and tibial nerves in demyelinating range.	All were NR	Absent	Not performed	RFR No denervation	AIDP
4.	Normal	Normal	Low left ulnar and left axillary nerve	None	All nerves were within normal limits.	All within normal limits	Absent	Prolonged Ipsi R1, Ipsi R2 and Contra R2 bilaterally	RFR No denervation	PCB

SNAPS-Sensory nerve action potentials

CMAPS-Compound muscle action potentials

NR-non-recordable

NCV-Nerve conduction velocities

EMG-Electromyography

RFR-Rapid firing units

AMSAN-Acute motor sensory axonal neuropathy

AIDP-Acute inflammatory demyelinating polyneuropathy

PCB-Pharyngeal cervical brachial variant

Ipsi-Ipsilateral

Table-2

Table 2: Details of Cerebrospinal fluid analysis

Patient	Glucose(mg/dl)	Protein(mg/dl)	Chloride(meq/L)	TLC	DLC	RBC's
1.	91	289	119	9	90% L 10% P	0
2.	77	60	133	14	60% P 40% L	1
3.	66	125	125	11	90% L 10% P	0
4.	82	31	124	2	NA	0

TLC-Total Leukocyte count DLC-Differential Leukocyte count P-Polymorph Neutrophils L-Lymphocytes

NA-Not applicable

DISCUSSION:

We report the first four cases of patients developing GBS after infection with the chikungunya virus from Pakistan. While cases of GBS after infection with chikungunya virus have been reported before, they remain rare. To the best of our knowledge 17 cases of GBS after infection with chikungunya virus have been reported (1, 6-9). There is no report of this feature from Pakistan in any of the recent or previous outbreaks. Additionally, while there are case reports on AMAN (acute motor axonal neuropathy) and AIDP (Acute inflammatory demyelinating polyneuropathy) variant of GBS associated with chikungunya virus, we report the first associated case of PCB (Pharyngeal-cervical-brachial) and AMSAN (acute motor and sensory axonal neuropathy) variants of GBS. The diagnosis of chikungunya virus infection was based on Anti- chikungunya virus immunoglobulin M (IgM). This is detected after 3-5 days of infections and remains elevated for 3-6 months(10). GBS was diagnosed on the clinical presentation along with findings on electrodiagnostic studies. The presence of Anti- chikungunya virus IgM and the absence of signs of other commonly associated infections and the outbreak of chikungunya virus was taken to mean that GBS was related to the chikungunya virus infection. Similar to our case the other reported cases happened during outbreaks of chikungunya virus and an increase in the incidence of GBS has been reported during these outbreaks(6). Hence index of suspicion for GBS should be kept high in places with chikungunya outbreak. Three of our four patients had mildly elevated

leukocytes in the CSF. This finding was not present in any of the other cases reported in literature.

All four patients in our series had a prior history of fever associated with either arthralgia or myalgia lasting for 2-12 days. There was a symptom-free interval between the chikungunya virus infection and the onset of weakness, the duration of which varied from 5 days to 3 months. This variation is comparable to the reported cases which show an onset of symptoms 3 days to 40 days after initially experiencing fever, myalgias and arthralgias(1, 6-9). The course was typically aggressive, with 3 of our 4 patients (75%) requiring ventilatory support with there being one mortality. In the previous 17 cases reported, 6 patients (35%) required ventilatory support. This figure is comparable to the rate of respiratory failure in GBS of one patient in three reported in the literature(11). There were no deaths reported in GBS associated with chikungunya in the previous reports.

Of note, was the diagnostic challenge encountered in the fourth case with pharyngeal-cervical-brachial (PCB) variant of Guillain-Barré syndrome. The predominant signs of brainstem weakness in our case suggested a stroke. This, along with unfamiliarity with PCB variant of GBS meant early diagnosis was focused on ruling out a stroke. In patients with a history suggestive of features not consistent with a stroke, PCB should be considered, as early diagnosis and treatment can improve outcome.

CONCLUSION:

Patients may present with GBS after infection with

chikungunya virus. This includes multiple variants of GBS including AIDP, AMAN, AMSAN and PCB. In places, with a chikungunya virus outbreak, there should be a high index of suspicion for GBS since this can lead to a timely diagnosis and treatment as the cases had a rapidly progressive disease course, especially progressing quickly to respiratory and bulbar symptoms.

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Salman Farooq; concept, data collection, data analysis, manuscript writing, manuscript review

Muhammad Imran; data collection, data analysis, manuscript writing, manuscript review

Ejaz Karim; data collection, data analysis, manuscript writing, manuscript review

Dureshahwar Kanwar; data analysis, manuscript writing, manuscript review

Muhammad Bilal Tariq; data analysis, manuscript writing, manuscript review