Original Article

Guillain-Barre Syndrome and Antibodies to Arboviruses (Dengue, Chikungunya and Japanese Encephalitis): A Prospective Study of 95 Patients Form a Tertiary Care Centre in Southern India

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Abstract

Objective: The aim of this study was to detect the presence of IgM antibodies against dengue (DEN), chikungunya (CHIK) and Japanese encephalitis (JE) in the serum and CSF of patients with Guillaine-Barre syndrome (GBS). **Methods:** GBS patients (>12 years of age) were included after informed consent. Data on history, clinical manifestations, treatment details, and outcome were collected. Serum and CSF were tested for IgM antibodies against DEN, CHIK, and JE. **Results:** From April 2018 to December 2019, 95 patients were included in this study. Anti-arboviral IgM antibodies were detected in 30 patients (31.5%) (CSF 11, serum 13, both CSF and serum 6). Serum IgM antibody was present in 19 patients (JE 8, DEN 5, CHIK 2, more than 1 virus 4). Of the 66 patients who underwent CSF studies, antibodies were present in 17 (CHIK 14, DEN 1, more than 1 virus 2). Antibody positivity did not affect the outcome of GBS. **Conclusion:** One-third of the GBS patients had evidence of recent infection by arboviruses. This suggests that DEN, CHIK, and JE could be the inciting event for GBS in endemic regions.

Keywords: Arboviruses, Chikungunya, Dengue, Guillain-Barre syndrome, Japanese Encephalitis

Introduction

Guillaine-Barre syndrome is an immune-mediated polyradiculoneuropathy that classically presents with areflexic ascending paralysis, sometimes causing respiratory muscle weakness. Following an infection, the antibodies against the pathogen cross react with the gangliosides on the myelin leading to demyelination (rarely axonal damage). The organisms that cause the initial infection include Campylobacter jejuni, influenza, HIV, and recently Zika.[1]

Arboviruses are viruses that are transmitted by insects. The important ones include dengue, chikungunya, Japanese encephalitis, and Zika. Though JE is an important cause of encephalitis and neurological complications have been reported with DEN and CHIK, their role in triggering GBS has not been well documented. Zika has been implicated in GBS by studies from French Polynesia and South America.[1] However subsequent studies in South America showed that the Zika outbreak occurred along with DEN and CHIK coinfections and that co-existing CHIK infection increased the risk of GBS due to Zika.[2]

Since GBS is an immune-mediated condition, the virus may not be detected at the onset of GBS, except Zika which can be detected in the urine.[3] Hence, detection of IgM antibodies, especially in the CSF, has been taken as evidence to show that the arbovirus is triggering GBS.[2]

GBS following DEN, CHIK, and JE are mostly restricted to case reports/series or small retrospective studies. Though India has a high burden of arboviral infections, we could not find any study that looked into the association of arboviruses and GBS. Hence this study was carried out to determine the presence of IgM anti-arboviral antibodies in GBS patients.

Materials and Methods

This was a prospective study done from April 2018 to December 2019 in the department of medicine, at a tertiary care center in southern India. Institute ethics committee approval was obtained. All consecutive patients (>12 years), diagnosed as GBS (as per Brighton Criteria)[4] were included. Those who were treated elsewhere and referred were excluded.

Data on demographic profile, symptoms, clinical findings, treatment details, and outcome at discharge were collected. Using Hadden criteria, patients were classified as AIDP,

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AMAN, AMSAN or Miller Fisher variants. CSF was analyzed for albumin cytological disassociation. Ethics approval obtained on 29/6/19.

Testing for arboviruses

Centrifuged serum and CSF were stored at -20 to -80 C. The following kits were used to detect IgM antibodies: IgM Capture ELISA (NIV, Pune, India) for DEN and CHIK, IgM Capture ELISA (MAC ELISA; InBios) for JE.

Statistical analysis

The independent variables analyzed were antiDEN positivity, antiCHIK positivity, antiJE positivity in serum or CSF, and type of GBS. The outcome variable was the presence or absence of a poor outcome. All the variables were analyzed by Fisher's exact test of statistical significance using the statistical package for the social sciences (SPSS) software, version 19.0 (IBM).

Results

A total of 95 patients (males-60, females- 35) were included in this study. The cases were evenly distributed across the year except for 2 peaks - January 2019 (n = 10) and September 2019 (n = 14).

45 (47%) patients gave history of infection preceding GBS (acute gastroenteritis-19, fever-19). No one had a confirmed diagnosis of recent arboviral infections.

Ascending type of motor weakness was the most common manifestation. Facial nerve involvement was present in 27 patients. The clinical and laboratory features are summarized in Table 1.

Albumin cytological dissociation was present in 57 of the 66 patients (87%) who underwent lumbar puncture. Of the 87 patients who underwent NCS, 33 were classified as AIDP (38%).

Plasmapheresis was done in 47 patients, IVIg was given in 27 patients, and 10 patients received both Plasmapheresis and IVIg. The remaining 11 improved spontaneously. 26 patients required mechanical ventilation. 2 patients died and 8 patients had poor outcome (Modified Hughes score 3 and more)[5] at the end of 3 months [Table 2].

Antibodies to arboviruses [Table 3]

IgM antibodies were detected in the serum and/or CSF in 30 patients (31.5%) (CSF -11, serum-13, both CSF and serum -6). 6 patients had antibodies to more than 1 virus (serum-4 patients and 2 in CSF). In the serum, anti JE was the most common, while anti-CHIK was most common in CSF.

Anti CHIK IgM was positive in 19 (serum -3, CSF- 16), anti-DEN IgM in 12 (serum- 9, CSF-3) and anti JE IgM in 12 (serum -11, CSF- 1)

19 serum samples were positive to anti-arboviral antibodies (JE-8, DEN-5, CHIK-2, DEN and JE-3, DEN and CHIK-1). Similarly, 17 CSF samples were positive for antibodies (CHIK-14, DEN-1, DEN and CHIK-1, DEN, CHIK and JE- 1)

Table 1: Clinical features at admission

Characteristic	Total $n=95$	IgM antibody present $n=30$	IgM antibody absent $n=65$	*P*
Mean age	43.43			
Males	60	17	43	0.493
History of Preceding infection	44 (46%)	15	29	0.663
Acute gastroenteritis	18	4	14	
Upper respiratory tract infections	6	2	4	
Undifferentiated fever	19	9	10	
Rash	1	0	1	
Degree of motor system involvement at time of admission	88 (92.6)	26	62	0.202
Lower limb Weakness	70	21	49	0.621
Upper limb weakness	2	1	1	0.534
All 4 limb Weakness	15	4	11	0.769
Bulbar weakness	1	0	1	
Modified Hughes score				
During admission				
1	4	2	2	
2	29	9	20	
3	35	12	23	
4	25	7	18	
5	2	0	2	
Cranial Nerve involvement	27 (28.4)	12	15	0.141
Facial nerve	21	10	11	
Glossopharyngeal or vagus nerve	13	2	11	
Other cranial nerves	3	1	2	
Sensory symptoms	16 (16.8)	6	10	0.569
Cerebellar symptoms	3 (3.2)	1	2	
Autonomic dysfunction	7 (7.3)	3	4	0.675
Brighton level of certainty				
1	57	20	37	
2	36	10	26	
3	2	0	2	

6 patients had antibodies in serum and CSF. All 6 CSF were positive for CHIK while in the serum, JE – 4, CHIK -1 and DEN-1.

Clinical features of antibody-positive patients [Table 4]

Axonal pattern was more common than demyelination (20 and 8 respectively). 9 patients needed mechanical ventilation. There was no difference in the outcome as compared to those who tested negative for antibodies. There was no mortality in antibody-positive group.

Discussion

Even though DEN and CHIK have been responsible for large outbreaks in south Asia and South America, it was ZIKA

Table 2: Management and outcome of the GBS patients

	Total *n*=95	IgM antibody present *n*=30	IgM antibody absent *n*=65	*P*
Treatment				
IVIg	27 (28)	10	17	
PLEX	47 (49.5)	14	33	
PLEX + IVIg	10 (10.5)	3	7	
Spontaneous recovery	11 (12)	3	8	
Mechanical ventilation	26 (27.4)	9	17	0.805
In hospital complications	32 (33.7)	11	21	0.816
Complications (*n*=32)				
Ventilator associated pneumonia	17 (53)	7	10	
Hospital-acquired infections	19 (59)	6	13	
Deep venous thromboembolism	6 (19)	2	4	
Severity of illness at time of discharge (modified Hughes score)				
1	39	12	27	
2	42	11	31	
3	12	7	5	
6	2	0	2	
In hospital death	2	0	2	0.140
Severity of illness at third month follow up post-discharge (modified Hughes score)				
0	11	6	5	
1	57	13	44	
2	17	6	11	
3	8	5	3	0.404
Poor outcome	10	5	5	

Table 3: Results of Anti- Arboviral IgM studies

Arboviral IgM Positive	Serum	CSF
Overall		
DEN IgM (12)	9	3
CHIK IgM (19)	3	16
JE IgM (12)	11	1
Patterns of IgM positivity[1]		
DEN	5	1
CHIK	2	14
JE	8	0
DEN + CHIK	1	1
DEN + JE	3	0
CHIK + JE	0	0
DEN, CHIK and JE	0	1
Total	19	17

[1]Some patients had antibodies to more than one virus

that had revived interest in the neurological complications of arboviruses especially GBS.[1] The first report of Zika causing GBS was from French Polynesia[6] followed by South American countries.[3] However, the Zika outbreaks of south America were later found to be associated with coexisting DEN and CHIK outbreaks, suggesting that GBS might not be only due to Zika but also to DEN and CHIK.

In a prospective study from northeast Brazil,[7] of the 148 patients with neurological illness following presumed arboviral infections, 47 patients had GBS. Dual infection with CHIK and ZIka had more severe outcome than mono-infection. Similarly, in a study of 71 of GBS patients, from northern Brazil,[2] Zika was present in 25, CHIK in 8, ZIKA plus CHIK in 14 and DEN in 1. The authors suggested that CHIK too is an important cause of GBS and coinfection with Zika might increase the severity of GBS. However, in a recent study of 97 patients from Mexico,[8] Zika (8) and Dengue (4) were found to have a stronger association with GBS than CHIK (1).

Large nationwide surveys using IgG antibodies have shown high seroprevalence of DEN (48·7%)[9] and CHIK (18·1%)[10] in India and the rates are even higher in southern India (DEN-76·9%, CHIK -43·1%), especially in younger population. Despite such high prevalence, Indian data on the association of GBS and arboviral infections is very scarce.

CHIK and GBS

CHIK has been shown to cause multiple neurological complications, including GBS.[11]

The first large study on neurological complications following CHIK was from the 2006 outbreak in Nagpur, western India.[12] 49 of 300 confirmed CHIK patients developed neurological complications including 14 GBS patients (0.046%). All had AIDP variant and had recovered completely.

In the 2016 outbreak from Delhi,[13] 42 of the 290 patients with confirmed CHIK infection developed neurological complications with 3 cases of GBS (0.01%).

In our study, antibodies to CHIK were present in 19 samples (CSF-16 and serum 3). Interestingly, of the 6 patients had antibodies in both serum and CSF, all 6 CSF were CHIK positive but only 1 serum was CHIK positive. This suggests that CHIK has a stronger association with GBS as compared to DEN and JE. This is similar to the studies from Brazil which have shown that along with ZIKA, CHIK is also an important risk factor for GBS.[2,7,14]

Dengue and GBS

GBS is an uncommon complication of dengue.[15] Most of the literature is restricted only to case reports/series.[15] In our study 12 patients had IgM antibodies to Dengue (serum -9, CSF-3). In a study from Lucknow[16] out of 26 patients with neurological manifestations due to Dengue, 3 were noted to have GBS. In a study from Malaysia,[17] 19 out of 95 GBS patients had anti-dengue IgM antibody in the serum. Most of the patients had flu or diarrhea prior to GBS and none had established Dengue infection. In our study, none of the patients had documented Dengue or chikungunya, prior to GBS. This

Table 4: Features of Arboviral IgM positive patients

Arboviral IgM	NCS (n=87)		Mechanical Ventilation	Outcome (expired)
	Axonal	Demyelination		
CHIK (n=18)[1]	13	4	6	0
DEN (n=12)	10	2	4	0
JE (n=12)	8	4	5	0
Overall, any antibody positive (n=28)	22	7	9	0

[1]87 of 95 patients had undergone NCS

may be because most arboviral infections are asymptomatic or have mild nonspecific symptoms.[18]

Japanese Encephalitis and GBS

Literature on GBS following JE is restricted to case reports. In our study, IgM anti-JE was present in 12 patients (11-serum, 1- CSF). In a recent prospective study from China,[19] of 161 patients with JE, 47 were diagnosed to have GBS. All had IgM antibodies in serum and CSF while virus was isolated only in 1 patient. Most of the patients had AMAN/AMSAN on NCS. Uncommonly, the death rate was very high in this cohort (21 of 47, 44.6%). In our study, there was no mortality in the antibody-positive cohort.

Positivity to more than one arbovirus

6 patients had IgM antibodies to more than 1 virus. Also some had antibody to one arbovirus in serum but antibody to another virus in CSF. The following reasons might explain this phenomenon.

1. There is a high degree of cross-reactivity among the arboviruses. Plaque Reduction Neutralizing Test (PRNT)[20] is used to identify the specific virus against which the antibodies are produced. But it is cumbersome and not widely available.
2. Acute infection by one arbovirus (Zika) can trigger anamnestic response leading to IgM antibodies against another arbovirus (Dengue) in a patient who would have had Dengue infection in the past.[20]
3. There can be more than 1 viral infection at the same time especially in highly endemic regions.[2]

Conclusion

Approximately 30% of the GBS patients had IgM antibodies to DEN/CHIK and/or JE in the serum/CSF. This suggests that arboviral infections could be responsible for a significant number of GBS patients especially in high endemic countries like India.

Limitations

Antibodies to Zika virus could not be studied due to delay in procuring the kit. CSF analysis was not done in all patients.

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Conflicts of interest

There are no conflicts of interest.

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