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Incidence, Prevalence and Clinicopathological Profile of Hepatitis-E Virus in Patients with Guillain-Barre Syndrome: A Prospective Study.

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ABSTRACT

Background: Guillain-Barre syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy that results in rapidly progressive symmetric ascending motor paralysis with hypotonia and areflexia. GBS is known to be preceded by a bacterial or viral infection by 1-3 weeks. The common triggering infections are Campylobacter jejuni, cytomegalovirus, Epstein-Barr virus and mycoplasma pneumonia. Association of hepatitis E virus with GBS has been topic of interest amongst many researchers particularly in developing countries where there are frequent outbreaks of epidemics of hepatitis E infection. **Methods:** This was a prospective study in which 34 patients admitted with symmetric ascending paralysis and were diagnosed to be having GBS were included on the basis of a predefined inclusion and exclusion criteria. Demographic details and history of antecedent illness was noted in all the cases. Thorough clinical examination was done in all the cases. Nerve conduction velocity and EMG was also done in all the cases. Asbury's criteria was used for the diagnosis of GBS. The incidence, prevalence and clinic-pathological profile of hepatitis-e virus in patients with GBS was studied. For statistical purposes p value less than 0.05 was taken as statistically significant. **Results:** Out of 34 patients there were 21 (61.76%) males and 13 (38.24%) females with M:F ratio of 1:0.61. The mean age of male patients was found to be 37 +/- 14.24 years whereas the mean age of female patients was 35.61+/- 12.31 years. There was no statistically significant difference in the mean age of affected males and females. In history of presenting illness all 32 (94.12%) patients had limb weakness. The uncommon symptoms included autonomic imbalance (8.82%) and gait abnormalities (2.94%). History of antecedent illness revealed that 6 patients (17.65%) had fever and 4 (8.82%) patients had history of respiratory illness 3 weeks before the onset illness. On clinical Examination quadriparesis with cranial nerve involvement with neck & truncal weakness (47.06%) and pure quadriparesis (35.29%) were common clinical features in studied cases. Acute inflammatory demyelinating polyneuropathy (AIDP) was the most common type of demyelination pattern seen in studied cases. Out of 34 patients 11 patients were found to have HEV-IgG positivity whereas HEV-IgM was not positive in any of the studied cases. **Conclusion:** GBS is an important extrahepatic consequence of hepatitis E infection particularly in developing countries and must be considered all the patients particularly those having elevated liver enzymes. HEV serology will be helpful in confirmation of the diagnosis. In our study it is concluded that chronic HEV infection is associated with GBS.

Keywords: Guillain-Barré syndrome, Hepatitis E virus, Serology, Elevated Liver Enzymes, Chronic HEV infections.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy that results in rapidly progressive symmetric ascending motor paralysis with hypotonia and areflexia accompanied by aleucocytic cerebrospinal fluid with elevated protein level.[1] GBS may clinically present in several forms and can be divided into subtypes such as Acute inflammatory demyelinating polyneuropathy (AIDP), Acute motor axonal neuropathy (AMAN), Acute motor–sensory axonal neuropathy (AMSAN) and Miller Fisher syndrome (MFS) depending upon neurological involvemen.[2] GBS is often preceded by a bacterial or viral infection and in over two third of cases infection precedes onset of neuropathy by 1-3 weeks. Most commonly identified triggering agents are Campylobacter jejuni, followed by cytomegalovirus, Epstein-Barr virus and mycoplasma pneumonia. In some studies HIV, shigella, clostridium, haemophilus influenza as well as hepatitis A, B and C are also identified as triggering agents.[3]

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There is a lot of controversy about etio-pathogenesis of GBS and the exact mechanism by which preceding bacterial or viral infection causes GBS is not completely known. It is thought that the infection evokes an immune response that cross-reacts with peripheral nerve components via molecular mimicry.[4] This molecular mimicry between offending viral agents and myelin of the host is thought to be responsible for production of antibodies against an infectious organism that shares epitopes with the host's peripheral nerves causing demyelination.[5] The nature of the epitope in most of the instances is thought to be a glycolipid.

The patients of GBS usually present with symmetrical ascending paralysis, hypotonia and loss of deep tendon reflexes. The other features may include diplopia, dysarthria and dysphagia due to cranial nerve palsies.[6] Pain and paraesthesia may also be seen in some cases. The most dreadful feature is respiratory paralysis which invariably will prove fatal unless assisted ventilation is provided.[7] Electromyography (EMG) and nerve conduction studies (NCS) are important for diagnosis and show features suggestive of demyelination. The management of GBS usually include supportive care along with intravenous immunoglobulin or plasma exchange. In majority of the hospital nowadays IVIG are preferred over plasma exchange for ease of administration.[8] There is no benefit of giving steroids and administration of corticosteroids is found to in fact delay the recovery and hence they are no longer recommended in patients with GBS. Long term rehabilitation and physiotherapy may be required in some cases.[9]

Hepatitis E virus (HEV) infection is one of the most common causes of acute viral hepatitis in developing countries including India and reported to be an important public-health problem causing substantial morbidity. The mode of transmission usually is through contaminated drinking water or consumption of uncooked meat. The disease is usually self-limiting and in majority of the cases there is a complete recovery. The mortality of hepatitis E is less than 5% but high mortality rates are reported in pregnant women.[10] Rarely it may cause complications such as acute fulminant hepatitis, cirrhosis, hepatic fibrosis and neurological complications such as GBS, cranial nerve palsies, myeloencephalitis and amyotrophy.[11]

Presence of hepatitis E should be ruled out in patients with GBS particularly in individuals presenting with ascending paralysis and elevated liver enzymes. We conducted this study to study the incidence, prevalence and clinic-pathological profile of hepatitis-e virus in patients with GBS.

MATERIALS AND METHODS

This was a prospective cohort study in which 34 patients admitted with symmetric ascending paralysis and were diagnosed to be having GBS were included on the basis of a predefined inclusion and exclusion criteria. The institutional ethical committee approved the study and informed consent was obtained from the patients included in this study. The study was conducted in the department of neurology of a tertiary care medical college situated in an urban area over a period of 2 years. Demographic details of all the patients such as age, sex, education, residential address and occupation was noted down in a proforma. A detailed history was taken in all the cases. A thorough clinical examination followed by neurological examination (sensory and motor) was done in all the cases. Baseline investigations such as complete blood count, hepatic and renal function tests were done in all the cases. Electromyography (EMG) and nerve conduction velocity (NCV) was also done in all the cases. CSF examination was done in selected cases only. Hepatitis E serology was done in all the cases. The patients were divided into subtypes on the basis of clinical findings and investigations. Asbury's criteria was used for the diagnosis of GBS12. IVIg were given to the patients whenever necessary. Patients were discharge with an advice to continue physiotherapy and were advised regular follow up. The data was tabulated using Microsoft office. Statistical analysis was done using SSPE 16.0. For statistical purposes p value less than 0.05 was taken as significant.

Inclusion criteria:

1. Patients fulfilling Asbury's diagnostic criteria for GBS
2. Those who have given informed consent to be part of the study

Exclusion Criteria:

1. Those who refused consent
2. Patients having neuropathy mimicking GBS in presentation such as subacute inflammatory demyelinating polyneuropathy,chronic inflammatory demyelinating polyneuropathy, Toxic neuropathies, metabolic neuropathies, Porphyric neuropathy and acute disseminated encephalomyelitis

RESULTS

Total 34 patients diagnosed with GBS were included in this study. Out of 34 patients there were 21 (61.76%) males and 13 (38.24%) females with M:F ratio of 1:0.61.

The demographic details showed that majority of the patients were residing in 26 (76.47%) rural areas where as 8 (23.53%) patients belonged to urban areas. The analysis of socio-economic status of the patients showed that out of studied cases most of the patients belonged to middle class (35.29%), followed by lower middle class (29.41%) and lower class (26.47%) . The study of educational

qualification of the patients showed that 12 (35.29%) patients studied up to HSC whereas 10 (29.41%) and 6 (17.65%) patients were qualified up to SSC and graduation.

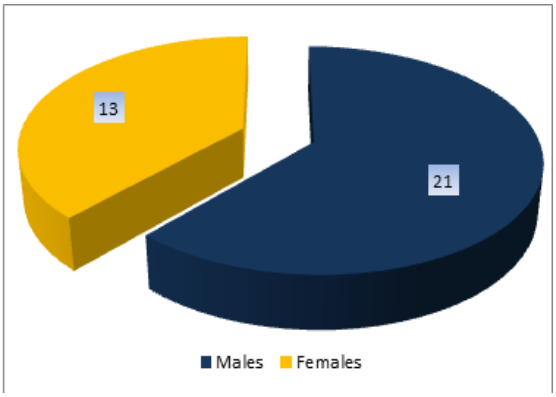

Figure 1: Gender Distribution of the studied cases.

Table 1: Demographic Details of the studied cases.

		No of Patients	Percentage
Residence	Urban	26	76.47%
	Rural	8	23.53%
	Total	34	100 %
Socio-Economic Status	Upper Class	1	2.94%
	Upper Middle	2	5.88%
	Middle	12	35.29%
	Lower Middle	10	29.41%
	Lower	9	26.47%
	TOTAL	34	100%
Educational Qualification	Below SSC	4	11.76%
	Upto SSC	10	29.41%
	Upto HSC	12	35.29%
	Graduates	6	17.65%
	Post-Graduates	2	5.88%
	Total	34	100%

Table 2: Gender wise distribution of the age groups of the studied cases.

Age Group	Males		Females	
	No Of Patients	Percentage	No Of Patients	Percentage
Up to 20 years	4	11.76%	3	8.82%
21-30 years	3	8.82%	1	2.94%
31-40 years	4	11.76%	2	5.88%
41-50 years	7	20.59%	6	17.65%
51-60 years	2	5.88%	1	2.94%
> 60 years	1	2.94%	0	0.00%
Total	21	61.76%	13	38.24%
Mean Age	37 +/- 14.24 years		35.61+/- 12.31years	
P= 0.77 (Not Significant)				

The analysis of age groups of the patients showed that the most commonly affected age group was between 41-50 years of age (38.24%) followed by less than 20 years (20.59%) and 31-40 years (17.65%). The mean age of male patients was found to be 37 +/- 14.24 years whereas the mean age of female patients was 35.61+/- 12.31 years. Overall mean age was found to be36.30 +/- 0.98 years. There was no statistically significant difference in the mean age of affected males and females.

In history of presenting illness all 32 (94.12%) patients had limb weakness. After limb weakness the other common features included sensory symptoms (47.06%) and cranial nerve palsies (47.06%). The uncommon symptoms included autonomic imbalance (8.82%) and gait abnormalities (2.94%).

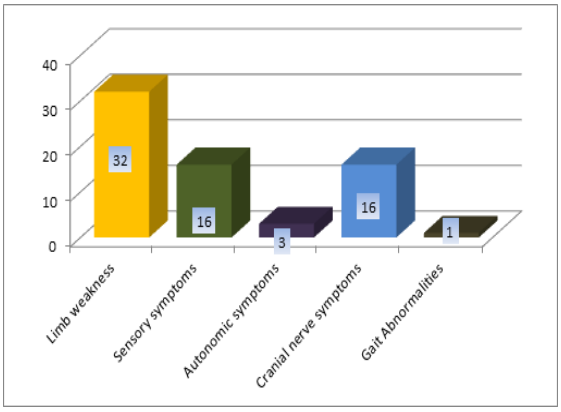

Figure 2: Presenting illness in the studied cases.

A careful history of antecedent illness history revealed that 6 patients (17.65%) had fever and 4 (8.82%) patients had history of respiratory illness 3 weeks before the onset illness. History of jaundice, snake bite and diarrhoea was present in 1(2.94%) patient each. 21 (61.76%) patients didn't give any history of antecedent illness of any kind.

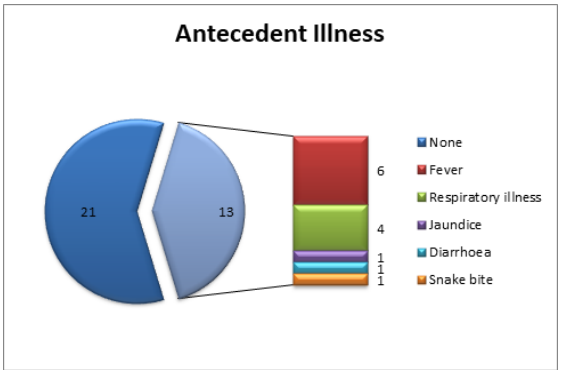

Figure 3: Antecedent Illness in the studied cases.

Clinical examinations of the studied cases showed that out of 34 patients 16 (47.06%) patients had quadriparesis with cranial nerve involvement with neck & truncal weakness whereas pure quadreparesis was seen in 12 (35.29%) patients. 4 (11.76%) patients had Lower limb predominant GBS, 1 (2.94%) patient had pure sensory involvement, although it has been reported in very

less number around the globe, we had 1 patient with pure sensory involvement with NCS corroborative to the clinical finding, 1 (2.94%) patient had ataxia with cranial nerve involvement.

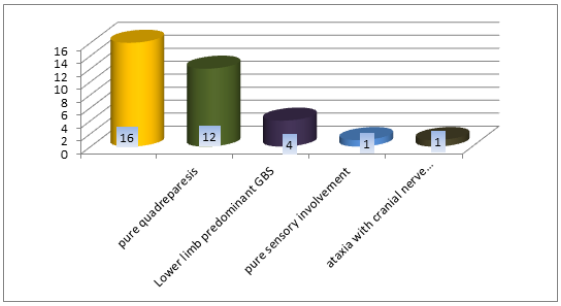

Figure 4: Clinical Findings in the studied cases.

Guarded cerebrospinal fluid analysis was done in 10 patients in that 7 people had albumin-cytological dissociation. Serum electrolytes were done in all 34 patients and it was found to be in normal range in 27 patients whereas 7 patients had low serum potassium level. Liver function tests were done in all patients and all had normal values except one patient who had mild elevation of liver enzymes.

Table 3: Investigations in the studied cases.

		No of Patients	Percentage
CSF Examination	Normal	3	30 %
	Albuminocytological Dissociation	7	70 %
	Total	10	100 %
Serum Electrolytes	Normal	27	79.41%
	Hypokalemia	7	20.59%
	Total	34	100%
Liver Function test	Normal	33	97.06%
	Raised Enzymes	1	2.96%
	Total	34	100%

Nerve conduction studies showed acute inflammatory demyelinating polyneuropathy (AIDP) pattern in 27 (79.41%) patients. Acute motor axonal neuropathy (AMAN) and Acute sensory motor axonal neuropathy (ASMAN) type of neuropathy was seen in 5 (14.71%) and 3 (8.82%) patients respectively.

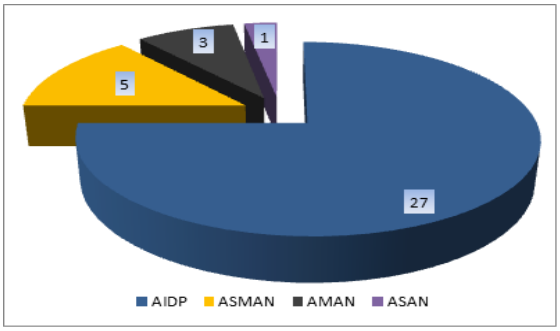

Figure 5: Nerve conduction velocity test in the studied cases.

Hepatitis E serology was done in all the cases. Out of 34 patients 11 patients were found to have HEV-IgG positivity whereas HEV-IgM was not positive in any of the studied cases.

Table 4: Hepatitis E virus Serology.

		No of Patients	Percentage
IgG	Positive	11	32.35 %
	Negative	23	67.65%
	Total	34	100 %
IgM	Positive	0	0 %
	Negative	34	100%
	Total	34	100%

IVIg was given to selected 18 (52.94%) patients who had rapid progression of symptoms and impending respiratory failure. Other 10 (29.41%) patients recovered from the disease without any IVIg treatment. IVIg administration was planned in remaining 6 (17.65%) patients but they were referred to higher centres for further management in view of rapid progression of the disease. Out of 34 patients 28 (82.35%) patients' completely recovered and 6 patients were referred to higher centre. There was no mortality in any of the studied cases.

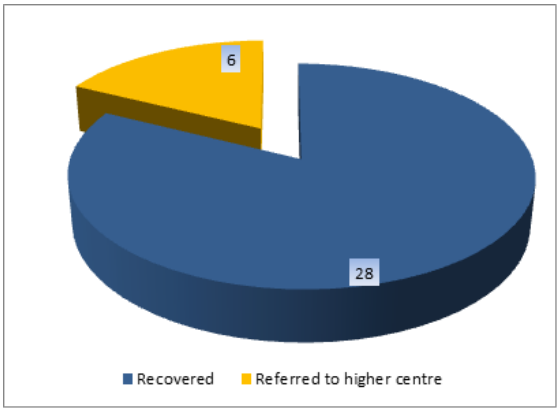

Figure 6: Outcome of the Studied cases.

DISCUSSION

We conducted this prospective study to study the incidence, prevalence and clinicopathological profile of hepatitis-e virus in patients with GBS. In this study there was a male predominance with a M:F ratio of 1:0.61. Males are affected more commonly than females and many studies have reported this predominance. Sudulagunta SR analysed data of 1,166 patients admitted with GBS or presented to outpatient department.[13] The authors found that males (605) were more commonly affected than females (561). Similar male preponderance was reported by the authors such as Blum S et al,[14] (M:F ratio of 1.61:1) and Cheng Q et al15 (M:F ratio of 1.61:1).

The mean age of the patients in our study was found to be 36.30 +/- 0.98. The mean age of the studied cases in our study was found to be comparable to the studies conducted by various other authors. The mean ages of male and female patients were 37 +/-

14.24 years (10-74 yrs) and 35.61+/- 12.31 years (20-60 yrs), respectively. Arami et al conducted a prospective population based study of 76 patients with a diagnosis of GBS. The authors found mean age of the studied cases to be 34.43 years (SD 23.9) (range 6 years to 79 years).[16]

In our study 26 patients hailed from rural region and 8 patients from urban region, on comparing with study by Arami et al,[16] on Epidemiology and characteristics of Guillain-Barré syndrome in the northwest of Iran they found that no significant difference between urban (5.1±5.6) and rural patients (5.7±7.5 days, P=not significant). The results in our study were different from that of Arami et al,[16] and in our study majority (76.47%) patients were found to be residing in rural areas.

In our study the analysis of signs and symptoms of the cases showed that 32 (94.12%) patients had limb weakness, 16 had sensory symptoms, 3 had autonomic symptoms, 16 (47.06%) patients had cranial nerve symptoms and 1 patients had unsteadiness of gait (2.94%). In antecedent illness history 6 (17.65%) patients had fever, History of jaundice, snake bite [who received antivenom] and diarrhoea was present in 1(2.94%) patient each. 4 (11.76%) patients there was history of respiratory illness 3 weeks before the onset illness. In the study conducted by Shrivastava M et al,[17] Flu-like illness as evidenced by fever and cough was found to be the most common antecedent event preceding GBS in 24.2% (n=16) followed by gastroenteritis in 13.6 % (n=9). One patient each presented with the uncommon antecedent events as food poisoning and malarial fever. All patients developed neurological illness within two weeks of the onset of the symptoms. Majority of the patients were admitted to the hospital with progressive weakness in all four limbs (quadriparesis) in 74.2 per cent patients (n=49) as a common clinical feature followed by paraparesis in 25.8 per cent patients (n=17). Dysphagia and respiratory distress were noted in eight patients (12.1%) each. None of the patients were found to have bladder and bowel involvement.

In the total 34 patients studied by us AIDP was found to be most common type of demyelination which was seen in 27 (79.41%) patients. The other patterns of demyelination were AMAN in 5 (14.71%) patients and AMSAN variant in 3(8.82%) patients. In a study by Zheng X et al among the 47 cases with available details of nerve conduction studies, 23(48.9%) had experienced AIDP.[18] Other variants of GBS, including AMAN, AMSAN, and sensory neuropathy, were also detected, similar type of observation were made in a study by Jo YS et al in their study.[19]

A study on Guillain-Barré syndrome associated with preceding hepatitis E virus infection by van den Berg B et al,[20] showed an increased ratio of anti-HEV immunoglobulin (Ig) M antibodies in 10 patients with GBS (5.0%) compared with 1 healthy control (0.5%, odds ratio 10.5, 95% confidence interval 1.3-82.6, p = 0.026). HEV- RNA was detected in blood from 3 of these patients and additionally in faeces from 1 patient. 70% of anti-HEV IgM-positive patients had mildly increased liver function tests. All CSF samples tested negative for HEV- RNA. The presence of anti-HEV IgM in patients with GBS was not related to age, sex, disease severity, or clinical outcome after 6 months. Their study concluded that in the Netherlands, 5% of patients with GBS have an associated acute HEV infection. In contrast to their study we found that had out of the 34 patients 11 patients had IgG antibody positivity alone with none of the patient having IgM antibody present in their serum. These findings suggest that significant number of our patients had exposure to Hepatitis E virus.

CONCLUSION

GBS is an important extrahepatic consequence of hepatitis E infection particularly in developing countries. Hepatitis E infection must be considered in all the cases presenting with features of GBS (ascending paralysis, hypotonia, loss of deep tendon reflexes and cranial nerve involvement) and elevated liver enzymes. The serological tests for HEV (HEV IgM and HEV IgG) can be helpful in confirming the HEV infection in these patients. In our study it is concluded that significant number of patients had anti-HEV igG positivity which denotes that these patients had exposure to HEV in the past which may have temporal association for causing GBS, This fact should be further confirmed by future studies.

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