Original Article

Children with Guillain-Barre Syndrome: A Comparison between AIDP and AMAN variants among Patients admitted in a Tertiary Care Hospital.

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Abstract

Background: Guillain-Barre syndrome (GBS) is the leading cause of acute flaccid paralysis in children. This study was aimed to compare the clinical spectrum and short-term outcome of children with acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) subtypes of GBS in children.

Methods: The study was a prospective cohort study done in a tertiary neurology hospital for 3 years. Children under 18 years of age fulfilling the Brighton diagnostic criteria for GBS were enrolled in the study. Based on the nerve conduction study, patients were subclassified as AIDP, AMAN, AMSAN, and others. Finally, a comparison was done in children with AIDP and AMAN subtypes.

Results: A total of 102 children have fulfilled the Brighton diagnostic criteria of GBS during that study period. Among them, 83 children were included in the final analysis as NCS findings suggestive of AIDP and AMAN were found in 29(28.43%) and 54(52.94%) of cases respectively. No patient died in this cohort and follow-up was done at 3 months after discharge. A comparison of clinical data between the two groups revealed similar clinical features in most of the cases. The mean age difference between the two groups was statistically significant and AIDP was found to be more frequent in the 1-5 years age group. There was a significant association between gastroenteritis and AMAN subtypes. On symptom analysis, pain and tingling sensation were found predominantly in AMAN subtypes.

Conclusions: AMAN was the commonest GBS subtypes in children. AIDP was more frequent in the younger age group. Children with AMAN appeared to have higher short-term morbidity and slower recovery than those with AIDP.

Keywords: Children, Guillain-Barre syndrome, AIDP, AMAN, Bangladesh

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Introduction:
Guillain-Barre syndrome (GBS) is an immunologically mediated disorder of the peripheral nerves triggered mostly by antecedent infections. It is the most common cause of the acute flaccid type of weakness occurring in all ages. GBS has been well characterized in pediatric patients in a good number of studies. The predominant complaints of children with GBS at presentation are difficulty in walking due to weakness of limbs, pain, and tingling. Some features are reported to have been more common in pediatric GBS like autonomic dysfunction (fluctuating blood pressure, tachy- and brady arrhythmias, abnormal sweating, papillary abnormalities). In addition to clinical and laboratory findings, electrophysiology plays an important role in establishing diagnosis and determination of subtypes. Among the subtypes, two are more common— acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor axonal neuropathy (AMAN). There is a considerable geographical variation of these subtypes. AIDP has been reported to be the commonest subtype in North America and Europe, while AMAN is the predominant subtype in Mexico, Bangladesh, and China. There are a good number of research articles on childhood GBS with only a few comparing the two major subtypes. Some studies have reported differences, while some could not find any. No such comparison in children has been reported from Bangladesh. Therefore, in this study, we have planned to compare AIDP and AMAN variants of GBS in children.

Material and methods:
This was a prospective cohort study done in the Department of Pediatric Neurology of the National Institute of neurosciences and hospital for a period of 3 years from July 2017 to June 2020. The study was approved by the ethical review committee of the hospital and informed written consent of the parents was taken before starting the study. Each consecutive child under 18 years of age fulfilling the Brighton diagnostic criteria for GBS was enrolled in the study. After admission socio-demographic and clinical data were entered in a preformed questionnaire. For all enrolled patients antecedent events, the interval from disease onset to admission, duration from onset of symptoms to nadir, muscle weakness, sensory disturbances, cranial nerve deficits, autonomic dysfunction, and treatment modalities were documented.

A nerve conduction study (NCS) was done within 72 hours of admission. In case of a normal first NCS, it was repeated 7 days later. CSF analysis was done in the second week of disease onset. Children having autonomic instability and requiring ventilatory support were transferred to the ICU of the same hospital. Patients were treated using a standard protocol. IVIG was given when patients came within 2 weeks of onset of weakness and were unable to walk unaided (GBS disability score e3). Peak disability was assessed by using Clinical Grading Scale (CGS, 0-10). Patients were discharged when vitals were within normal limits and no further progression of the weakness or there was an improvement of motor function. Follow-up was done at 3 months of discharge using the GCS scale.

NCS of the right upper limb (median and ulnar nerves) and left lower limbs (tibial, peroneal, and sural nerves) were done in all patients using the Neuropath S1 machine by Nihon Kohden. In motor nerve conduction study (MNCS), distal latency (DL), amplitude and duration of compound muscle action potential (CMAP), conduction velocity (CV), conduction block (CB), and temporal dispersion (TD) were recorded. F wave was recorded in Median, Ulnar, and Tibial nerves where minimal latency was measured after supramaximal stimulation and identifying 10 F-waves in each motor nerve. H reflex was recorded from soleus. In the sensory nerve conduction study, peak latency, sensory nerve action potential (SNAP) amplitude, and velocity were measured. MNCS showing two or more demyelinating features in two or more nerves was categorized as AIDP. AMAN was considered when MNCS showed unrecordable or reduced distal CMAP (<80% of the lower limit of normal in at least 2 nerves) with normal sensory nerve conduction study. Sural sparing was defined as normal or relatively preserved Sural SNAP compared with at least two abnormal SNAPs in the upper limb.

Patients having NCS findings suggestive of AIDP and AMAN were finally included in the study and analyzed. Other GBS variants like AMSAN, MFS, and inexcitable, equivocal, or normal NCS findings were excluded from the study. The socio-demographic, clinical, and outcomes were compared between the children with AIDP and AMAN. Data were analyzed using SPSS version 20. Continuous data were presented as means and standard deviations whereas categorical data were presented as proportions. Chi-square tests were done to test differences in proportions. For continuous variables, the Student-test or Mann-Whitney U test was used to compare values between groups. p < 0.05 was considered to be significant for all statistical tests.
Results:
A total of 102 children had fulfilled the Brighton diagnostic criteria of GBS during that study period. NCS findings suggestive of AIDP and AMAN were found in 29(28.43%) and 54(52.94%) of cases respectively. Therefore 83 children were included in the final analysis. No patient died in this cohort and follow-up was done at 3 months after discharge. The mean age of presentation of this cohort was 12.79±5.14 years and the majority of the patients were in the age group of 14-17 years. Most of them were males and belonged to the middle and low-income groups. An antecedent event was present in 48.2% of cases, the commonest being gastroenteritis. They were admitted to the hospital after a mean duration of 5.44±3.36 days of symptom onset and maximum weakness was reached at a mean duration of 7.38±2.53 days after onset of symptoms (Table 1). Weakness and walking difficulty were the most common symptoms in both groups followed by pain and tingling sensation (Table 2).

A comparison of clinical data between children with AIDP and those with AMAN revealed that the majority of the clinical features were similar in the two groups. The mean age difference between the two groups was statistically significant and AIDP was found to be more frequent in the 1-5 years age group (p<0.05). There was a significant association between gastroenteritis and AMAN variants (Table 1). On symptom analysis, pain and tingling sensation in the limbs were found predominantly in AMAN variants (p<0.05) (Table 2). Respiratory distress and assisted ventilation were needed in 22.89 % and 14.45% of cases respectively and the majority of them were from the AMAN group (p<0.05). The mean duration of hospital stay was significantly higher in the AMAN group. No significant difference in the peak disability was identified between the two groups. Although the mean disability score at discharge between the groups was not statistically significant, the mean disability scores at three months after discharge were significantly higher in the AMAN group (Table 3).

| Variables                        | Total (83) | AIDP (29) | AMAN (54) | p value |
|----------------------------------|------------|-----------|-----------|---------|
| Age (mean±SD) (years)            |            |           |           |         |
| Range (years)                    | 12.79±5.141-17 | 11.04±5.94 | 13.73±4.43 | 0.022   |
| Age group (years)                |            |           |           |         |
| 1-5                              | 7 (24.14%) | 2 (3.70%) | 0.008     |
| 6-9                              | 3 (10.34%) | 7 (12.96%)| 0.51      |
| 10-13                            | 23 (27.7%) | 6 (20.69%)| 17 (31.48%)| 0.44    |
| 14-17                            | 41 (49.4%) | 13 (44.83%)| 28 (51.85%)| 0.64    |
| Sex                              |            |           |           |         |
| Male                             | 54 (65.1%) | 18 (62.07%)| 36 (66.67%)| 0.81    |
| Female                           | 29 (34.9%) | 11 (37.93%)| 18 (33.33%)|         |
| Residence                        |            |           |           |         |
| Urban                            | 36 (43.3%) | 15 (51.72%)| 21 (38.89%)| 0.35    |
| Rural                            | 47 (56.6%) | 14 (48.27%)| 33 (61.11%)|         |
| Income                           |            |           |           |         |
| Low                              | 29 (34.9%) | 10 (34.48%)| 19 (35.18%)| 0.94    |
| Middle                           | 30 (36.1%) | 10 (34.48%)| 20 (37.04%)|         |
| High                             | 24 (28.9%) | 9 (31.03%) | 15 (27.78%)|         |
| Antecedent event                 |            |           |           |         |
| Gastroenteritis                  | 25 (30.1%) | 2 (6.7%) | 23 (42.59%)| 0.001   |
| Upper respiratory tract infection| 15 (18.1%) | 7 (24.14%)| 8 (14.81%) | 0.37    |
| Fever                            | 12 (14.4%) | 5 (17.24%)| 7 (12.96%) | 0.74    |
| Time from symptom onset to admission (days) (mean±SD) | 5.44±3.36 | 4.5±2.23 | 5.95±3.79 | 0.23    |
| Onset to maximum progression of weakness (days) (mean±SD) | 7.38±2.53 | 7.41±2.99 | 7.36±2.32 | 0.95    |
| Treatment with IVIG              | 57 (68.67%) | 18 (62.07%)| 39 (72.22%)| 0.34    |
Discussion:
GBS is the commonest cause of acute flaccid paralysis in children after the reduction of polio\textsuperscript{23-26}. There are several electrophysiological subtypes. Several studies have been done to compare the features of two more common subtypes, AIDP and AMAN. In Bangladesh, no study was done in the past to compare these two subtypes among the children. This study was intended to carry out a comparison between the two variants.

A total of 83 children were analyzed in the study of which AMAN was more frequent than AIDP. There is striking geographical variation between these two subtypes. The frequency of AIDP in children ranged between 32% and 74%, and AMAN between 11% and 48% in different literature. AIDP has been reported to be more common in Argentina, Germany, Iran, Turkey, Oman, and Northeast China\textsuperscript{4,15,16,27,28}, whereas AMAN was found to be more common in Japan, China, Mexico, Bangladesh\textsuperscript{5,17,29,30}. Although possible reasons for this geographical variation of electrophysiological subtypes remain to be elucidated, the heterogeneity of the antecedents infections and the indigenous risk factors are speculated to be important factors\textsuperscript{31}.

The mean age of presentation of this cohort was 12.79±5.14 years and the majority of the patients were in the age group of 14-17 years. The mean age of patients in this study appears to be higher in comparison to similar studies done elsewhere\textsuperscript{32}. The higher mean age of presentation in this study is probably the reflection of the inclusion of more children of higher age. Most of the children were males and belonged to the middle and low-income groups. This is in line with other studies\textsuperscript{5,32-34}. The cause of male predominance still remains unknown.

A history of antecedent infections was present in 48.2% of cases, the commonest being gastroenteritis. A study by Singh et al\textsuperscript{35} found a history of antecedent infections in 43% of children. In this study, the patients were admitted to the hospital after a mean duration of 5.44±3.36 days of symptom onset and maximum weakness was reached at a mean duration of 7.38±2.53 days after onset of symptoms. Weakness and walking difficulty were the most common

| Variables                      | Total (83) | AIDP (29) | AMAN (54) | p value |
|-------------------------------|------------|-----------|-----------|--------|
| Tingling                      | 25 (30.1%) | 3 (10.34%)| 22 (40.74%)| 0.005  |
| Numbness                      | 7 (8.4%)   | 1 (3.45%) | 6 (11.11%) | 0.41   |
| Paraesthesia                  | 14 (16.9%) | 2 (6.7%)  | 12 (22.22%)| 0.12   |
| Pain                          | 31 (37.3%) | 6 (20.69%)| 25 (46.30%)| 0.03   |
| Weakness                      | 72 (86.7%) | 24 (82.76%)| 48 (88.89%)| 0.50   |
| Walking difficulty            | 54 (65.1%) | 19 (65.52%)| 35 (64.81%)| 0.57   |
| Urinary retention             | 1 (1.2%)   | 1 (3.45%) | 0         | 0.34   |
| Respiratory distress          | 19 (22.89%)| 3 (10.34%) | 16 (29.63%)| 0.046  |
| Dysphasia                     | 5 (6.0%)   | 1 (3.45%) | 4 (7.41%)  | 0.65   |
| Cranial nerve involvement     | 15 (18.1%) | 4 (13.79%)| 11 (20.37%)| 0.55   |

| Variables                      | Total (83) | AIDP (29) | AMAN (54) | p value |
|-------------------------------|------------|-----------|-----------|--------|
| Mechanical ventilation        | 12 (14.45%)| 1 (3.34%) | 11 (20.37%)| 0.036  |
| Duration of hospital stay (mean±SD) | 14.90±6.25 | 12.97±5.57 | 15.94±6.4 | 0.038  |
| Peak disability score (CGS 0-10) (mean±SD) | 6.06±1.70 | 5.82±1.96 | 6.18±1.55 | 0.36   |
| Disability score at discharge (CGS 0-10) (mean±SD) | 5.02±1.57 | 4.76±1.70 | 5.17±1.50 | 0.26   |
| Disability score at 3 months (CGS 0-10) (mean±SD) | 2.99±1.28 | 2.56±1.35 | 3.20±1.20 | 0.041  |
symptoms in both groups followed by pain and tingling sensation.

AIDP was found to be more frequent in the 1-5 years age group (p<0.05). There was a significant association between gastroenteritis and AMAN subtypes. Gastroenteritis or C. jejuni infection has been linked as a triggering factor for AMAN\textsuperscript{36,37}. Autoantibodies against GM1 or GD1\textsubscript{a} are produced in GBS patients following C. Jejuni infection which decreases ganglioside density leading to the destruction of sodium channels at the nodes of Ranvier\textsuperscript{38,39}. Serological studies for C. jejuni infection in our cases could not be performed due to lack of facility.

Pain and tingling sensation in the limbs were found to be significantly common in AMAN subtypes (p<0.05). This is somewhat contradictory to the findings of previous studies where sensory symptoms were found to be less common\textsuperscript{17,40}. Ventilatory support was needed in 14.45% of cases and the majority of them were from the AMAN group (p<0.05) which was consistent with other studies\textsuperscript{15,31}. The mean duration of hospital stay was significantly higher in the AMAN group. Although no significant difference in the peak disability and mean disability at discharge were identified, the mean disability scores at three months after discharge were significantly higher in the AMAN group which is consistent with other studies\textsuperscript{17,31}. There are certain limitations of the study. The study design was not adequately powered to evaluate the differences between the two common subtypes of GBS. An adequately designed study with a larger sample would produce a better impact.

Conclusion: AMAN was the commonest subtype of GBS in this cohort which had a significant association with gastroenteritis. Patients with AMAN had more sensory and respiratory symptoms, required a longer duration of hospital stay and a slower recovery than AIDP at three months follow up. Children with AMAN subtypes were more in need of ventilatory support than the AIDP in this study.

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Conflict of interest
There is no conflict of interest with any of the authors of this article.

Author’s contribution
Bithi Debnath designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Mohammad Enayet Hussain reported NCS and managed the literature searches. Rajib Nayan Chowdhury and Narayan Saha managed the analyses of the study. All authors read and approved the final manuscript.

Consent
Written informed consent was taken from the parents or guardians before inclusion in the study.

Ethical approval
Ethical clearance from the ethical review committee (ERC) of the hospital was taken before starting the study.

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