

## ORIGINAL ARTICLE

## FACTORS AFFECTING THE OUTCOME OF GUILLAIN-BARRE SYNDROME AMONG PEDIATRIC PATIENTS IN TIKUR ANBESSA SPECIALIZED HOSPITAL

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## ABSTRACT

**Introduction:** Guillain-Barré syndrome is an immune mediated acute illness featured by continual weakness and loss of deep tendon reflexes. The causes that govern the variant clinical presentations and outcome of this disease are not understood well. Neither are they studied in our setup.

**Objectives:** Assessed the factors affecting the outcomes of Guillain-Barré syndrome among children <15 years in Tikur Anbesa Specialized Hospital.

**Methods:** Institution based retrospective study was done among 91 patients with Guillain-Barré syndrome on follow-up identified by chart tracing and reviewed at Tikur Anbesa specialized hospital from October 1/2012 to January 30/2019. Required data was collected using a check list. The data was entered to computer using Ep-info and exported to Statistical Package for Social Sciences Version 23 for analysis.

**Results:** There were 91 patients with a male to female ratio of 1.1:1 and 80 % of them were between 2-10 years of age. Respiratory infections were the commonest preceding events in 27/91(29.7%). Cranial nerve involvement was found in 24/91(26.4 %) and 36/91(39.6%) patients had dysautonomia. The commonest sub-type was acute motor axonal neuropathy, 67/91 (73%). Functional independence was achieved by 47/91(52%) patients at 3 months and 80/91(88%) at 6 months. Poor functional outcome was significantly associated with the presence of sensory symptoms, dysautonomia, the need for mechanical ventilation, severity of weakness at nadir and longer hospital stay,  $P < 0.05$ .

**Conclusion:** The severity of motor weakness at nadir is associated with lower likelihood of functional independence signifying the requirement of longer time for self-efficient functionality.

**Key words:** Guillain-Barré syndrome, outcome, pediatric patients.

## INTRODUCTION

Guillain-Barré syndrome (GBS) is considered to be an autoimmune disease which is thought to mostly present post-infections. It affects the motor, sensory and autonomic nerves and it has a slight male preponderance with seasonal variation (1,2). Diagnosis of GBS is made by cerebro-spinal fluid (CSF) analysis and nerve conduction test (NCT). There are several treatment options like intravenous immunoglobulin (IVIg) and plasma exchange but outcomes of the disease are variable despite the uniform treatment modalities for unknown reason.

Furthermore, it has variable outcomes like decreased mobility, severe long-term fatigue syndrome and chronic pain(3–5). Since the elements that govern the different clinical and laboratory profiles of GBS and outcome are poorly understood, it creates an open ground for studies.

It has been shown in several studies that GBS is preceded by bacterial and viral infections and occasionally by vaccinations (6,7)but there hasn't been a strong evidence linking vaccination to GBS. Besides, it is a well-known fact that the benefits of vaccines outweigh the risk (8–10).

The nerve damage caused by GBS is histopathologically classified as demyelinating and axonal degenerating type. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) accounts for 80-90% of the cases in Europe and North America making it the commonest seconded by Acute motor axonal neuropathy (AMAN) accounting for 10-20% in the western countries and 50-60% in China and Japan (11–13).

There are various grading scales for prognostication of GBS based on which therapeutic strategies are planned.

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Some commonly used are Medical Research Council (MRC) score, the Erasmus GBS outcome score (EGOS), Erasmus GBS respiratory insufficiency score (EGRIS) and Hughes functional grading scale (HFGS) (12,14–16). Our study uses the HFGS which is an assessment of functionality of patients from their history since it is more practical for retrospective studies than the other modalities.

In a study done in South Africa, bulbar dysfunction, autonomic dysfunction and upper limb paralysis significantly predicted the need for mechanical ventilation (17,18). In a previous study done in our setup, the demographic and clinical characters were determined but outcome of patients on follow-up in clinic was not assessed. Furthermore, factors associated with poor outcome were not looked into (7).

Therefore, the main purpose of this study is to assess the 3<sup>rd</sup> and 6<sup>th</sup> month outcome of GBS patients in clinics with the available treatment modalities and to determine the factors affecting poor outcome. This is important in order to prepare one in anticipation of complications for better resource allocation, early intervention and better counseling of patients and care givers about the disease and future outcome.

## MATERIALS AND METHODS

**Study Area:** the study was done in TASH which is the largest tertiary hospital and one of the few with pediatric intensive care units (ICU) in Ethiopia. It manages many patients that require ICU and hence, many of the national GBS cases.

**Study design:** The study was a hospital based retrospective study, conducted between May and July 2019 in TASH, Addis Ababa, Ethiopia.

**Sample size:** The calculated sample size using  $N = Z^2P(1-p) / d^2$ , where p was taken to be 15%,  $d=0.05$  and  $Z=1.96$  was 215, but only 94 patients with a diagnosis of GBS were identified from October, 2012 to January 2019, from which one left against medical advice, one was referred out and the last one didn't fulfill the inclusion criteria making the total sample size 91. Those children who fulfilled the diagnostic criteria for GBS as per the operational definition were enrolled into the study.

**Sampling procedure and data collection:** A check list was prepared by using selected variables taken from patient health records and used as data collection tool.

I, the principal investigator, collected the data. Consecutive sampling was used to collect medical record numbers of patients admitted with the assessment of GBS from the health management information system (HMIS) in all pediatric wards and cross referenced with the pediatric neurology clinic HMIS for follow-up. Data was extracted from the retrieved cards by the medical record keeping department and it was then checked, cleared and coded.

**Data analysis and statistical methods:** The data was entered to a computer using Ep-info and exported to Statistical Package for Social Sciences Version 23.0 for analysis. Univariate analysis was used for percentage and frequency distribution of the demographic and few other variables in the check list. Factors with significant association with the outcome on univariate analysis were selected for multivariate logistic regression which was used to identify independently associated factors with the outcome. Statistically significant association was taken to be a p-value of  $<0.05$ .

### Operational definition

1. Pediatric patients- It is defined as children under the age of 14 years based on the hospital protocol.
2. Features Required for diagnosis of GBS based on NINDS diagnostic criteria (14).
  - A. Progressive motor weakness of more than one limb with hyporeflexia or areflexia (loss of tendon jerks) and
  - B. Cerebrospinal fluid features strongly supportive of the diagnosis or
    - i. CSF cells Counts of 10 or fewer mononuclear leukocytes/mm<sup>3</sup>.
    - ii. Elevated protein levels more than 0.5g/L
  - C. Positive electro-diagnostic test as stated on the nerve conduction test.

Areflexia: Deep tendon reflex = 0/4

Hyporeflexia: deep tendon reflex = ¼

Albumin-cytological dissociation: It is defined as elevated protein levels more than 0.5g/L with normal cell counts; fewer or equal to 10 mononuclear cells in CSF.

Preceding event: It is defined as the presence of respiratory, gastrointestinal, febrile illness or vaccination in the preceded 4 weeks to the onset of illness.

**Prolonged intubation:** It is defined as intubation for more than two weeks requiring tracheostomy for ventilation.

Hughes scale (15,16).

1. Healthy
  2. Minor symptoms/capable of running
  3. Walk 5 meters without support /unable to run
  4. Able to walk with an appliance
  5. Confined to bed/chair
  6. Requires assisted ventilation
  7. Death
3. Outcome
- A. Good – hughes score  $\leq 2$
  - B. Poor – hughes score  $\geq 3$

**Ethical consideration:** The research approval was made by the pediatric and child health department's research and publication committee (DRPC).

## RESULTS

A total of 91 children were included in the final analysis. All demographic characters are well stated in Table 1. Around 62/91(68%) had a preceding event prior to the development of weakness while the remaining 29 (31.9 %) had no documented preceding event. Except 3 (3.3 %) children, all the remaining 88 (96.7%) had Hughes functional score above 2 at the time of nadir weakness.

**Table1:** Socio-demographic characteristics of GBS patients in TASH 2012-2019GC, AA, Ethiopia

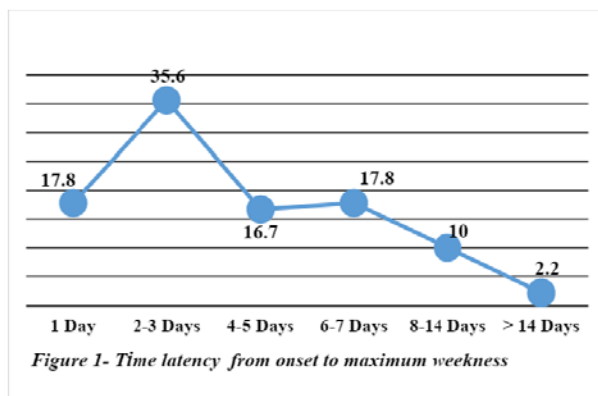
Variables		F	Percent %,
Age (years)	<2	7	7.7
	2-5	40	44.0
	5-10	33	36.3
	>10	11	12.1
Sex	M	47	51.6
	F	44	48.4
Residence	AA	39	42.9
	Oromia	31	34.1
	Others	11	12.1
Seasonal variation	Autumn	22	24.2
	Winter	19	20.9
	Spring	19	20.9
	Summer	31	34.1
Preceding event	Respiratory tract infections	27	29.7
	Acute gastroenteritis	22	24.2
	Vaccine	13	14.3
Hughes score at nadir	None	29	31.9
	$\leq 2$	3	3.3
	$>2$	88	96.7

The median duration of hospital stay is 13 days with inter-quartile range of 19 days. The maximum stay was 123 days. Patients in recovery phase were not admitted making the minimum days of stay zero. More than half of the patients, 50/91(55%) had a hospital stay of 2 weeks or less.

Another 22 patients had a hospital stay of 2-4 weeks making the hospital stay less than a month in 79 % of the patients. The median duration from the onset of the weakness to hospital admission was 5 days with inter-quartile range of 2 to 7 days.

The median duration from the onset of weakness to achieve maximum weakness was 3 days with inter-quartile range of 2 to 6 days. In most of the children, as depicted in the figure below, progression from onset to nadir weakness occurred on the 2<sup>nd</sup> and 3<sup>rd</sup> days of illness. More than a third of the children, 88% reached nadir weakness by one week, and progression was rare (2.2%) after 2 weeks.

The lower limb power was below 3 in 64/91 (70.4%) of the children at the time of presentation, with the remaining having a power of three to four. Lower limbs were areflexic in 47(51.5%) and hyporeflexic in 44 (48.4%) at presentation and 57 (62.7 %) had upper limb power 3-5.



Sensory symptoms of paresthesia and numbness were present in 40 (44 %), cranial nerve palsy in 24 (26.4 %), and features of dysautonomia in 36 (39.6 %) of the children. Of all patients with dysautonomia, 34/36 (94.4 %) had labile blood pressure and 15/36 (41.6 %) had arrhythmia but most (41.6%) had a combination of two or more.

Among the 73 patients with CSF analysis, 67/73 (91.8%) had albumino-cytologic dissociation (ACD). NCT was done for 59/91 (65%) of the children; accordingly, commonest subtype was AMAN-43/59 (73 %) followed by AIDP-14/59 (24 %), and the pattern of AMSAN was described only in 2/59 (3 %) children.

From all the patients admitted, 20/91 (22 %) required mechanical ventilation for respiratory failure, out of whom, 17/20 (85 %) had prolonged intubation. Children who received a total dose of 2 grams of intravenous immunoglobulin (IVIg) in five days accounted for 45/91 (50 %) of them.

**Table 2:** List of Investigations, treatment modalities and complications of patients with Guillain-Barre Syndrome (GBS) in TASH 2012-2019GC, AA, Ethiopia

Character		N	Percent
CSF analysis	No albumin-cytological Dissociation	12	13.2
	Albumin-cytological dissociation	61	67.0
	Not done	18	19.8
Nerve conduction test Sub-type	AMAN	43	47.3
	AIDP	14	15.4
	AMSAN	2	2.2
	No NCT	32	35.2
Mechanical ventilation	No	71	78.0
	Yes	20	22.0
Intravenous immunoglobulin	No	45	50.0
	Yes	45	50.0
Prolonged intubation	No	74	81.3
	Yes	17	18.7
Complications	No	64	70.3
	Yes	27	29.7

From a total of 91 patients, data at 3<sup>rd</sup> -month shows functional outcome of the first set of 50 patients only. Analysis of outcome at the 3<sup>rd</sup> month for these 50 cases showed that 26/50(52 %) children improved to Hughes score of  $\leq 2$ . The second set of 50 patients from a total of 91 had their functional outcome analyzed at 6<sup>th</sup> month follow-up. By this time, only 6/50 (12 %) had Hughes functional score of  $> 2$ , only 4/50 (8 %) had lower limb power of below three, and only 2/50 (4 %) had absent Deep Tendon Reflex (DTR). None had upper limb power below 3 and absent DTR on 6<sup>th</sup> month.

On the analysis of bivariate association, different variables were significantly associated with functional outcome at three months. Poor functional outcome of GBS was significantly associated with the presence of sensory symptoms, dysautonomia and the need for mechanical ventilation  $P < 0.05$ , the severity of weakness at nadir, use of Intravenous Immunoglobulin IVIg, mean length of hospital stay and the presence of complications  $P \leq 0.005$  and the duration to nadir weakness  $P = 0.006$ .

**Table 3:** Functional outcome of GBS patients in TASH 2012-2019GC, AA, Ethiopia

Follow up time		3 month N (%)	6 month N (%)
Hughes score	≤ 2	26 (52.0)	44 (88.0)
	> 2	24 (48.0)	6 (12.0)
LLP	<3	4 (8.0)	0
	3-5	46 (92)	50 (100)
LLR, DTR	.00	2 (4.0)	0
	1.00	28 (56.0)	13 (26.0)
ULP	2.00	20 (40.0)	37 (74.0)
	<3	1 (2.0)	0
ULR	3-5	49 (98)	50 (100)
	.00	2 (4.0)	0
Sensory	1.00	20 (40.0)	10 (20.0)
	2.00	28 (56.0)	40 (80.0)
Pain	No	50 (100)	49 (98.0)
	Yes	0	1 (2.0)
	No	47 (94.0)	48 (96.0)
	Yes	3 (6.0)	2 (4.0)

**Table 4:** Bivariate association of predictor variables with 3<sup>rd</sup> month functional outcome of GBS patients in TASH 2012-2019 GC, A.A, Ethiopia

Variables	Hugh's score at 3 months		N (%)	P-value
	Good outcome ≤2	Poor outcome >2		
Age in Years	<2	2 (7.7)	1 (4.2)	0.959
	2-5	11 (42.3)	11 (45.8)	
	5-10	10 (38.5)	9 (37.5)	
	>10	3 (11.5)	3 (12.5)	
Sex	Male	14 (53.8)	10 (41.7)	0.389
	Female	12 (46.2)	14 (58.3)	
Lower Limb power	0-2	9 (34.6)	23 (95.8)	0.000
	3-5	17 (65.4)	1 (4.2)	
Sensory symptoms	No	16 (61.5)	8 (33.3)	0.046
	Yes	10 (38.5)	16 (66.7)	
Cranial Nerve palsy	No	20 (76.9)	14 (58.3)	0.159
	Yes	6 (23.1)	10 (41.7)	
Dysautonomia	No	20 (76.9)	11(45.8)	0.024
	Yes	6 (23.1)	13 (54.2)	
Nerve conduction test Subtype	AMAN	16 (61.5)	12 (50.0)	0.690
	AIDP	3 (11.5)	3 (12.5)	
Mechanical ventilation	No	23 (88.5)	15 (62.5)	0.032
	Yes	3 (11.5)	9 (37.5)	
IV Immunoglobulin	No	19 (73.1)	8 (33.3)	0.005
	Yes	7 (26.9)	16 (66.7)	
Prolonged intubation	No	23 (88.5)	16 (66.7)	0.063
	Yes	3 (11.5)	8 (33.3)	
Complications	No	22 (84.6)	11 (45.8)	0.004
	Yes	4 (15.4)	13 (54.2)	
Time to Nadir	≤ 3day	9 (34.6)	17 (65.4)	0.006
	> 3 days	17 (73.9)	6 (26.1)	
Hospital Stay in days (mean± SD)		11.5 ± 12	35.5 ± 30	0.001

Those variables which were significantly associated with poor functional outcome were computed in multivariate analysis, only the severity of weakness at nadir was significantly associated with 3<sup>rd</sup> month poor functional outcome with AOR 30.115 (1.44- 628.7) at 95% CI.

Association of factors affecting outcome are only done on the 3<sup>rd</sup> month's follow-up to avoid bias secondary to inter-individual difference in genetic polymorphism since different sets of 50 patients had the 3<sup>rd</sup> and 6<sup>th</sup> months follow-up.

**Table 5:** Binary logistic regression of predictor variables with 3- month poor functional outcome of GBS patients in TASH 2012-2019GC, AA, Ethiopia

Variables		Hughes score at 3 months		P-value	AOR	95 % CI	
		≤2 N (%)	>2N (%)				
Lower Limb power	0-2	9 (34.6)	23 (95.8)	0.000	30.11	1.44	628.7
	3-5	17 (65.4)	1 (4.2)				
Sensory symptoms	No	16 (61.5)	8 (33.3)	0.046	.93	.13	6.61
	Yes	10 (38.5)	16 (66.7)				
Dysautono-mia	No	20 (76.9)	11(45.8)	0.024	.37	.05	2.74
	Yes	6 (23.1)	13 (54.2)				
Mechanical ventila-tion	No	23 (88.5)	15 (62.5)	0.032	.04	.00	1.28
	Yes	3 (11.5)	9 (37.5)				
IV immunoglo-bulin	No	19 (73.1)	8 (33.3)	0.005	4.98	.50	49.48
	Yes	7 (26.9)	16 (66.7)				
Complication	No	22 (84.6)	11 (45.8)	0.004	5.86	.23	150.4
	Yes	4 (15.4)	13 (54.2)				
Time to Nadir	≤ 3 D	9 (34.6)	17 (65.4)	0.006	1.20	.14	10.23
	> 3 D	17 (73.9)	6 (26.1)				
Hospital Stay in days	≤2wks	22(78.5)	6(21.4)	0.001	1.10	.99	1.21
	> 2wks	8(36.4)	14(63.6)				

## DISCUSSION

In our study, acute motor axonal neuropathy (AMAN) and ascending weakness are the commonest variants. There are relevant numbers of patients requiring mechanical ventilation. Most of our patients showed a good functional out come with 88% functional independence at 6<sup>th</sup> month follow up. The severity of motor weakness at nadir is independently associated with poor functional outcome.

On the previous study in our setup, AMAN was the most common subtype accounting for 80% and AM-SAN < 10% (7). In our study, the most common variant was AMAN which accounted for 73% of the cases followed by AIDP in 24% of the cases which is slightly higher than the previous study. This is in sharp contrast with western reports. AMSAN was the rarest variant which accounted for 3% of the cases strengthening the rarity of this variant in other reports (11–13).

In this study, 22% of children required mechanical ventilation for respiratory failure strengthening the general recommendation on meticulous follow up of respiratory status of GBS patients. There is an increase in use of the mechanical ventilation as compared with the previous study in our set up, 12.5% (7) which justifies the increased availability of the ICU setting.

In our study, 92.3% had ascending type of weakness which was in line with the research done by Saroj Kumar Bhagat et al in eastern Nepal showing 93.5% predominance(19). This pattern of motor weakness also accounted for 82.1 % of the 112 patients in the former study on GBS by Tigist et al. (7) in our setup.

It has been reported that, 85% of GBS patients will be functionally independent by one year, 10% will have functionally disabling weakness, and the rest 5% will die due to the GBS(15).

In our study, 14% became functionally independent (Hughes score  $\leq 2$ ) on discharge, 52% at three months and 88% at six months.

In contrast, the outcome on discharge in the study by Tigist et al. with mean duration of hospital stay being 18 days showed a 27.7 % good outcome and 36.6 % poor outcome with in-hospital GBS mortality of 8% and residual weakness frequency of 37 %(7). The in hospital mortality of GBS in our study was 2.2% comparable to that reported in the study by Alsheklee A et al. (2.58%) in the United states of America (20) and in a study by Mahmoud Reza Ashrafi et al. (2.2%) in Iran(21). The lower mortality in our study compared to the previous study in TASH may indicate improvements achieved in health care quality in subsequent years, especially ICU care for respiratory failure. 38% of children did not improve completely in our study similar to the previous study (7). This observation is very similar with the general descriptions on the prognosis of GBS showing a relatively benign process compared to other neurologic conditions causing weakness (15,20,21).

Some clinical variables at presentation can indirectly suggest the poor likely hood of recovery and longer hospital stay; such as the severity of weakness at nadir, the rapidity of disease course and the presence of early cranial nerve palsies(21).

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In our study, one variable which became independently associated with poor functional outcome on multivariate analysis was the severity of muscle weakness at nadir ( $p = 0.028$ , AOR -30.115, 95%CI-1.44-628.7). The larger confidence interval shows the lesser power of the study due to the smaller sample size than calculated which signifies the requirement of a large size study for better assessment of predictive factors of outcomes of patients with GBS.

## Conclusion

Most patients with GBS have good prognosis with highly improving functional independence in the first 6 months after initial presentation and the severity of motor weakness at nadir is associated with lower likelihood of functional independence.

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## Conflict of interest

The authors have no conflict of interest to declare.

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