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GUILLAIN-BARRÉ SYNDROME;
AUTONOMIC DISTURBANCES IN CHILDREN

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ABSTRACT… Objectives: To determine the outcome of autonomic disturbances in children with Guillain Barre Syndrome. **Study Design:** Case series study. **Setting:** Pediatric ICU and Neurology ward of Nishtar Medical University/hospital Multan. **Period:** 9th June 2014 to 8th June 2015. **Methods:** 48 children having age less than 18 years. Clinical examination of central nervous system was conducted by single examiner to see presence of acute flaccid paralysis and to detect autonomic dysfunction. Cerebrospinal fluid analysis for albumino-cytologic dissociation, electromyography and nerve conduction studies was done in every patient of Guillain Barre Syndrome. Outcome was noted as expired, discharged or LAMA. **Results:** Mean age was 5.4 years and male female ratio was 1.2:1. Total 34 children were found to have clinical evidence of autonomic instability. Among 48 children, 17 children (35.4%) received no therapy, 28 children (58.3%) received Intravenous immunoglobulin (IVIG) therapy, and 3 children (6.3%) received plasmapheresis. In children with autonomic disturbance, 24 children (70.6%) were discharged, 8 children (23.5%) expired and 2 children (5.9%) LAMA. Of the total 14 children without autonomic disturbance, 11 children (78.6%) were discharged, 3 children (21.4%) expired and no child LAMA (p-value >0.05). Mean duration of stay for patients with autonomic instability was 130 days versus 63 days in patients without autonomic instability (p-value <0.005). Demyelination variety was seen in 35 children (72.9%) and axonal degeneration in 13 children (27.1%). Mortality was high in children who had axonal degeneration but with insignificant p-value of >0.05. **Conclusions:** Autonomic instability is common in patients of GBS and is associated with increased risk of morbidity. Prompt recognition and treatment of autonomic instability can improve the outcomes of children with GBS.

Key words: Guillain Barre Syndrome, Polyneuropathies, Demyelination.

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INTRODUCTION

Guillain Barre Syndrome (GBS) is an acute or subacute polyneuropathy in which abnormal immune responses are directed against peripheral nerves.[1] Several variants of GBS are described including acute inflammatory demyelinating polyneuropathy, acute axonal neuropathy and Miller Fisher Syndrome, all of these have some immunological basis.[2] Light microscopy reveals an intense lymphocytic inflammatory infiltrate at the site of demyelination.[3] More than half of patients describe an antecedent viral infection. Clinical features are so stereotyped that the diagnosis is usually established without lab confirmation.

Two essential manifestation of GBS are progressive motor weakness and areflexia.[2] Pain and paraesthesia are the commonest features at presentation. Bilateral facial weakness is seen in as many as half cases. Autonomic symptoms such as constipation, urinary retention and vasomotor disturbances are also quite frequent in GBS.[2] Over-activity of vagal function may lead to serious cardiac disturbances ranging from bradycardia to asystole and in some cases ST segment elevation. Recovery begins 2-4 weeks after progression stops. In children, who recover, recovery is almost complete but may take several months. Most serious complication and cause of fatal outcome is respiratory failure and 10% patients require ventilatory support.[3]

CSF protein is elevated in all children while

cell count is not proportionately raised, albuminocytologic dissociation. Nerve Conduction studies show patchy conduction block consistent with demyelination. CSF protein and NCS may be normal during initial weeks of illness. Electro-diagnostic studies are helpful in diagnosis and differentiation of Guillain Barre Syndrome into axonal and demyelinating types.[4,5]

Treatment is mainly supportive and physiotherapy is essential. Specific attention should be paid to monitor respiratory function and autonomic instability. Respiratory failure needs ventilation and cardiac arrhythmias may need pacemaker insertion. Specific treatment is in the form of steroids, Intravenous Immunoglobulin or Plasmapheresis. This treatment is less beneficial in treatment of axonal GBS.[6] In addition to respiratory failure, fatality in Guillain Barre Syndrome is due to serious disturbances in autonomic function.[7] Fluctuation in blood pressure, arrhythmias, bowel and bladder paralysis are cause of serious concern as these add in the morbidity associated with Guillain Barre Syndrome and quite often may be the cause of fatality.[7] This study was conducted to see the frequency and outcome of different autonomic disturbances in Guillain Barre Syndrome so that the need for proper monitoring and timely intervention may be improved.

METHODS

This case series included 48 children having age less than 18 years who were admitted in pediatric ICU and neurology ward of Nishtar Medical University/hospital Multan. The study was carried out within a duration of one year from 9th June 2016 to 8th June 2017. Cases of acute flaccid paralysis other than GBS were excluded. Signs were taken from parents of each children on a written informed consent after describing them about confidentiality of children data included in this study. Ethical committee of the hospital gave approval for this study.

Demographic profile of all admitted children including age, gender and locality was recorded. Detailed history was taken regarding onset and progression of paralysis, associated symptoms like dysarthria, dysphagia, nasal regurgitation and any history of preceding gastrointestinal or respiratory infection. Special attention was paid to symptoms of autonomic dysfunction like urinary retention, constipation, palpitation and sweating. Clinical examination of central nervous system was conducted by single examiner to see presence of acute flaccid paralysis and to detect autonomic dysfunction. Pulse rate, rhythm, blood pressure and urine output was strictly monitored. Cerebrospinal fluid analysis for albumino-cytologic dissociation, electromyography and nerve conduction studies was done in every patient of Guillain Barre Syndrome. Other investigations like complete blood count, blood culture arterial blood gases, urine examination and culture, electrocardiography was done accordingly.

A child was supposed to have autonomic disturbance if he or she had clinical evidence of any one of the following; Palpitation, sweating, constipation, urinary retention with palpable bladder and urinary catheterization, bradycardia, tachycardia, irregular pulse rhythm, hypertension, hypotension and ECG evidence of sinus tachycardia, sinus bradycardia, tachyarrhythmia, bradyarrhythmia.

Blood Pressure was plotted on standard centile charts specific for age and sex and hypertension was defined as average systolic or diastolic blood pressure greater than or equal to 95th percentile for age and height measured at least on 3 separate occasions[10] and hypotension was documented clinically by poor peripheral pulses, and decreased urine output. Bradycardia and tachycardia was documented after consulting standard tables showing upper and lower limits of normal heart rate specific for age and sex.[11] Outcome was noted as expired, discharged or LAMA.

For data analysis, we used computed software SPSS v19. Male female ratio for gender distribution was calculated. Mean ± SD for age and duration of symptoms was calculated. Frequencies and percentages were computed to present all categorical variables including history of onset, symptoms, variety of GBS and outcome. Chi-

square test was applied to compare significance of proportions of autonomic disturbances and outcome and independent sample statistics were used to compare hospital stay at $p<0.05$ of significance.

RESULTS

The mean age was 5.44 years and median age was 4.5 years with standard deviation of 3.72 years. The most affected age groups were 2-5 years and 10 -12 years, with 54.3 % and 22.9% of all cases respectively. Of the total 48 cases, 27 were males (56.3%) and 21 were females (43.8 %). Male female ratio was 1.2:1.

Autonomic Disturbances

Mean duration of illness prior to coming to hospital was 5.06 days. Among 48 children with Guillain-Barré syndrome, clinical evidence of autonomic disturbance was seen in 34 children (70.8%). In 14 children (29.2%), no clinical evidence of autonomic disturbance was seen. Palpitations, tachycardia, hypertension, constipation and sweating were the commonest presenting autonomic disturbance symptoms of GBS children (Table-I).

Variable		Frequency	Percentage
Palpitation	Present	22	64.7
	Absent	12	35.3
Sweating	Present	18	52.9
	Absent	16	47.1
Constipation	Present	23	67.6
	Absent	11	32.4
Urinary Retention	Present	21	61.8
	Absent	13	38.2
Pulse Rate	Tachycardia	28	82.4
	Normal	6	17.6
Pulse Rhythm	Irregular	5	14.7
	Regular	29	85.3
Blood Pressure	Hypertension	29	85.3
	Normal	5	14.7
Catheteri-zation	Catheterized	13	38.2
	Not Catheterized	21	61.8
ECG	Sinus Rhythm Tachycardia	22	64.7
	Sinus Bradycardia	7	20.6
	Tachyarrhythmia	5	14.7

Table-I. Frequency of various symptoms of autonomic disturbances in children with GBS.

Requirement of Specific Therapies

Among 48 children, 17 children (35.4%) received no therapy, 28 children (58.3%) received Intravenous immunoglobulin (IVIG) therapy, and 3 children (6.3%) received plasmapharesis. In children with autonomic disturbance, 10 children (29.4%) received no therapy, 21 children (61.8%) received IVIG, and 3 children (8.8%) received plasmapharesis. Of the total 14 children without autonomic disturbance, 7 children (50%) received no therapy, 7 children (50 %) received IVIG, and no child received plasmapheresis (p-value >0.05) [Figure-1].

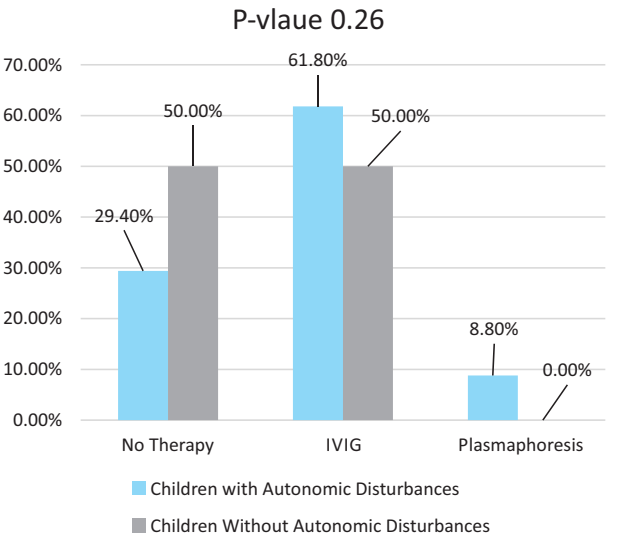

Figure-1. Comparison of specific therapies in children with autonomic disturbances and without autonomic disturbances.

Study Outcomes

Out of total 48 children, 35 children (72.9%) were discharged, 11 children (22.9%) expired and 2 children (4.2%) LAMA. In children with autonomic disturbance, 24 children (70.6%) were discharged, 8 children (23.5%) expired and 2 children (5.9%) LAMA. Of the total 14 children without autonomic disturbance, 11 children (78.6%) were discharged, 3 children (21.4%) expired and no child LAMA (p-value >0.05).Mean duration of stay in hospital was 105 days. Mean duration of stay for patients with autonomic instability was 130days. For patients without autonomic instability, mean duration of illness was 63 days (p-value <0.05). There was insignificant difference in hospital stay in patients with Autonomic Disturbances and

Without Autonomic Disturbances (p-value >0.05) [Table-II].

Study Outcomes	Children with AD (N=34)	Children without AD (N=14)	P-value
Discharged (%)	24 (70.6%)	11 (78.6%)	0.62
Expired (%)	8 (23.5%)	3 (21.4%)	
LAMA (%)	2 (5.9%)	0 (0.0%)	
Hospital Stay (%)			
< 10 days	13 (38.20%)	06 (42.90%)	0.22
10-20 days	11 (32.40%)	4 (28.60%)	
20-30 days	3 (8.8%)	4 (28.60%)	
1-2 months	5 (14.70%)	0.0 (0.0%	
>2 months	2 (5.90%)	0.0 (0.0%	

Table-II. Comparison of study outcomes in children with autonomic disturbances and without autonomic disturbances (ad).

Mechanical Ventilation

Out of 48, only 20 children required mechanical ventilation. In children with autonomic disturbance, 15 children (44.1%) were ventilated and in children without out autonomic disturbance, only 5 (35.7%) children were ventilated (p-value >0.05). Among these 20 children, 13 children (65.0%) were discharged, 5 children (25%) expired and 2 children (10%) LAMA. Among 28 children who were not ventilated, 22 children (78.6%) were discharged, 6 children (21.4%) expired and no child LAMA (p-value >0.05) [Figure-2].

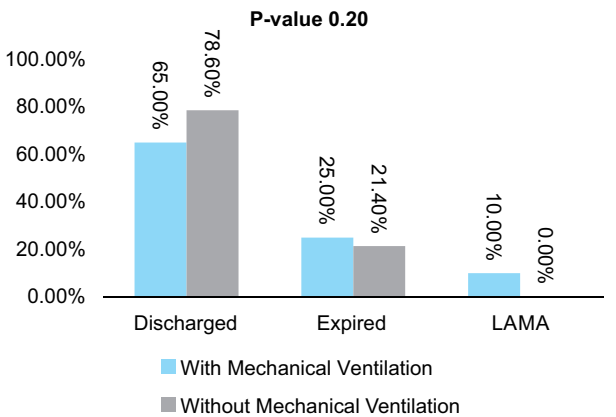

Figure-2. Comparison of study outcomes in children who underwent mechanical ventilation with those without mechanical ventilation.

Electrophysiology Studies

Among 48 children with Guillain-Barré syndrome, demyelination was seen in 35 children (72.9%) and axonal degeneration in 13 children (27.1%). Among 35 children with demyelinating variety, 27 children (77.1%) were discharged, 6 children (17.1%) expired and 2 children (5.7%) LAMA. Among 13 children with axonal degeneration, 8 children (61.5%) were discharged, 5 children (38.5%) expired. Mortality was high in children who had axonal degeneration but with insignificant p-value of >0.05.

Among 35 children with demyelinating variety, 16 children (45.7%) required ventilation while 19 Children (54.3%) did not. Among 13 children with axonal degeneration, 4 children (30.8%) required ventilation while 9 children (69.2%) did not.

Among 35 children with demyelinating variety, 25 children (71.4%) had autonomic disturbance while 10 children (28.6%) were without it. Of 13 children with axonal degeneration, 9 children (69.2%) had autonomic disturbance while 4 children (30.8%) were without it (Figure-3).

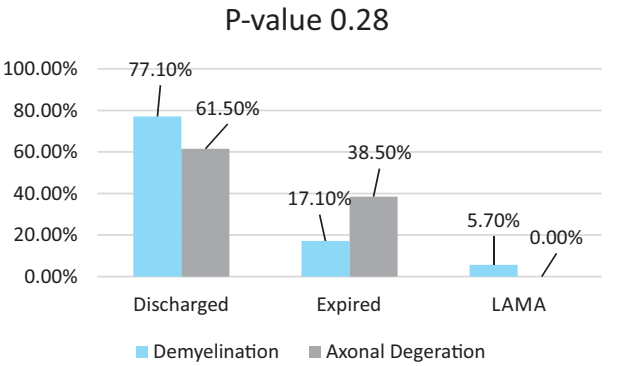

Figure-3. Comparison of study outcomes in children having demyelination with those having axonal degeneration disease.

DISCUSSION

Guillain Barre Syndrome is the commonest post infectious polyneuropathy presenting as acute flaccid paralysis. As the neuropathy also involves the autonomic fibers in peripheral nerves, so patients exhibit various manifestations of autonomic dysfunction.

In our study, total 48 patients with GBS were studied prospectively, this is one of few largest series described from Pakistan. Before this Ali et

al.[8] described a series of 51 patients but they also included adult patients. Mean age in this study was 5.44 years. In some western studies median age 2.9 to 3.5 years have been described.[9,10]

Male Female ratio in our study was 1.2:1.Kalra et al. and Verma et al. also found similar proportion of male to female ratio.[11,12] Yakoob et al.[13] found this ratio as 1.6:1 which is comparable. However Ali et al.[8] described this ratio as 4:1.

Previous history of upper respiratory tract infection was seen only in 43% of children and previous history of gastroenteritis in 60% children. This is comparable to a study done by Yakoob et al.[13]

In our study, there were 73% children had demyelinating variety of GBS while 27% children had axonal variety of GBS. Sadeket al.[9] also found higher prevalence (52%) of demyelinating variety versus only 36.0% axonal variety. Lee et al. and salehiomran et al. also found similar results.[14,15] On the contrary, Verma et al.[12] found higher prevalence (66.7%) of axonal variety as compared to only 33.3% with demyelinating variety. Kumar et al. also found higher prevalence of axonal variety as compared to demyelinating variety.[16] Children who had axonal degeneration had a poor out come with mortality of 38% as compared to 17% mortality in those with demyelinating variety of GBS. This is comparable to a study done by Khan et al.[4] Khan et al.[17] also showed that axonal variety responds badly to treatment.

In our study, 41.7% of total children required mechanical ventilation; however children who had autonomic disturbance were more likely to be ventilated. Yakoob et al.[13] quoted respiratory failure in 56% patients which is higher than ours. While Shahet al. [18] quoted respiratory failure in 33%. Ramachandran et al.[19] described need for assisted ventilation in 41.8% patients.

In our study, 58.3% of children received IVIG and 35.4% were managed without any specific treatment. 3 children who required Plasmapheresis had evidence of autonomic instability. Patients who received specific therapy had a mortality rate of 32% as compared to 23.5% and difference is statistically not significant. This was also described by Yakoob et al.[13] in their study.

70.8% patients had clinical evidence of autonomic dysfunction without any sex predilection. This is almost comparable to Yakoob et al.[13] which showed autonomic dysfunction in 61.8%.

Palpitation, Hypertension, Sinus tachycardia and constipation were commonest manifestations of autonomic dysfunction in total 34 children with autonomic instability. Various case reports have showed that cardiovascular dysfunction is most common and lethal manifestation of autonomic dysfunction in children with Guillain-Barré syndrome.[20-23]

Vomiting, respiratory distress and tachypnea at presentation had a significant correlation as risk factor for autonomic dysfunction. Sundar et al.[24] showed in their study that autonomic instability predicted the development of neuromuscular respiratory paralysis and poor outcome in GBS.

Total 72.9% children were discharged and all had residual damage at discharge. None of patient had complete recovery. 22.9% children expired and 4.2% LAMA and they were critically sick being ventilated for respiratory failure. Children without autonomic dysfunction had higher discharge rate and less mortality. Shah et al.[18] described mortality rate of 12.5%, while Ali et al.[25] described mortality rate of 28.6%.

CONCLUSION

After eradication of Poliomyelitis, GBS is the most common cause of acute flaccid paralysis. Autonomic dysfunction is common in children with GBS. Patients, who have autonomic instability have higher mortality, need more often specific therapy, more prone to respiratory failure requiring mechanical ventilation and have higher mortality rate. Early recognition and prompt treatment of autonomic dysfunction can improve outcome in children with GBS. More studies are required to evaluate risk factors for autonomic dysfunction.

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The supreme art of war is to subdue the enemy without fighting.

– Sun Tzu –

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	M. Ahmed Zia	Conceived, Designed, Data analysis and editing of manuscript.	
2	Yasser Masood	Did data collection and manuscript writing.	Yasser Masood
3	M. Kashif Salman	Helped in writing the manuscript and did review	