



Assessment of Autonomic Dysfunction in Childhood Guillain-Barré Syndrome

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ABSTRACT

Introduction: Autonomic dysfunction (AD) is a common and important complication in Guillain-Barré syndrome (GBS) and may be the cause of significant morbidity or death. Limited studies have evaluated this complication in childhood GBS. Our objectives were to show the prevalence of AD in children with GBS and investigate its association with the severity of the disease.

Methods: Study included 28 children admitted with a diagnosis of GBS. Heart rate variability (HRV), motor function disability of the upper limbs and GBS disability scores were measured at admission and the results were compared with 20 healthy age/gender matched subjects (2-13 years; 43% male). GBS subtypes were defined by electromyography: acute inflammatory demyelinating polyneuropathy (AIDP) or acute motor axonal neuropathy (AMAN).

Results: The mean age was 5.5 ± 3.4 years (range 1.5-14 years; 50% male). AIDP and AMAN subtypes comprised 57.1% and 42.9% of cases, respectively. In the upper limbs, 85.7% and in the GBS disability grading, 50% of patients had ≤ 3 scores, implying less severe motor dysfunction. There was no difference in the mean heart rate between patients vs. controls (103.9 vs. 98.2 bpm; $P = 0.16$), but half of patients showed AD and HRV was significantly reduced in patients compared to controls. Of the 16 patients with AIDP, 11 (68.8%) showed reduced HRV compared to 3 (25%) out of 12 AMAN cases ($P = 0.02$). There was no significant relation between HRV and motor disability scores.

Conclusion: AD was present in half of children with mild GBS and it showed no significant association with disease severity.

Introduction

The term Guillain-Barré syndrome (GBS), first described in 1916 in two soldiers by French neurologists Georges Guillain, Jean-Alexandre Barré and Andre Strohl, defines a recognizable clinical entity that is characterized by rapidly evolving symmetrical limb weakness, loss of tendon reflexes, absent or mild sensory signs, and variable autonomic dysfunction (AD). Since the virtual elimination of poliomyelitis, GBS has become the leading cause of acute flaccid paralysis in western countries.¹ The condition, however, is known to occur at all ages, though it is rare in infancy, affecting approximately 0.3 to 2 per 100,000 children per year.²⁻⁴ Weakness can develop acutely (within days) or subacutely (up to 4 weeks) and reaches a plateau, with subsequent spontaneous resolution of paralysis. Although the pathogenesis of GBS remains incompletely defined, there is increasing support for the concept that GBS results from an aberrant organ specific immune response.⁵

GBS is now classified into two major demyelinating [acute

inflammatory demyelinating polyneuropathy (AIDP)] and axonal [acute motor axonal neuropathy (AMAN)] categories according to clinical, electrophysiological, and pathological criteria.⁶⁻⁸ Rare subtypes are acute motor sensory axonal neuropathy, accompanied by the variant of the Fisher syndrome presenting with ophthalmoplegia, ataxia, and areflexia. Very rare pure autonomic variants of GBS, defined as pandysautonomia were also reported.⁹ The most frequent subtype of GBS in North America and Europe is AIDP, which accounts for 90% of GBS cases, while in Asia, South and Central America, the axonal form of GBS constitutes 30% to 47% of cases.¹⁰ Only about 5% to 10% of patients in North America and Europe have an axonal subtype. AD is a common and important complication in GBS and occurs in approximately two-thirds of patients and is often associated with a variety of derangements including cardiovascular, vasomotor, or dysfunctions in both the sympathetic and parasympathetic systems¹¹.

The analysis of variations in the heart rate (HRV) has

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been used to determine the balance between cardiac sympathetic and vagal nerve activities.¹² There have been only a few studies which used this technique for evaluation of AD in GBS. Flachenecker *et al.* indicated that 24-h heart rate power spectrum is a powerful predictor of serious autonomic complications in patients with GBS, and may help to identify patients at risk of potentially life-threatening arrhythmias.^{13,14}

The natural course of GBS is characterized by the onset of symmetric weakness with an initial rapid progressive phase, a second plateau phase at the maximum disability level, and a third phase of recovery. Disability level in GBS is often measured using the Hughes clinical grading scale (Motor Disability Grading Scale) scored from 1 to 7, with 1 being normal, 6 being the point where patients require mechanical ventilation, and 7 equating with death (Table 1).¹⁵

The AIDP and AMAN may have different immunopathogeneses and target molecules, which could be the cause of the difference in patterns of involvement of the autonomic nervous system. While many authors report these findings in adult GBS patient series, studies on affected children with AD are sparse.^{16,17} On the other hand, many reports suggest that AD is present more often in those with severe motor deficits and with respiratory failure,¹⁸⁻²⁰ while others found no relationship between the severity of AD and the degree of motor disturbances.^{17,21-23} Therefore, there still is debate whether there is any relationship between AD and the degree of motor disturbances. Thus, we undertook the present prospective study to examine the prevalence of AD in childhood GBS and whether there is any association between AD and the severity of illness in these patients.

Materials and Methods

Patients

Twenty eight GBS patients and 20 normal subjects were studied. All patients fulfilled the clinical criteria for GBS.² Motor function was evaluated according to the GBS disability grading system (Table 1). Weakness of arms was graded according to Table 2. Subtypes of GBS were determined from electromyograms and nerve conduction studies, which were obtained from all patients.

Evaluation of autonomic function

The parameters of HRV were gathered from a 24-h Holter Monitoring. All recordings were analyzed using the AB-180R Holter monitoring software system (Advanced Biosensor, USA) with DL800 Holter Recorder (Norav Medical Ltd., USA) and manual correction of artifacts. HRV was assessed in two ways: (1) time domain analysis and (2) frequency domain analysis. The following time domain indexes were obtained: (1) the standard deviation (SD) of all R-R intervals (SDNN; which estimates overall HRV), (2) the SD of the averages of R-R intervals during all 5-min periods that constitute the 24-h day (SDANN; which reflects circadian rhythmicity of autonomic function), (3) the root mean square of successive differences (RMSSD; which estimates the short-term components of HRV and provides a vagal index), and (5) The integral of the density distribution (i.e. number of all NN intervals plotted in a histogram) divided by the maximum of the density distribution (HRV-triangular index; which estimates the overall HRV). In the frequency domain analysis: (1) low frequency (LF) power, the power between the 0.04 to 0.15 Hz, and (2) high frequency (HF) power, the

Table 1. Motor disability grading scale in Guillain-Barré Syndrome

0	Healthy
1	Minor signs or symptoms
2	Able to walk 5 m without walker or support
3	Able to walk 5 m with walker or support
4	Bed- or chair-bound: unable to walk 5 m with walker or support; can rise the leg
5	Bed- or chair-bound: unable to walk 5 m with walker or support; cannot rise the leg
6	Requires assisted ventilation
7	Dead

Table 2. Upper limb disability grading scale

0	Normal
1	Can move his arm vertically above his head while the elbow is extended
2	Can move his arm vertically above his head only while the elbow is flexed
3	Cannot move the arm above the head but can bring the glass of water to the mouth
4	Cannot bring the glass of water to the mouth but can bring the hand to the mouth
5	Cannot bring the hand to the mouth but can touch small objects
6	Cannot use the hands
7	Complete paralysis

power between the 0.15 and 0.40 Hz were measured. Measurement of LF and HF power components were presented in absolute values of power (ms^2). HF generally represents parasympathetic activity and is therefore generally considered to be a marker of vagal activity. LF is influenced by both sympathetic and parasympathetic activity.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation. All continuous variables were checked with the Kolmogorov-Smirnov normality test to show their distributions. Continuous variables with normal distributions were compared using the unpaired Student *t*-test. Continuous variables with abnormal distributions were compared using the Mann-Whitney U-test. For categorical variables, the chi-square test was used. Values for $P < 0.05$ were considered statistically significant. SPSS 13.0 (SPSS Inc., Chicago, IL, USA) was used for data storage and analysis.

Results

The mean age was 5.5 ± 3.4 years (range 1.5-14 years; 50% male). The control group had an age range between 2-13 years and 43% were male. AIDP and AMAN subtypes comprised 57.1% and 42.9% of cases, respectively. According to the upper limb motor function, 13 patients (46.4%) were in stage 1, 7 patients (25%) in stage 2, 4 ones (14.3%) in stage 3, 2 patients (7.1%) in stage 4, and 2 patients (7.1%) were in stage 5. Based on GBS disability score, 5 patients (17.9%) were in stage 2, 9 (32.1%) in stage 3, 7 (25%) in stage 4, 6 (21.4%) in stage 5, and 1 (3.6%) in stage 6. Altogether, in the upper limbs, 85.7% and in the GBS disability grading, 50% of patients had ≤ 3 scores, implying less severe motor dysfunction. As stated earlier, there was no death during the study and only one patient needed mechanical ventilation. There was no difference in the mean heart rate between patients and controls (103.9 vs. 98.2 bpm; $P = 0.16$), but half of patients showed AD and HRV was significantly reduced in some time domains (SDNN and HRV-triangular index; $P = 0.001$ in both; Table 3) in patients compared to controls. The LF domain was significantly increased in patients vs. controls ($P = 0.01$; Table 3). Of the 16 patients with AIDP, 11 (68.8%) showed reduced HRV in the SDNN of the time domain category (Table 4) compared to 3 (25%) out of 12 AMAN cases ($P = 0.02$). There was no significant association between the presence of AD and the grades of upper or total GBS disability scores.

Discussion

Our study had three major findings. First, there was a 50% prevalence of AD in mild childhood GBS. Second, the prevalence of AD was much more common in the AIDP subtype than the AMAN subtype. Third, there was no association between the presence of AD and the severity

Table 3. HRV in patients vs. controls in both time and frequency domains

HRV domains	Patients	Control	P
SDNN (ms)	101.62 $\pm$ 29.01	138.6 $\pm$ 35	0.001
SDANN (ms)	78.02 $\pm$ 68.42	97.3 $\pm$ 25	0.96
RMSSD (m/s)	76.38 $\pm$ 39.25	85 $\pm$ 30	0.36
HRV-TI (ms)	20.96 $\pm$ 96	33.34 $\pm$ 11	0.001
LF (ms^2)	187.37 $\pm$ 49.25	158.39 $\pm$ 33	0.01
HF (ms^2)	153.68 $\pm$ 41.94	169.5 $\pm$ 38	0.14

SDNN= SD of all R-R intervals; SDANN= SD of the averages of R-R intervals during all 5-min periods that constitute the 24-h day; RMSSD= the root mean square of successive differences; HRV-TI= The integral of the density distribution (ie number of all NN intervals plotted in a histogram) divided by the maximum of the density distribution; LF= Low Frequency power; HF= High Frequency power.

Table 4. Comparison between GBS subtypes according to the number (%) of patients showing reduced HRV in both time and frequency domains

Abnormal HRV domain	GBS subtype		P
	AIDP	AMAN	
SDNN n(%)	11 (68.8%)	3 (25%)	0.02
SDANN n(%)	10 (62.5%)	8 (66.7%)	0.82
RMS-SD n(%)	5 (31.3%)	4 (33.3%)	0.90
HRV-TI n(%)	10 (62.5%)	8 (66.7%)	0.82
LF power n(%)	1 (6.3%)	1 (8.3%)	0.83
HF power n(%)	8 (50%)	4 (33.3%)	0.37

SDNN= SD of all R-R intervals; SDANN= SD of the averages of R-R intervals during all 5-min periods that constitute the 24-h day; RMSSD= the root mean square of successive differences; HRV-TI= The integral of the density distribution (ie number of all NN intervals plotted in a histogram) divided by the maximum of the density distribution; LF= Low Frequency power; HF= High Frequency power.

of motor dysfunction in this subset of patients.

The use of the GBS Motor Disability Scale of 7 grades of impairment, which was initially used in the study of adult patients with severe GBS to compared plasmapheresis with conventional therapy,²⁴ has enabled an integrated method for analyzing motor disability and predicting outcome. Currently, scores ≥ 3 usually need medical support. In the present study, upper limb motor function and GBS disability grading showed ≤ 3 scores, in 85.7% and 50% of patients, respectively. This implies that motor dysfunction

in our cohort was mild with no death and only one patient with respiratory failure.

Cardiovascular autonomic neuropathy is a common and potentially grave complication in GBS, however, quantitative tests to assess such patients have rarely been used. The main reason for this shortcoming is that patients with severe motor disability are usually unable to perform standardized tests of autonomic function appropriately.¹⁹ HRV analysis is non-invasive and easily applicable, requiring no active motor tasks, and is therefore feasible, even in severely affected patients.^{13,14} Normal HRV depends on the balance between the sympathetic and parasympathetic systems. A high variability in heart rate is a sign of a healthy functioning autonomic control mechanism, especially the parasympathetic nervous system. The loss of this HRV due to an imbalance in sympathovagal system can predispose to various tachy- and bradyarrhythmias in both in-vivo and in-vitro conditions.²⁵ Mild autonomic disturbance is reported to occur in 65% of patients with GBS.²⁰ Sinus tachycardia is one of the most frequent manifestations and hypertension and postural hypotension are common.²² Some reports suggested a worse prognosis in the presence of AD, but others have refuted this.²⁶ Furthermore, many reports suggest that AD is present more often in those with severe motor deficits and with respiratory failure,¹⁸⁻²⁰ while others found no relationship between the severity of AD and the degree of motor disturbances.^{17,21-23} Our findings are more in accordance with the latter studies with no relation between the presence of AD and the stage of motor disability. It seems that the consequences of involvement of the autonomic nervous system in GBS are negligible in many patients but on occasion they can be life threatening. Severe GBS is associated with progressive motor disability leading to respiratory failure. About a third of children with GBS experience severe motor disability and approximately 15% to 24% require mechanical ventilation due to respiratory failure (8% of the current series).^{2,27-31} AD has been reported in up to 90% of patients with moderate to severe GBS.^{19,21-23}

There are very few studies which have specifically evaluated AD in childhood GBS.^{16,17,32} Cooper *et al.*¹⁶ retrospectively studied 30 children with GBS and found a 66.7% prevalence of AD. Similarly, DiMario *et al.*¹⁷ studied 26 patients retrospectively with a mean age of 11.3 years (range 6-17 years) with about half having mild GBS and showed AD in up to 77% of them. Only one small study of 5 patients has evaluated AD in mild adulthood GBS with various noninvasive tests, not including Holter monitoring and HRV testing.³² This study had no control group for comparison, nonetheless, no patient showed tachycardia or bradycardia during hospitalization. All patients in this study initially showed moderate AD according to the calculated composite autonomic score, described by Flachenecker *et al.*¹⁹ We used HRV measured

during Holter monitoring in 28 children with mild GBS and showed a 50% prevalence of AD, mostly in the AIDP subtype. SDNN, and HRV-triangular index, which estimate the overall HRV in the time domain, were significantly reduced in our patients compared to controls. In the frequency domain analysis, the HF domain was decreased in patients vs. controls but it did not reach statistical significance, again due to a small sample size. On the other hand, the LF power was significantly increased, implying sympathovagal imbalance with the tendency for increased sympathetic drive in affected patients. This confirms the previous study that AD not only occurs in moderate to severe GBS but also in mild forms of the disease with rather high prevalence. The mean heart rate was higher in our patients vs. controls but it did not reach statistical significance probably due to a small patient population. In our patients AD was significantly more prevalent in AIDP vs. AMAN cases. This is in accordance with a previous report that showed the patterns of AD are different for the two subtypes of GBS.³³ This is the only report that has evaluated differences of autonomic manifestations between AIDP and AMAN subtypes.³³

Our results suggest that HRV parameters may be used for early detection of any AD in patients with GBS. Cardiovascular response may be different in AMAN and AIDP patients, and this difference may play a role in the underlying pathogenesis, the clinical outcome, and in determining appropriate care for these patients. More conclusive results may be gained with larger study groups comprised of different subtypes of GBS. In addition, evaluating the impact of AD in the course of treatment or its interaction with the type of delivered treatment (plasmapheresis or intravenous immunoglobulin) would be valuable in future studies.

Conclusion

AD was prevalent in mild childhood GBS, more so in the AIDP subtype, and showed no significant association with the severity of motor dysfunction in this subset of patients.

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Ethical issues: All patients gave written informed consents and the study was approved by our local Ethics Committee.

Conflict of interests: The authors declare no conflicts of interest.

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