REVIEW

Autonomic involvement in Guillain–Barré syndrome: an update

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Abstract

Background Guillain–Barré syndrome (GBS), an inflammatory, usually demyelinating polyradiculopathy, is characterized by ascending symmetrical limb weakness, sensory disturbances, and absent or reduced deep tendon reflexes. There is extensive literature suggesting that GBS is associated with autonomic dysfunction in up to two-thirds of patients. However, it is interesting that there is still no consensus amongst medical professionals regarding whether GBS patients should be routinely screened for autonomic nervous system (ANS) neuropathy. This is an important issue, as the mortality rate from presumed ANS abnormalities now exceeds that of respiratory failure. Given the long interval since this literature was last comprehensively reviewed, an update on this topic is warranted.

Methods A PubMed search yielded 193 results with the terms "GBS or Guillain–Barré syndrome and autonomic symptoms" and 127 results with the terms "GBS or Guillain–Barré syndrome and dysautonomia."

Results This review will summarize the current literature involving GBS and autonomic dysfunction in terms of presentation, management, and a brief discussion of prognosis. We also examine prospective approaches that may be helpful and update a proposed management plan.

Keywords GBS · Dysautonomia · Autonomic failure · Autonomic testing

Introduction

Guillain–Barré syndrome (GBS), an acute inflammatory and usually demyelinating polyradiculoneuropathy (AIDP), was first described by Georges Guillain, Jean-Alexandre Barré, and Andre Strohl in 1916 [1]. It is postulated to arise from an autoimmune response to peripheral nerves and is usually characterized by ascending symmetrical limb weakness, sensory disturbances, and absent or reduced deep tendon reflexes [2]. Interestingly, it is now the most common cause of flaccid paralysis globally, following the eradication of poliomyelitis. In Alberta, Canada, the mean incidence of GBS over 11 years was 1.6/100,000 [3]. The annual incidence of GBS globally is around 1–2/100,000, and does not seem to be more prevalent in any particular populations [3, 4].

There is extensive literature suggesting that GBS is associated with autonomic dysfunction in up to two-thirds of patients [5]. This includes blood pressure fluctuations, arrhythmias, vasomotor dysfunction, and gastrointestinal (GI) motility dysregulation. While this association may have been described as early as 1982 by Osler, it is only recently that the full extent of this dysautonomia is being understood [6]. Given that these patients are often stable on initial presentation, it is important to emphasize early monitoring for respiratory or cardiovascular collapse. Mortality can be as high as 7% in this patient population, and early recognition with appropriate management is the key to addressing the number of deaths secondary to dysautonomia [7].

A PubMed search yielded 193 results with the terms "GBS and autonomic symptoms" and 127 results with the terms "GBS and dysautonomia." After duplicate articles were removed, 75 papers were reviewed. Of these, 50 were chosen for this review. The excluded papers included information that was already present in other papers or were not available in English.

It is interesting that there is still no consensus amongst medical professionals regarding whether GBS patients should be routinely screened for ANS neuropathy. Given the

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long interval since this literature was last comprehensively reviewed [7], an update on this important topic is warranted. This review will summarize the current literature involving GBS and autonomic dysfunction in terms of presentation, management, and a brief discussion of prognosis.

Cardiovascular

Midway through the twentieth century, multiple case series described the death of GBS patients secondary to circulatory failure rather than respiratory muscle weakness. For example, in 1949, Haymaker and Kernohan reported that 3/50 fatal cases were attributed to cardiovascular compromise [8]. Another series examined 100 GBS patients for evidence of dysautonomia including severe arrhythmias. Eleven of 33 patients on artificial ventilation suffered significant cardiac arrhythmias, and seven of these patients died. Around half of the patients experienced attenuated RR interval variation in the setting of sinus arrhythmia, and a quarter of the patients had reduced systolic blood pressure or sinus tachycardia [9]. Clarke et al. described three patients with circulatory failure, one of which was thought to be successfully treated with cortisone [10]. Disturbances in cardiac rate and rhythm and the myocardium, or acute coronary syndromes, EKG changes, and blood pressure variability are amongst the common cardiovascular complications.

Bradyarrhythmias, sustained sinus tachycardia, and atrial or ventricular arrhythmias are well recognized in GBS, with sinus tachycardia being the most common abnormality (Fig. 1). Arrhythmias are thought to be associated with autonomic afferent demyelination from the heart or direct myocardial involvement, or secondary to respiratory dysfunction. It has been theorized that there are pathological lesions around the vagal nuclei and that it is this involvement of the vagal center in the brainstem that contributes to autonomic cardiac dysfunction [11–14, 71]. Other studies have demonstrated risk factors independent of the autonomic

cardiac innervation that include direct and associated interstitial infiltration of the myocardium, with mononuclear and polymorphonuclear cells along with myocardial necrosis [15]. Interestingly, such changes are also noted in poliomyelitis [16].

Greenland and Griggs [17] described a retrospective study of 16 GBS patients admitted to the intensive care unit (ICU) primarily for respiratory dysfunction. Thirteen of these patients experienced bradyarrhythmias (atrioventricular [AV] block or sinus arrest) or tachyarrhythmias (supraventricular and ventricular), with two patients requiring pacemaker insertion because of asystolic episodes. While some literature suggests that bradyarrhythmias are far more common in severely disabled patients requiring mechanical ventilation, more recent studies note that these can occur in patients who have never required artificial ventilation and can walk more than 5 m independently [9, 18]. Thus, the relationship between potential ANS abnormalities, including those that may be life-threatening, and the severity of GBS disability remains unclear. An analysis of 13 patients revealed vagal overactivity in 30% of patients who had mild to severe motor disability. Abnormal sensitivity to appropriate manual eye globe pressure testing may be a useful predictor of severe bradyarrhythmias in comparison to measures such as heart rate, blood pressure fluctuations, and standardized autonomic function tests [19]. Mild manual pressure was applied bilaterally for 25 s or until there was a manifestation of abnormal bradycardia, defined as a heart rate below 40 beats/min. EP was able to identify two out of three patients who eventually required cardiac pacing or CPR secondary to subsequent cardiac arrest. Normal responses were seen in eight of ten patients who did not have any bradyarrhythmic episodes. Given these results, EP could be utilized at the bedside of GBS patients to predict the risk of severe bradyarrhythmias. The 24-h heart rate power spectrum can also provide sensitive and specific markers for determining which patients will develop clinically significant arrhythmias [20]. This is a form of noninvasive testing

Fig. 1 Rhythm strip ECG tracings from a 44-year-old man with a 2-day history of motor and sensory loss diagnosed as demyelinating GBS. The upper strip captures part of a 12-s episode of supraventricular tachycardia that was associated with mild chest discomfort. The tachycardia resolved without treatment, and a normal rhythm strip a few minutes later is shown below

that utilizes the RR interval to analyze neural regulation of the cardiac function. Thus, using a mathematical algorithm, the heart rate (or time domain) can be converted into a power spectrum (or frequency domain). In healthy controls, power and frequency can be plotted on a graph as a straight line with a slope of approximately −1. Thus, when viewed on longer time plots, there is an increase in the RR intervals which results in a power law. This explains the "1/f" fluctuations which indicate that power has decreased in proportion to the reciprocal of frequency. Here, f is frequency, the y-axis plots the spectral power, and the x-axis equals frequency (Hz). With dysautonomia, the slope is closer to −2, making it much steeper. In summary, patients with dysautonomia can present with reduced frequencies, whereas higher frequencies (> 0.15 Hz) are more indicative of respiratory sinus arrhythmia.

Sustained sinus tachycardia, the most common abnormality observed in monitored GBS patients, rarely needs to be treated, as it is usually transient. In a study conducted by Pfeiffer et al., only 25% of GBS patients (9/36) had mean heart rates greater than 125 beats/min [21]. While β-blockers can be used to treat sustained or symptomatic tachycardia, their use in elderly patients with coronary artery disease should be applied very cautiously. Their administration may be associated with hypotension and bradycardia. Irrespective of age, however, cardiovascular agents may be less well tolerated in GBS patients and should be used with extreme care. In some patients, hypersensitivity of denervated ANS targets may explain this important risk. As a general rule, anti-arrhythmics should not be used in patients with denervated hearts, as they can exacerbate arrhythmias [22].

Cardiomyopathy and left ventricular dysfunction

Although echocardiogram examinations are not frequently carried out in GBS patients, these individuals can rarely present with transient cardiomyopathy [23]. These findings are in keeping with the direct changes identified in cardiac muscle in pathological studies described above. In one reported instance, transthoracic echocardiogram demonstrated left ventricular (LV) hypokinesia and an ejection fraction (EF) of 48% [23]. This patient received intravenous immunoglobulin (IVIG) treatment, and after 9 months there were no signs of residual cardiac involvement. Another case study demonstrated normal chamber sizes but LV global hypokinesia and an EF of 31% not explained by other pathology [24]. Fugate et al. describe an 82-year-old woman whose course with GBS was further complicated by Takotsubo cardiomyopathy (TC) and posterior reversible encephalopathy syndrome (PRES) [25]. The echo findings resolved within 2 weeks. TC is a transient cardiac syndrome that was first described

in 1990 in Japan. The syndrome can be associated with emotional stress and presents as LV apical akinesia. A more recent case of TC associated with GBS in a 70-year-old woman was reported by Gill et al. [26]. This had resolved at follow-up 4 months later. TC can be treated with angiotensin-converting enzyme (ACE) inhibitors and β-blockers, but given the risk of arrhythmias in GBS patients, it is important to apply caution, and when possible, to avoid β-blockade. LV dysfunction and transient cardiomyopathy have been associated with high catecholamine levels that damage myocardial tissue [23, 27].

Arterial blood pressure fluctuations

Blood pressure variability is a hallmark feature of GBS that may be closely related to transient rises in catecholamine levels and dysregulation of baroreceptor reflexes [28]. Demyelination of preganglionic sympathetic axons or axonal degeneration in postganglionic axons may result in alterations in feedback control or generate inappropriate ectopic discharges that account for the fluctuations observed. Elevated levels of norepinephrine are associated with increased sympathetic outflow. Drastic fluctuations between hypotension and hypertension have been described in GBS patients, which can result in cardiovascular collapse. A given GBS patient might experience hypertension, transient hypotension, or sustained hypotension [7]. Hypertension has been noted in 27% of patients, and in 3% of individuals it is sustained. Cases of severe hypertension can result in sudden death, given the hypersensitivity to vasoactive agents.

Interestingly, postural hypotension is present in 43% of patients, and episodic hypotension is noted in 57% of individuals. In normal controls, mean arterial pressure (MAP) can be maintained as an individual changes position, because the muscle sympathetic nerve activity rises [7]. However, in GBS, the sympathetic nerve supply is targeted and the vasculature is not able to maintain its resistance. Thus, unlike in healthy individuals, there is no increase in the amount of resistance, such as splanchnic, blood flow. Zhang et al. describe a man who presented with new-onset orthostatic hypotension prior to the development of motor and sensory symptoms of GBS. He was successfully treated with IVIG, and his hypotension resolved over the next 2 months [29]. Orthostatic hypotension can improve with gains in mobility as the disorder resolves, but in severe cases, intravenous fluids, salt tablets, or hydrocortisone may be needed. Despite treatment, postural hypotension may persist, and patients must not be left unsupervised in a sitting position. Many GBS patients are on mechanical ventilation and receive sedation or analgesia, which may have the potential to alter MAP. However, Pfeiffer et al. noted that despite receiving no sedation, 13/36 patients became hypotensive during the

course of their GBS [21]. In any GBS patient, of course, it is critical to exclude alternative causes of hypotension including sepsis, GI bleeding, pulmonary embolism, and metabolic abnormalities [7]. Systolic blood pressure variation of > 85 mmHg daily is described to be a sensitive threshold for autonomic dysfunction. Patients with GBS with labile blood pressures and diurnal tachycardia should be monitored carefully, as they are at higher risk for arrhythmias [21].

There are currently 11 published reports of posterior reversible encephalopathy syndrome (PRES) occurring in patients with GBS [30–36]. All of these patients presented with hypertension thought most likely to be associated with dysautonomia. Generally, PRES presents an average of 6 days after GBS symptoms and can be associated with IVIG therapy [37–42]. Patients may require treatment with antiepileptic medications and antihypertensives immediately upon diagnosis. Intravenous labetalol, esmolol, or nitroprusside can be used to treat MAP > 125 mmHg, with precautions as described above. Treatment in a carefully supervised setting such as an ICU with continuous blood pressure monitoring is likely indicated.

Cardiac arrest and EKG changes

GBS can present with ascending paralysis and sudden cardiac arrest simultaneously. Minor autonomic stimulation may result in sinus arrest. Earlier recognition of these complications has been made possible by technological advances in the area of cardiac pacing. Recently, an association between the anti-GQ1b antibody and autonomic dysfunction was discovered, including a reported instance of sinus arrest complicating Miller Fisher syndrome (MFS) that did not recur after improvement in the condition [43]. Given the risk of cardiac asystole and hypoxic cardiac arrest with endotracheal suctioning, temporary pacemakers may be placed. After examining noninvasive transcutaneous pacing in 35 patients with GBS, Madsen et al. determined that this method of pacing was safe and effective and avoided the risk of cardiac cannulation [44]. If required for a short period of time, clinicians may opt for transcutaneous pacing for GBS patients admitted to the ICU. In GBS patients with severe dysautonomia and arrhythmias, permanent pacemaker insertion can also be considered, given the uncertainty regarding the duration of risk. However, there is a risk of infection and the possibility that the patient may recover uneventfully without further serious events, requiring a later decision on the safety of its removal. Kordouni et al. report treating an MFS patient with severe bradycardia and asystole by initially placing an external pacemaker (active fixation lead), and then replacing this with a dual-chamber permanent pacemaker after 5 weeks [45]. The advantage of this approach is that GBS patients are allowed time to recover from their

illness, while potentially avoiding a fatal outcome. However, there is limited published evidence for this approach, and clinicians may be hesitant given that invasive conventional pacing is not without risk.

Gastrointestinal dysmotility and genitourinary dysfunction

Up to 40% of GBS cases in the Western Hemisphere have been preceded by a *Campylobacter jejuni* infection [46]. There have been reports that *C. jejuni* infection may result in greater irreversible damage in GBS patients as compared to other infections. One study found that 23% of 101 GBS patients with *C. jejuni* were unable to ambulate without assistance after 1 year, whereas only 9% of the uninfected patients had a similar outcome.

The intimate supply of the GI tract with autonomic parasympathetic and sympathetic nerves can be targeted by GBS. The vagus nerve provides parasympathetic supply to the colon, small intestine, and stomach. The distal colon receives parasympathetic supply from sacral parasympathetic fibers. The splanchnic and the lumbar colonic nerves provide sympathetic supply to the colon, small intestine, and stomach [47].

Paralytic ileus, gastroparesis, delayed gastric emptying, diarrhea, and fecal incontinence have all been described in GBS patients. Adynamic ileus was noted in 15% (17/114) of GBS patients admitted to the ICU [47]. In five, the dysmotility occurred in the acute phase of GBS, in four during the plateau phase, where the motor strength was either stable or improving, and in eight from unrelated causes. Of the five patients who developed it in the acute phase, there was also evidence of cardiovascular dysautonomia (resting tachycardia, hypertension; four patients) and urinary retention (three patients), suggesting an underlying mechanism of sympathetic overactivity and vagal dysfunction (ileus). This is thought to result from dysregulation of GI intrinsic and extrinsic neural control. Oropharyngeal dysphagia and respiratory dysfunction secondary to aspiration pneumonia can also result from bulbar symptoms. While bulbar and oculomotor nerve involvement are more common in patients with Miller-Fisher syndrome, these can be observed in patients with typical GBS a well. Because many patients with severe GBS require ICU admission, it is unclear whether associated ileus is secondary to dysautonomia or immobility and use of pharmacological treatments such as opioids.

The contribution of autonomic dysfunction to intestinal paralysis is difficult to differentiate from the confounding effects of mechanical ventilation, immobility, and medications (e.g. narcotics) in these patients. Immobility and critical illness, common features of severe GBS, can contribute to dysregulation of peptide secretion, decreased mesenteric

blood flow, and disturbances in the neural supply to the GI system.

Fewer case series have addressed the autonomic mechanisms underlying bowel and bladder function in GBS, and dedicated laboratory testing is lacking. Video urodynamic studies in a GBS patient with acute urinary retention, showed that internal urethral sphincter obstruction (from hyperactive sympathetic nerves) was the underlying mechanism, and not bladder paralysis (parasympathetic failure) [48]. Treatment with an alpha-adrenergic antagonist led to successful relaxation of the urethra in this patient and reduced the post-void residual urinary volume, supporting the idea that sympathetic hyperactivity was the underlying cause. In a larger study in 65 consecutive GBS patients (AIDP, 28; acute motor axonal neuropathy [AMAN], 37), about 27.7% had urinary dysfunction, which included urinary retention in 9.2% [49]. Other urodynamic abnormalities included underactive detrusor, overactive detrusor, and to a lesser extent, hyperactive sphincter. The urinary involvement was more common in AIDP than AMAN, and correlated with disease severity and the presence of bowel dysfunction. As was reported by Zochodne [7], patients with GBS can experience sexual dysfunction, facial flushing, pupillary abnormalities, bronchospasm, and temperature dysregulation. Of note, patients who recover from GBS can present with erectile dysfunction. However, these manifestations of dysautonomia are less common.

Autonomic testing

Given the significant clinical risk of autonomic morbidity and mortality in GBS, identifying autonomic neuropathy early in its course may be important. Here, we discuss potential prospective approaches that may be helpful in GBS patients (Table 1). Since none have had prospective evaluation of their predictive value in large series of GBS patients, they can only be regarded as investigational at this stage. Several are simple to perform, and thus could be used by clinicians to gain additional information about their patients. Microneurography or sudomotor testing, listed at the bottom of the list might not be widely available.

Using formal laboratory testing in experimental models and in patients with GBS, a number of studies have elucidated the pathogenesis, type, severity, distribution, and temporal course of the autonomic dysfunction associated with the disorder. Overall, most studies identify sympathetic hyperactivity and vagal dysfunction in the acute phase of the disease, although several variations exist.

Measurement of neurotransmitter levels in serum and urine as surrogate markers of autonomic functional status in GBS has been used in older studies, though these measures are limited by a number of confounding variables including age, stress caused by the disease, instability of the neurotransmitter with storage, and differences in measurement techniques [50–54]. In general, studies suggest excessive sympathetic hyperactivity in the acute phase of GBS as reflected by elevated plasma [50] or urinary [54] levels of catecholamine (norepinephrine and epinephrine) or their metabolites and cortisol, which may explain the episodes of hypertension in such patients. Conversely, other studies show a lack of correlation of the urinary metabolites, i.e. vanillylmandelic acid (VMA), and catecholamine with episodes of hypertension [51]. Levels of these neurotransmitters normalize after recovery from GBS, which is in agreement with recovery of physiologic autonomic parameters. Elevated levels of atrial natriuretic factor (ANF) [55, 56], and not vasopressin, may correlate with BP fluctuations

Table 1 Autonomic testing in GBS

Test	Description
Eyeball pressure testing [19]	Manual pressure applied bilaterally for 25 s or until manifestation of abnormal bradycardia, defined as heart rate below 40 beats/min
24-h heart rate power spectrum [20]	Utilizes the RR interval to analyze neural regulation of the cardiac function
Head-up tilt test [60]	Change in systolic/diastolic pressure in response to posture
Hand grip testing [60]	Blood pressure measurements in response to hand grip and standing
Cold pressor test [60]	Hand is placed in frigid water for approximately 1 min, and changes in heart and blood pressure are measured
Atropine test [60]	Atropine (0.02–0.04 mg/kg) is administered to differentiate bradycardia that is secondary to vagal stimulation vs myocardial in origin
Catecholamine testing [50, 54]	Elevated plasma/urinary norepinephrine and epinephrine associated with excessive sympathetic hyperactivity
Microneurographic studies [57, 58]	Microelectrodes used to measure muscle/skin sympathetic nerve activity
Sudomotor testing [59]	Assessment of sympathetic nerve fibers by skin sweat responses to ACh, tactile/mental stimulation, and Doppler measurement of skin blood flow

ACh acetylcholine

in patients with severe GBS. Hence, in three of 12 GBS patients who had severe cardiovascular dysautonomia (MAP fluctuation > 50 mmHg from baseline), the plasma ANF levels were markedly increased during episodes of hypertension. In one patient, the levels were elevated during both severe hypertension and hypotension. The levels in control patients (nine with GBS with no significant cardiovascular dysautonomia, and six with acute spinal cord injury) did not show any major changes in ANF levels. The vasopressin levels were higher in more severely affected patients who needed ventilatory support, but they did not correlate with the cardiovascular dysautonomia. The authors postulated that the increase in ANF may be a secondary phenomenon from increased catecholamine levels in GBS.

The most intriguing findings have been observed in studies that have directly measured the nerve activity from the sympathetic fibers innervating either the muscles or the skin [57, 58]. Serial microelectrode recordings of muscle nerve activity were performed in three patients with moderate to severe GBS during the acute phase of the disease when transient hypertension and tachycardia were present [57]. The sympathetic activity was significantly higher than that in the normal subjects and in four GBS patients without any autonomic symptoms. Similar but less robust findings were reproduced by microneurographic recordings of the skin sympathetic nerve activity (SSNA) in four patients with GBS that were associated with autonomic dysfunction [58]. In the acute phase of the disease, the basal or resting
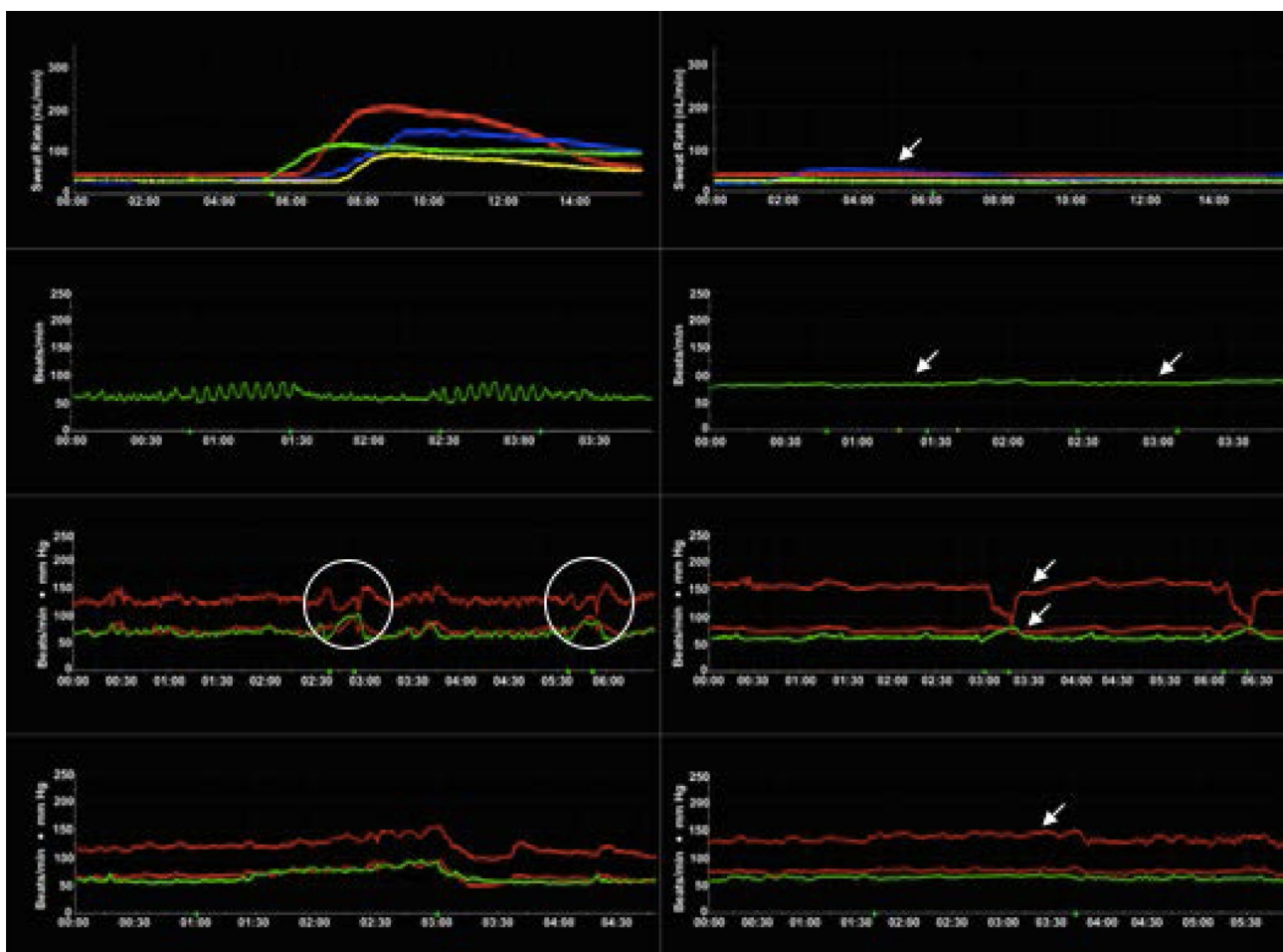

Fig. 2 Autonomic testing in various patients after recovery from a GBS episode (left column shows normal results, right abnormal). **a** Sweat (sudomotor) test at four sites: forearm, proximal and distal leg, and foot. **b** Heart rate variability to deep breathing. **c** Beat-to-beat blood pressure responses to Valsalva maneuver. **d** Systolic blood pressure response to isometric grip. **e** Tilt table test. Blood pressure (systolic and diastolic) and heart rate responses are depicted in red and green, respectively. The sweat test, which assesses post-ganglionic sympathetic fibers, can remain reduced after GBS (arrows), suggesting a residual autonomic neuropathy in a subpopulation of GBS patients (**a**). Reduced heart rate variability in response to deep breathing (**b** arrows) and Valsalva maneuver (**c**, arrow) are indicative of residual parasympathetic dysfunction. Cardiovascular sympathetic adrenergic response remains abnormal in some patients after GBS. These include loss of the typical blood pressure phases (**c**, circled) in response to Valsalva maneuver, attenuated blood pressure increase with sustained hand grip (**d** arrow), and orthostatic hypotension on tilt table testing (**e**, arrows)

SSNA was increased and sympathetic discharges in response to physiologic stimuli were excessive as compared to the controls. In all likelihood, this sympathetic hyperactivity underlies the transient elevations in blood pressure and heart rate in acute GBS. The underlying etiology for the higher firing rate of sympathetic nerve fibers is likely secondary to a lack of inhibitory afferents from the vagus nerves, which are commonly involved in GBS.

Other investigators have studied the pattern and extent of autonomic involvement in various forms of GBS using a battery of physiologic cardiovascular tests to draw inferences indirectly about the integrity of the ANS [59, 60]. These tests have the advantage of being non-invasive, quantitative, and reproducible, and include assessment of heart rate variability (HRV) during deep breathing, Valsalva maneuver for parasympathetic testing, and change in systolic and/or diastolic blood pressure to posture (head-up tilt test), hand grip, eyeball pressure (EP), and mental tasks for sympathetic responses. The EP test is simple to apply in a patient unable to cooperate for other tests, but care should be taken not to injure the eye and to have resources immediately available should bradyarrythmia from the test be prolonged. The skin sweat response to acetylcholine, tactile or mental stimulation, and Doppler measurement of skin blood flow (vasomotor) is used to assess the integrity of sympathetic nerve fibers. Among these, the sweat response to acetylcholine application is a valuable tool for differentiating pre-ganglionic from post-ganglionic involvement. These tests support the results of direct nerve recordings, though it appears that the pattern and extent of autonomic involvement may vary depending on the GBS subtype—AIDP, AMAN, or MFS. Indices that suggest sympathetic hyperactivity, i.e. heart rate and plasma noradrenaline concentration, were found to be elevated in eight AIDP patients but not in 15 patients suffering from AMAN [59]. Conversely, skin blood flow was generally preserved in both groups, whereas skin sweat responses were impaired in severely affected patients in both groups. In summary, AIDP is characterized by cardiosympathetic hyperactivity with preserved skin vasomotor function. The sweat response may be excessive or reduced depending on the severity of the disease. Autonomic dysfunction is not commonly detected in AMAN, with the exception of sympathetic dysfunction shown by reduced sudomotor function in patients with severe neurological deficits. The older literature also suggests an increased incidence of HRV abnormalities and patchy anhidrosis, irrespective of disease severity, though the disease variants had not been elucidated in that era [61].

Autonomic symptoms are not commonly reported in the MFS variant of GBS (with ataxia, ophthalmoplegia, areflexia). Interestingly, about 83% of patients exhibited subclinical autonomic dysfunction on formal autonomic testing in the absence of overt signs or symptoms of dysautonomia

Table 2 Summary of results for autonomic tests performed on 26 patients with GBS

Variable/tests	Total
No. of patients	26
Age in years: mean, SD	55.0 (11.5)
Gender: male/female	9/17
ODSS[a], mean (SD)	1.8 (1.9)
Abnormal autonomic test	
Sweat test	3 (11.5%)
Heart rate variability	
Deep breathing	1 (3.8%)
Valsalva ratio	4 (15%)
Orthostatic hypotension[b]	15 (57.6%)
Sustained isometric grip test[c]	17 (65%)

[a]Overall disability sum score ranges from 0 (normal) to 12 (lack of any functional movement of arms or legs)

[b]Drop in systolic blood pressure ≥ 30 mmHg on tilt table test

[c]Rise in diastolic blood pressure ≤ 16 mmHg in the contralateral arm

[62]. Serial autonomic testing was performed in nine MFS patients with no signs of cardiovascular, bowel/bladder, or other autonomic symptoms during active disease. All had good recovery. Initial testing within about 12 days of disease onset showed involvement of both the sympathetic (systolic blood pressure to hand grip and standing) and parasympathetic (HRV) parameters. On subsequent tests, most abnormalities improved within 4–12 weeks after the onset of neuropathy. Sympathetic responses were more commonly targeted, leading the authors to suggest that the parasympathetic fibers may be less vulnerable than the sympathetic fibers in MFS. The autonomic testing battery employed in this study [62] did not differentiate between pre- and post-ganglionic involvement, and it is possible that there may be a central component of autonomic dysfunction.

Confounders in autonomic testing

It is important to remember that GBS patients often require mechanical ventilation and can suffer complications as a result of their ICU stay. Prior to attributing autonomic symptoms to their disease, one should rule out electrolyte disturbances, pulmonary embolus, ventilator-associated infections, and pre-existing heart disease [7]. In addition, critical illness neuropathy and myopathy from prolonged ICU admissions may interfere with autonomic testing. Given that many of these patients need an ICU or, at the very least, a step-down ward, certain autonomic tests (e.g. hand grip testing) are not useful in the acute setting. It is in these instances that HRV and EP testing may be of greater utility [19].

Long-term prognosis of autonomic dysfunction

Follow-up laboratory studies of autonomic dysfunction associated with GBS are rare. In patients with MFS [62] and mild GBS [63], longitudinal laboratory tests show that most sympathetic and parasympathetic indices tend to improve over time [62–65], leading to the conclusion that subclinical autonomic dysfunction is common in GBS, though it is temporary and resolves spontaneously. No clinically significant residual autonomic dysfunction was reported in these studies after a year. In contrast, Kopeppen et al. showed persistent abnormalities in cardiovascular indices when studied 7–86 months after onset of GBS [66]. In 34 patients with GBS (including five patients with MFS), autonomic function testing of the cardiovascular system showed abnormal blood pressure response to standing in 27 of 33 patients (82%). Our laboratory data also support this finding [67]. We performed comprehensive autonomic testing in 26 patients 3–8 years after the onset of GBS. These patients had good motor recovery as shown by low overall disability sum scores [68]. Abnormalities in parasympathetic indices, i.e. heart rate response to deep breathing and Valsalva maneuver (Fig. 2a, b), were rare. Tests of sympathetic indices, on the other hand, showed orthostatic hypotension and an abnormal increase in blood pressure to sustained hand grip (Fig. 2c, d) in a larger number of patients (Table 2) with no overt clinical manifestations of orthostatic hypotension. In summary, most studies show that clinical autonomic dysfunction after GBS is transient and resolves over time. Subclinical abnormalities, particularly of the sympathetic indices, may

Fig. 3 Proposed schemata for management of GBS patients with dysautonomia (modified from with permission from Zochodne 1994)
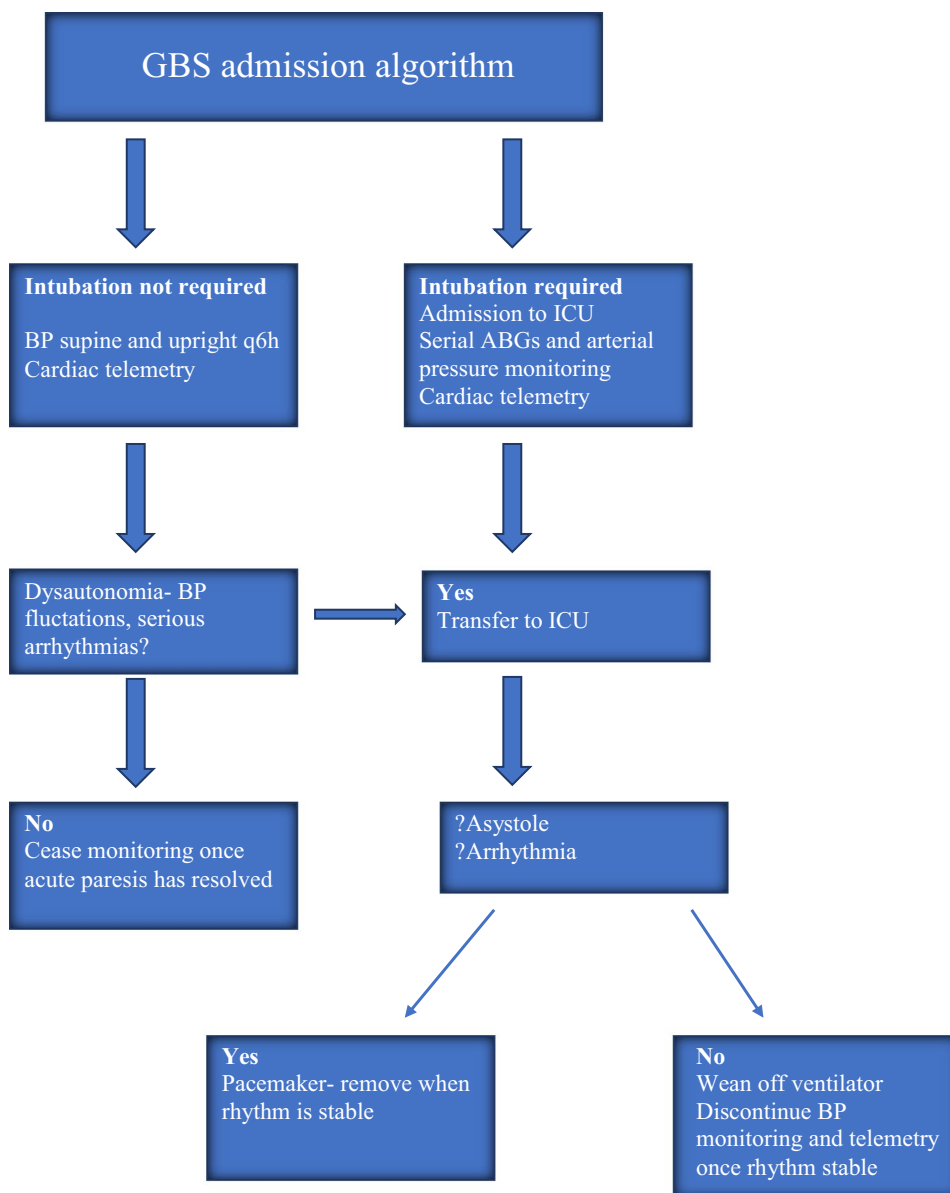
still be detectable on dedicated laboratory testing long after the GBS episode.

Immunotherapy for dysautonomia

As discussed earlier, GBS is an autoimmune polyradiculoloneuropathy. Two types of immunotherapy used to treat GBS and its sequelae are plasmapheresis (PLEX) and IVIG [69]. PLEX involves the exchange of an individual's plasma with a different solution to remove autoantibodies. In IVIG, pooled immunoglobulin from numerous donors is administered at a dose of 0.4 g/kg per day for 5 days, with a maximum total dose of 2 g/kg. It is unclear whether early treatment with PLEX or IVIG could also contribute to improvement in autonomic symptoms.

In a meta-analysis of six trials, PLEX was compared with supportive treatment alone [70]. Results demonstrated that PLEX was effective in reducing the numbers of days patients were intubated and was associated with a decline in the number individuals requiring mechanical ventilation. In addition, there was significant improvement in muscle strength after 1 year and in the ability to walk without aid. In trials comparing IVIG to PLEX, there was no difference found in disability, mortality, or need for mechanical ventilation. In fact, mortality is usually secondary to complications resulting from a prolonged hospital stay. These immunotherapies are best implemented within 2 weeks from onset of symptoms. Further analysis from newer trials with autonomic measures would be needed to establish whether immunotherapy is helpful.

Conclusions

Given that autonomic dysregulation may precede neurological deficits in GBS patients, early identification of dysautonomia could hasten diagnosis and management. Autonomic dysfunction, if not discovered and managed early, may be associated with significant mortality. Thus, we recommend that GBS patients receive regular negative inspiratory force/vital capacity assessments and close observation of blood pressure, and be admitted to a unit with cardiac telemetry. The importance of the multidisciplinary team cannot be overstressed when discussing this unique syndrome; involvement of the respiratory therapist and the intensivist, and clear communication with the ward nursing staff regarding the monitoring of vital signs is essential. While many of the bedside tests discussed in this review are not offered as first-line investigations for GBS patients, they likely have utility given the appropriate clinical setting (Fig. 3).

Compliance with ethical standards

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