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REVIEW

Autonomic dysfunction in the neurological intensive care unit

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Abstract
Autonomic dysfunction is common in neuro-critical care patients and may compromise the function of various organs. Among the many diseases causing or being associated with autonomic dysfunction are traumatic brain injury, cerebrovascular diseases, epilepsy, Guillain–Barré syndrome (GBS), alcohol withdrawal syndrome, botulism and tetanus, among many others. Autonomic dysfunction may afflict various organs and may involve hyper- or hypo-activity of the sympathetic or parasympathetic system. In this short overview, we address only a small number of neuro-intensive care diseases with autonomic dysfunction. In GBS, autonomic dysfunction is frequent and may account for increased mortality rates; rapid changes between sympathetic and parasympathetic hypo- or hyper-activity may cause life-threatening cardiovascular complications. Paroxysmal sympathetic hyperactivity occurs after brain injury, hypoxia and cerebrovascular and other events, causes paroxysmal tachycardia, hypertension, tachypnoea and hyperthermia and is associated with a poorer prognosis and prolonged intensive care treatment. Other, at times life-threatening autonomic complications with exaggerated sympathetic activity and compromised baroreflex sensitivity arise during the alcohol withdrawal syndrome triggered by abrupt cessation of alcohol consumption. Botulism and tetanus are examples of life-threatening autonomic dysfunction caused by bacterial neurotoxins. Common neurological diseases, such as epilepsy, stroke or subarachnoid haemorrhage, are also associated with autonomic dysfunction that can on occasion cause critical deterioration of disease severity and prognosis.

Keywords Autonomic dysfunction · Neurological intensive care medicine · Guillain–Barré-syndrome · Tetanus · Botulism · Alcohol withdrawal syndrome · Paroxysmal sympathetic hyperactivity

Introduction

Autonomic dysfunction is common in patients requiring neurological intensive care treatment [97, 98]. Among the numerous neurological diseases associated with or caused by autonomic dysfunction are seizures, ischaemic or haemorrhagic stroke, subarachnoid haemorrhages, brain tumours, traumatic brain injury (TBI), Guillain–Barré syndrome (GBS), botulism, tetanus, drug or alcohol withdrawal syndrome (AWS) and many others [97, 98]. Autonomic symptoms may afflict many organs and manifest e.g., predominantly as cardiovascular autonomic dysfunction, thermoregulatory or sudomotor, gastrointestinal, bladder or genital dysfunction or as a combination of multiple organ involvement [61, 85]. Dysfunction may involve the sympathetic as well as the parasympathetic and enteric system [61, 85] and result in reduced or excessive activity of the autonomic nervous system branches [61, 85]. Particularly in GBS, rapid changes and varying combinations of hypo- and hyperactivity of both the sympathetic or parasympathetic system may cause significant and at times fatal complications and pose major therapeutic challenges [40, 89].

This short overview will address only a few of the neuro-intensive care diseases with autonomic dysfunction and mention only the most prominent clinical aspects of autonomic dysregulation.

Paroxysmal sympathetic hyperactivity

Paroxysmal sympathetic hyperactivity (PSH) may develop in patients, particularly in those with acquired brain injury due to trauma, but also after hypoxia and cerebrovascular

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and other events [79]. This syndrome is characterized by paroxysmal tachycardia, hypertension, tachypnoea, hyperthermia and decerebrate body position upon afferent stimulation [69]. The prevalence of PSH in patients admitted to the intensive care unit (ICU) varies between studies conducted at different times and in various countries [11, 31, 83]. In a prospective observational study of 79 patients with moderate or severe TBI admitted to the ICU from 2004 to 2006, Baguley et al. [11] observed PSH in 24% of patients on day 7 and in 8% on day 14 after ICU admission [11]. In a retrospective study of 333 Italian patients in vegetative state admitted from 1998 to 2005, Dolce et al. found PSH in 26.1% of the patients [31]. In a follow-up study of 169 patients in vegetative state admitted from 2006 to 2010, these same authors found PSH in only 18% in patients admitted due to TBI and 7% in patients admitted due to other causes [83]. The question which arises is whether advances in neuro-intensive care treatment had any effects on the manifestation of PSH.

The syndrome is often associated with a poorer prognosis and prolonged hospitalization; intensive care treatment may be challenging, and the patients needs individualized medication and nutritional replacement of energy and fluid losses due to increased metabolism, fever and excessive sweating [69, 79]. Several studies have shown that PSH is associated with worsening of the short- and long-term prognosis [69]. In a Chinese study of 87 patients with severe TBI, Lv et al. found that PSH occurred in 16 (18.4%) patients and was associated with longer ICU and hospital stays, longer duration of tracheotomy and mechanical ventilation, and a higher degree of long-term disability as assessed by Glasgow Outcome Scale (GOS) 12 months after the injury [62]. Similarly, Dolce et al. also found that the occurrence of PSH has negative effects on the short-term outcome at the time of ICU discharge [31]. In a prospective observational study of 343 adult patients with severe TBI, Mathew et al. found that approximately 8% of the 343 patients developed PSH, and that these 29 PSH patients had more severe disability upon discharge from ICU and a less favourable outcome after 6 months, with higher mortality rates than the patients without initial PSH [63]. Similarly, Fernandez-Ortega et al. showed in a case–control study that patients with PSH require longer mechanical ventilation, longer intensive care treatment and longer hospitalization than do patients without PSH; surprisingly, after 12 months the GOS scores did not differ between the patients with and those without PSH [36, 37]. However, most studies do show that PSH is associated with poorer prognosis [69].

Treatment is not standardized due to the poor understanding of the pathophysiology of the syndrome [8, 69, 79]. In a recent review, Meyfroidt et al. postulated that the three major treatment goals are (1) avoiding the triggers to provoke PSH, (2) mitigating the increased sympathetic activity and (3) reducing the damage to related systems and organs [69]. At the present time, there are no available randomized controlled clinical trials on the management of PSH. Therapeutic evidence is based on retrospective studies or case series. Many different classes of medications have been used to treat patients with PSH; among these are opioids, intravenous anaesthetics, beta-adrenergic blockers, alpha2-agonists, neuromodulators and benzodiazepines, as well as sarcolemmal Ca^{2+} release blockers [69]. The most effective pharmacological management is achieved with opioids, such as morphine or fentanyl, and with beta-adrenergic blockers [69, 84]. In their retrospective case–control study of 35 patients with dysautonomia after severe TBI, Baguley et al. reported that cessation of morphine and midazolam resulted in a significantly increased heart rate and respiratory rate. These authors also suggested the use of intravenous morphine, benzodiazepines, propanolol, bromocriptine and possibly intrathecal baclofen for the pharmacological management of TBI-induced dysautonomia [9]. In two patients with PSH due to benign tumors compressing the brainstem, Lee et al. found that fentanyl patches significantly improved PSH symptoms [59].

While opioids should be considered with utmost care in an era of epidemic opioid misuse, beta-adrenergic blockers, such as labetalol, also have been shown to sufficiently supress PSH after TBI [30]. Alpha2-agonists, such as clonidine, reduce the plasma catecholamine levels in patients after severe TBI and are helpful in treating hypertension and tachycardia in PSH patients [84]. A few case reports describe beneficial effects of the dopamine D_2 agonist bromocriptine on fever and excessive sweating in TBI-induced PSH [18, 93]. In patients with acute brain injury, the withdrawal of the gamma-aminobutyric acid B ($GABA_B$) agonist baclofen may cause PSH presenting features [23, 111], while oral or intrathecal baclofen administration may alleviate PSH features after severe TBI [15, 26]. Baguley and co-workers also reported beneficial effects of gabapentin on PSH in a few patients with severe TBI [10].

Proposed pathophysiological mechanisms include disconnection between cortical inhibitory brain regions, such as the insula or cingulate cortex, and centres in the hypothalamus, diencephalon and brainstem that control sympatheticoutflow [69]. Another model, the excitatory:inhibitory ratio model, assumes that there is a disconnection of descending inhibitory pathways from brainstem nuclei to spinal reflex arcs [8, 69]. These descending pathways normally assure an adequate balance between excitatory and inhibitory spinal interneurons [8, 69, 79]. The model postulates disinhibition, which may result in exaggerated motor and sympathetic output in response to normal, i.e. usually non-noxious, sensory stimuli [8, 69, 79].

Guillain–Barré syndrome

Sympathetic hyperactivity may also occur in patients with GBS. However, autonomic dysfunction in GBS is typically characterized by rapid changes between sympathetic and/or

parasympathetic hyper- or hypo-activity [60, 89]. Autonomic dysfunction occurs in almost two-thirds of GBS patients [89]. In various studies on GBS patients, paroxysmal hypertension has been in 24% of the GBS patients participating in the study [108], orthostatic hypotension (OH) in 43% [60], sustained sinus tachycardia in 25–38% [74], bradyarrythmias in 7–34% [38], urinary dysfunction in 27% and urinary retention in 9%s [95] and adynamic ileus in 15% [19]. Anandan et al. evaluated nation-wide inpatient sample data from 2010 to 2011 of 2587 GBS patients in the USA and found that 16% of GBS patients had diarrhea, 15% had hyponatraemia, 5% had bradycardia, 4% had urinary retention, 3% had tachycardia, 1% had reversible cardiomyopathy and 1% had Horner syndrome [3]. Among the symptoms caused by sympathetic underactivity are orthostatic syncope, bradycardia and anhidrosis [60, 110]. Sympathetic overactivity may trigger paroxysmal hypertension, paroxysmal tachycardia, extrasystoles and peripheral vasoconstriction, as well as profuse hyperhidrosis [27, 60, 108]. Parasympathetic underactivity may cause tachycardia, bladder and gastrointestinal dysfunction [60], while parasympathetic overactivity accounts for paroxysmal bradycardia, reflex asystole, generalized warmth or gastrointestinal hypermotility [60, 117]. Sudomotor dysfunction may result in patchy anhidrosis as well as hyperhidrosis [110]. Vasomotor dysfunction may cause dry and pale or erythematous skin [73, 110]. Other possible symptoms include altered fluid and electrolyte regulation with fluid retention and electrolyte imbalance, including low sodium and potassium levels; gastrointestinal dysfunction may manifest as diarrhea, constipation, gastropareses and ileus [80, 117].

Blood pressure may rapidly change from postural or episodic hypotension to episodic or sustained hypertension, while heart rate often varies between sinus tachycardia and tachyarrhythmia or bradycardia, bradyarrhythmia and asystole [60, 80, 108, 116, 117]. Patients are often hypersensitive towards vasoactive drugs [60, 80, 108, 116, 117]. Among the common, usually benign cardiac autonomic changes are sinus tachycardia and postural hypotension as well as minor electrocardiographic changes [117]. In contrast, several serious cardiovascular changes require particular attention; these include sustained or episodic hypertension which may lead to papilloedema or even seizures, increased intracranial pressure and subarachnoid haemorrhage, but also episodic hypotension, bradyarrhythmias with bradycardia and asystole as well as tachyarrhythmias [117]. Often there is excessive cardiovagal hyper-reactivity to mild stimuli, such as mild ocular pressure or protruding of the tongue, which may trigger bradycardia or even sinus arrest [40, 70]. Events of asystole cannot be predicted and may occur unexpectedly [40].

Management of autonomic dysfunction in GBS is multimodal. Paroxysmal hypertension is mostly short-lived and often does not require treatment [44, 108]. However, if fluctuations are severe enough to cause end-organ damage, treatment with short-acting medications that can be quickly titrated, such as hydralazine and labetolol, is recommended to manage hypertension and to avoid subsequent hypotension [21, 44, 74]. In the case of severe hypertension, the use of labetalol, esmolol or nitroprusside may be indicated [74]. However, there do not seem to be specific recommendations regarding the target blood pressure in GBS patients [74]. Thus, the treating physician must consider the specific cardiovascular condition of each individual GBS patient.

Potential treatments of hypotension include leg elevation, intravenous fluids, compression stockings and medications such as midodrine or intravenous vasopressors (e.g. norepinephrine or phenylephrine) [44]. Sedated patients on mechanical ventilation should also be monitored for sudden hypotensive episodes [44, 74]. As early as 1984, Truax recommended not leaving GBS patients unattended in an upright or sitting position without prior assessment of OH, and to avoid treating GBS patients with OH with drugs that lower blood pressure, such as diuretics [108]. In most cases, OH responds to volume expansion with the intravenous administration of fluid and usually resolves with GBS improvement [108]. In patients with refractory OH, treatment with sodium chloride tablets, fludrocortisone or midodrine could be considered [21].

Vagal hypersensitivity is one of the major causes of mortality in GBS patients [39] and may cause bradycardia and cardiac arrest triggered by, for example, common nursing activities, such as tracheal suction, cleaning the patient's teeth or applying minor pressure onto the eyes during nursing activities [21, 39, 70, 108]. Consequently, such activities or changing of tracheal tubes require specific caution, and atropine and cardiac pacing should be at hand [74]. In the case of asystole, trans-venous pacemakers at best provide an interim, short-term prophylaxis since long-term use may be associated with an increasing risk of endocarditis [5, 20]. Therefore, the use of a transthoracic pacemaker with pre-set stimulation parameters and predefined positioning of electrodes may help prevent fatal asystole and bridge the time until a trans-venous or permanent-pacemaker can be placed [48].

In cases of sinus tachycardia, conditions such as dehydration, fever, hypotension or infection need to be considered. If these causes of tachycardia are ruled out, short-acting beta-blockers, such as labetalol, may be helpful in patients with hypertension and tachycardia [74]. However, there is a risk of aggravating underlying hypotension and bradycardia [81, 82, 91], and beta-blockers must be carefully titrated [21].

Urinary dysfunction may occur in the early stages of GBS in GBS patients [95, 108]. Sakakibara et al. observed bladder dysfunction in 27% of their GBS patients and found correlations with motor weakness[95]. Management ofurinary dysfunction is mainly supportive [95]. Drugs such

muscarinic agonists may exacerbate cardiovagal hypersensitivity and are therefore not recommended for the treatment of GBS-related urinary retention [108]. Instead, urinary retention is usually managed by indwelling bladder catheters [95, 115] that are more practical than intermittent catheterization [21, 52, 108, 115]. However, a sterile, closed urinary drainage system must be used to reduce the risk of bladder infection [52].

Gastrointestinal autonomic dysfunction may manifest as constipation, gastric immotility and adynamic ileus. Therefore, GBS patients should routinely undergo clinical abdominal examination and auscultation to identify bowel silence and incipient ileus at an early stage [52]. Opioids should be avoided, and enteral feeding might have to be paused to avoid progression of pre-ileus symptoms [52]. While erythromycin and neostigmine may be used to treat paralytic ileus [52], prokinetic drugs such as neostigmine may increase the risk of cardiovagal hyperactivity with bradyarrhythmia or asystole [115]. Instead, stool softeners, enema, manual dis-impaction or decompressive colonoscopy may alleviate symptoms of gastrointestinal hypomotility [108, 115]. To date, there are no reports on the benefits or risks of novel prokinetics, such as the 5-HT4 agonist prucalopride that stimulates colonic peristalsis; this drug has been approved for the treatment of adult chronic idiopathic constipation in Europe and is currently seeking approval in the USA by the U.S. Food and Drug Administration [94].

The rapid changes between over- and underactivity of both autonomic branches may result from inflammatory lesions causing multifocal nerve demyelination and unstable conduction blocks which may compromise the afferent branches of the baroreflex arc, as well as by efferent sympathetic and parasympathetic fibres [80]. However, the pathology is more complex: there is evidence of lymphocyte and macrophage infiltration in tissue surrounding endoneural vessels, accounting for the inflammatory peripheral neuropathy [7]. Among other findings, there is also evidence of degeneration in abdominal sympathetic ganglia, of demyelination and axonal degeneration of the vagus nerve [92] and of the involvement of the glossopharyngeal nerve [4, 7], inflammation of the superior cervical ganglion [45], demyelination in the paravertebral sympathetic chain and inflammatory infiltration in intra-cardiac ganglia [56]. Furthermore, there may be involvement of autonomic visceral sympathetic and parasympathetic fibres [117]. In their study, Birchfield et al. reported chromatolytic changes in the intermediolateral cell column [17], while Panegyres et al. observed inflammatory infiltration of the hypothalamus and brainstem in GBS patients [76].

In summary, autonomic dysfunction poses a significant risk in GBS patients and increases mortality rates [60], particularly since there is no clear association between the severity of motor weakness and the severity of autonomic disturbances [110]. GBS patients with autonomic dysfunction have a poorer prognosis than GBS patients without involvement of the autonomic nervous system [53] and also an increased risk of sudden death [117]. Also, a recent meta-analysis of nine studies in GBS patients with and without autonomic dysfunction showed in six of these studies, patients with autonomic dysfunction required intubation and ventilation more frequently than did their counterparts without autonomic instability [42]. Moreover, autonomic dysfunction may manifest during the early phase or the recovery phase of GBS, when patients are commonly thought not to be at increased risk [28]. Therefore, GBS patients should undergo autonomic testing even at stages of motor weakness when they do not require intensive care treatment. In 25 GBS patients who did not need intensive care therapy, we tested heart rate variability and found altered autonomic modulation both at rest and during metronomic breathing, active standing-up and the Valsalva maneuver in 24–40% of the patients (unpublished data.). In a recent study using the Health Cost and Utilization Project Nationwide Inpatient Sample, the authors identified 2587 GBS patients hospitalized during 2010 and 2011. Autonomic dysfunction resulted in diarrhoea/constipation (15.5%), hyponatremia (14.9%), syndrome of inappropriate antidiuretic hormone secretion (SIADH) (4.8%), bradycardia (4.7%) and urinary retention (3.9%) [3]. In 28 children with GBS, Samadi et al. recorded heart rates to be similar to those of 20 healthy age- and gender-matched persons while they found significantly reduced heart rate variability in the GBS patients [96]. Since GBS patients might develop critical cardiovascular dysfunction rather quickly and unexpectedly, careful autonomic monitoring is indicated in these patients.

Alcohol withdrawal syndrome

Alcohol withdrawal syndrome is associated with another rather frequent and dangerous array of autonomic disturbances [66]. AWS is usually induced by the abrupt cessation of alcohol consumption by alcohol-dependent patients [66]. Delirium tremens—the most severe form of AWS, occurring in approximately 5% of hospitalized patients with AWS [66]—in particular is accompanied by life-threatening autonomic symptoms, such as tachycardia, increased blood pressure, sweating, nausea, palpitations and tremulousness, and is frequently associated with seizures or even status epilepticus [66, 67]. Acute AWS is often accompanied by exaggerated sympathetic modulation and impaired baroreflex sensitivity [12], with the latter considered to be a marker of poor prognosis [58, 72, 75, 86, 101]. However, cardiovascular autonomic parameters usually change during the treatment of AWS. Kähkönen et al. showed that changes in heart rate, blood pressure and total peripheral resistance observed upon

acute alcohol withdrawal attenuated over the first 10 days of hospitalization and alcohol withdrawal, following which time the autonomic and cardiovascular parameters no longer differed from those recorded in patients who had been suffering from alcohol abuse but had been abstinent for at least 1 month [55].

The management of AWS should include a thorough review of the patient's medical history, with a specific focus on any recent change in alcohol use or abstinence. Particularly in patients with a history of chronic alcohol abuse, other medical conditions that might mimic AWS should be excluded [46, 64, 99]. Symptoms suggesting AWS might be due to conditions such as meningitis, brain trauma, hepatic or renal failure, electrolyte abnormalities, drug effects (particularly drug-overdosing) or post-surgical confusion and so-called "post-surgical aggression syndrome" with stress-induced sympathetic hyperactivity and endocrine alterations due to post-surgical intermittent hypothalamic and pituitary gland dysregulation [100, 114] or due to sedating medication, among others [46, 64, 99]. The administration of sedating drugs, commonly used in AWS, would very likely worsen such diseases or conditions [46]. Patients with early and mild stages of AWS may not necessarily need pharmacological treatment but could be managed with supportive and general care; if benzodiazepines are to be avoided, alternative drugs may be used, such as carbamazepine [13], valproate or gabapentin, among others [71]. Early diagnosis of AWS is essential to avoid the development of delirium tremens, which is associated with high mortality rates if left untreated[29, 57, 99]. Patients with delirium tremens must be treated on ICUs [99]. Commonly, benzodiazepines, such as diazepam, lorazepam or chlordiazepoxide, need to be administrated intravenously to sedate patients and reduce sympathetic hyperactivity [66, 99]. Often a combination therapy of benzodiazepines with neuroleptic medication, such as haloperidol [15, 64, 99], barbiturates [29, 64] or the alpha2-adrenoceptor agonists clonidine or dexmedetomidine [29, 105], is needed. A combination of benzodiazepines with propofol may improve the symptoms of patients requiring mechanical ventilation [25, 64, 65, 99]. Patients with AWS usually have a history of malnutrition and are vitamin deficient, particularly in vitamin B1 [50, 51, 64]. Thus, early and high doses of thiamine and multivitamin supplements is essential [64]. Moreover, fluid and electrolyte replacement, re-adjustment of fluid and electrolyte balance and the adjustment of respiration and acid–base balance may be needed to stabilize the patient [64, 99]. Continuous monitoring of vital parameters is essential to prevent critical derangements [64, 99]. In recent decades, the mortality rate of patients with delirium tremens has decreased from > 30% to < 5% [35, 66] due to a better understanding of the pathophysiology, earlier diagnosis and improved ICU management [29, 57]. Khan et al. found that early-onset hyperthermia occurring within the first 24 h and persistent tachycardia, both in association with delirium tremens, increase the mortality rates of patients with delirium tremens [57].

AWS should be differentiated from Wernicke's encephalopathy and from Korsakoff's psychosis. In Wernicke's encephalopathy, the typical triad of encephalopathy, oculomotor dysfunction and gait ataxia, is only present in < 20% of patients and may account for misdiagnoses [102, 107]. Korsakoff's psychosis with severe anterograde and retrograde amnesia, disorientation and confabulation might also be misdiagnosed as delirium tremens [103]. However, reports of recent cessation of alcohol consumption point towards AWS, while increased blood alcohol levels or reports of continuous alcohol consumption with oculomotor dysfunction or severe amnesia facilitate the diagnosis of Wernicke's encephalopathy or Korsakoff's psychosis, respectively [103]. All three disorders require vitamin B1 replacement therapy.

Botulism

Botulism is caused by the deadly, neuroparalytic toxin of the obligate anaerobic bacillus *Clostridium botulinum* [6]. According to Jeffrey and Karim [54], 3618 botulism cases were recorded in the USA between 1975 and 2009, with an overall mortality of 3.0% during this time span. In comparison, the number of annual cases were higher between 2011 and 2015, amounting to 162 patients per year [54]. A common type of bolulism is the food-borne botulism, resulting from the ingestion of toxin contained in, for example, home-canned food or fermented uncooked dishes [6]. Infantile botulism arises from the colonization and proliferation of *C. botulinum* in an infant's gastrointestinal or bronchial tract due to an inadequate immune system [6, 54]. Wound botulism is frequently also due to *C. botulinum* proliferation, but in anoxic, devitalized tissue—for example, as a result of injecting illicit drugs contaminated by *C. botulinum* spores [6, 54]. Botulinum toxin binds presynaptically onto cholinergic nerve terminals and blocks the release of acetylcholine [34]. The resulting botulism is characterized by facial and bulbar motor weakness, ptosis, ophthalmoplegia, dysphagia, dysphonia, dysarthria and finally by descending paralysis, including respiratory failure due to paralysis of the diaphragm, as well as prominent autonomic dysfunction [6, 54]. Autonomic symptoms include blurred vision, dry mouth, constipation or ileus, flaccid bladder and urinary retention, hypohidrosis, high resting heart rate, altered heart rate variability and baroreflex function, supine hypertension and orthostatic hypotension [54, 106]. There are reports of botulism manifesting as pure autonomic failure, with transient bladder and gastrointestinal dysfunction and persistent anhidrosis and erectile dysfunction [68]. While there seem to be no data on the prevalence of

autonomic dysfunction in botulism, autonomic dysfunctions are the key features of this disease and account for its major initial symptoms.

In one case study, 2 weeks after disease onset six patients with botulism still had absent sympathetic skin response (SSR), significantly decreased heart rate variability (HRV) during rest and deep breathing and significantly lower plasma norepinephrine levels in the supine and standing position. Both SSR and HRV improved after 6 months [22]. Vita and co-workers reported early dysfunction of heart rate and blood pressure control in four patients with botulism and showed that recovery of autonomic dysfunction may be slower than neuromuscular recovery. The authors also underlined the relevance of autonomic testing to identify patients at increased risk of cardiovascular or respiratory complications [112]. Similarly, Patural et al. recorded cardiovascular autonomic dysfunction in three infants aged 17, 30 and 180 days, respectively, with infantile botulism at the disease onset and confirmed the persistence of autonomic dysfunction beyond the stages of physical recovery; again, the authors emphasized the importance of close autonomic monitoring to reduce the risk of potentially fatal cardiovascular complications [78]. In contrast, Topakian et al. assessed cardiovascular autonomic function in four patients with botulism; these patients initially had more prominent autonomic dysfunction than motor dysfunction but their cardiovascular parameters recovered 12 weeks after the intoxication [106]. Thus, there seems to be individual variability in terms of the recovery times of autonomic dysfunction in botulism. Therapy includes the administration of anti-toxin, close cardiovascular and respiratory monitoring, intubation and mechanical ventilation when needed, wound excision and debridement, including antibiotic therapy in the case of wound botulism [54]. Previous case reports suggest the benefits of long-term cardiopulmonary monitoring [22, 78, 106, 112]. According to our personal—unpublished—experience with single cases of food-borne botulism, autonomic cardiovascular dysfunction may persist beyond the need of intensive care treatment.

Tetanus

Tetanus, another toxin-induced, life-threatening disease, is caused by the Gram-positive *Clostridium tetani*, which secretes tetanospasmin and tetanolysin under anaerobic conditions [24]. Tetanus has a high risk of mortality, particularly in the developing world, with an estimated incidence of at least 700,000 cases per year [6]. Tetanospasmin inhibits the pre-synaptic release of glycine and GABA [34]. Thus, in theinitial phase of infection, inhibitory neurons are compromised, resulting in a loss of inhibitory control of motor neurons; subsequently, preganglionic sympathetic neurons and parasympathetic centers are also affected. The toxin also compromises motor neurons and reduces the release of acetylcholine into the neuromuscular junction, which may cause motor weakness between episodes of spasm. However, the toxin's disinhibitory effect on motor neurons outweighs the effects of reduced acetylcholine release at the neuromuscular junction and accounts for the typical tetanic rigidity, with muscle spasms causing the "*risus sardonicus*" or even opisthotonus [24]. Accurate data on the prevalence of autonomic dysfunction in tetanus are seemingly unavailable, but even with the early implementation of intensive care treatment the more severe stages of tetanus, particularly Ablett stages III and IV, have been reported to be associated with prominent and life-threatening autonomic dysregulation, particularly with sympathetic instability [1, 24, 47].

Autonomic dysfunction primarily affects the sympathetic system and results in persistent tachycardia, hypertension, vasoconstriction and fever with elevated catecholamine levels that may alternate with severe arterial hypotension, bradycardia and even asystole due to excessive vagal activity [24]. To date, there have been no large-scale studies with the aim to determine specific preferences for the treatment of tetanus-associated autonomic symptoms. In a review of the pharmacological management of tetanus, Rodrigo et al. recommend several key principles, including sedation and muscle relaxation, surgical debridement and antibiotic treatment, toxin neutralization and intensive care treatment of all concomitant autonomic symptoms [88]. Benzodiazepines are recommended due to their muscle relaxant, sedating, anxiolytic and anticonvulsant effects. Intravenous magnesium sulfate, which is widely used in eclamptic women, may be beneficial in tetanus patients to alleviate tetanic spasms but may also be associated with lower catecholamine, in particular adrenaline release [104]. Rodrigo and co-workers concluded that magnesium has beneficial effects not only on muscle spasms, but it also mitigates autonomic instability [88]. Beneficial effects on sympathetic hyperactivity have also been observed with clonidine [43], dexmedetomidine [41], labetalol [32], esmolol [14], morphine [87] and epidural blockade with bupivacaine and sufentanil [16]. However, larger clinical trials are needed to provide more clinical evidence.

Despite advances in the neuro-intensive care treatment of tetanus patients [24, 109], autonomic instability remains a major cause of the high mortality rates in patients with this disease [2, 24, 113]. Patients with more severe manifestations of tetanus, particularly those with grades Ablett III and IV [1], have prominent and life-threatening autonomic dysfunction which compromises prognosis and requires intensive care treatment [2, 24]. Specific symptoms such as tachy-/bradycardia, hypo-/hypertension, tachypnea/apnea, ileus or diarrhoea require individualized treatment, the

Table 1 Epidemiology, autonomic characteristics, treatment and prognosis of paroxysmal sympathetic hyperactivity, alcohol withdrawal syndrome, tetanus, and botulism

Disease	Epidemiology	Autonomic characteristics	Treatment	Prognosis
PSH	Prevalence of PSH ranges from 8 to 33% after TBI or other brain injuries in various studies [11, 37, 69, 83]	Paroxysmal tachycardia, hypertension, tachypnoea, hyperthermia and decerebrate body position upon afferent stimulation [69]	Opioids; beta-adrenergic blockers; alpha2-agonists; bromocriptine; gabapentin; baclofen; benzodiazepines, among others [9, 10, 15, 18, 26, 30, 59, 69, 111]; monitoring of vital signs, i.e. heart rate, blood pressure, respiration, temperature, and sweating, muscle tone	Independently associated with poor short- and long-term prognosis, e.g. longer duration of mechanical ventilation and hospital stay, poor neurological recovery and increased mortality rates [31, 36, 37, 61–63]
AWS	20% of men and 10% of women in Western countries have an alcohol-use disorder [54]. About 50% of persons with alcohol-use disorder will develop AWS [54]. 5% of hospitalized patients with AWS might develop delirium tremens [74]	Exaggerated sympathetic modulation and impaired baroreflex sensitivity; tachycardia, increased blood pressure, sweating, nausea, palpitations and tremulousness [66]	Intravenous administration of benzodiazepines, such as diazepam and lorazepam [99]; nutrition therapy with thiamine and multivitamins [99]; monitoring of vital signs every 15–30 min [99]	Mortality of untreated delirium tremens is > 30% but can be decreased to < 5% with intensive care therapy [35, 66]; early-onset hyperthermia within the first 24 h and persistent tachycardia are associated with increased mortality in patients with delirium tremens [57]
Tetanus	At least 700,000 per year globally [6]	Sympathetic activation with tachycardia, hypertension, vasoconstriction and fever may alternate with excessive vagal activity and severe arterial hypotension, bradycardia and even asystole [24]	Sedation and muscle relaxation; surgical debridement and antibiotic treatment; toxin neutralization; intensive care treatment [9]	Autonomic instability in severe disease is associated with high mortality rates in tetanus patients [2, 24, 111]; specific interventions targeting autonomic dysfunction need more clinical evidence.
Botulism	Around 160 cases per year in the USA [54]	Blurred vision, dry mouth, hypo-/anhidrosis, constipation or ileus, flaccid bladder and urinary retention, erectile dysfunction, high resting heart rate, altered heart rate variability and baroreflex function, supine hypertension and orthostatic hypotension [54, 106]	Antitoxin wound excision and debridement'; antibiotic therapy; cardiovascular and respiratory monitoring; intubation and mechanical ventilation when required [54]	Overall mortality was 3.0% in the years 1975–2009 in the USA [54]. Long-term cardiopulmonary monitoring is beneficial to avoid cardiovascular complications

PSH Paroxysmal sympathetic hyperactivity, *AWS* alcohol withdrawal syndrome, *TBI* traumatic brain injury

Table 2 Epidemiology, monitoring and treatment of autonomic dysfunction in Guillain–Baré syndrome

Characteristics of autonomic dysfunction in GBS	Epidemiology	ICU monitoring	Treatment
Paroxysmal hypertension	24% of GBS patients [108]	Intra-arterial monitoring for significant blood pressure fluctuation [74]	For severe hypertension short-acting labetalol, esmolol or nitroprusside [108]. Short-acting, quickly titratable medications, such as hydralazine and labetalol, for severely fluctuating blood pressure [44, 90]
Orthostatic hypotension	50% of GBS patients [38]	Pulse and blood pressure monitoring and assesment of OH [52]	Intravenous fluids, low-dose phenylephrine [90]. If refractory, NaCl tablets, fludrocortisone or midodrine could be considered [44]. Other options include leg elevation and the use of compression stockings
Sustained sinus tachycardia, bradyarrhythmias, asystole and various conduction blocks	Sustained sinus tachycardia in 25–38% of GBS patients and bradycardia in 34% [74],	Continuous ECG monitoring	Self-limiting sinus tachycardia usually requires no treatment [74] Atropine and long-term temporary pacing [74] Transcutaneous pacing for a short-term period [53] Asystole usually requires implantation of a pacemaker [77]
Urinary retention	Urinary dysfunction in 25% and urinary retention in 9% of GBS patients [44]	Close monitoring of fluid status	Indwelling bladder catheter [44]
Constipation, gastric immotility and ileus	15% of severely affected GBS patients have adynamic ileus and 14% have constipation [19]	Daily output monitoring [44], abdominal auscultation and monitoring of opioid administration [52]	Cessation of enteral feeding, gastric decompression [44] and reduced opiate medications [44]. Treatment of ileus by erythromycin and neostigmine [52]

GBS Guillain–Baré syndrome, *ICU* intensive care unit, *OH* orthostatic hypotension, ECG electrocardiogram

discussion of which is beyond the scope of this paper and dealt with in manuals of intensive care medicine.

Conclusions

The epidemiology, autonomic characteristics, treatment, and prognosis of paroxysmal sympathetic hyperactivity, AWS, tetanus, and botulism are summarized in Table 1. The epidemiology, monitoring and treatment of autonomic dysfunction in GBS are summarized in Table 2.

While these few examples underline the relevance and risk of autonomic dysfunction in neurological intensive care patients there are many other diseases with autonomic irregularities that may complicate treatment and prognosis [33, 49] and therefore require special monitoring and therapeutic intervention.

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