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The use of the PSH-AM in patients with diffuse axonal injury and autonomic dysregulation: A cohort study and review

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ABSTRACT

Purpose: 1) To determine the clinical expression and consequences of autonomic dysregulation in patients with diffuse axonal injury (DAI), and 2) to study the use of the "paroxysmal sympathetic hyperactivity assessment measure" (PSH-AM).
Methods: Patients clinically diagnosed with autonomic dysregulation were selected from a cohort involving 116 patients with DAI. We studied the incidence of autonomic features, treatment, and outcome. In addition a systematic review was performed.
Results: Autonomic dysregulation was diagnosed in 19 of 116 (16.4%). Lower age (OR 0.95) and higher DAI grade (OR 7.2) were risk factors for autonomic dysregulation. Autonomic dysregulation was associated with an unfavourable outcome (OR 5.6) and a longer ICU and hospital stay. On the PSH-AM 57.9% ($n = 11$) scored a probable paroxysmal sympathetic hyperactivity (PSH), 36.8% ($n = 7$) scored possible, and 5.2% ($n = 1$) scored unlikely.
The review yielded 30 articles. The incidence of autonomic dysregulation after TBI varied from 7.7–32.6% (mean 13.5%). TBI patients with autonomic dysregulation had a longer ICU stay and poorer outcome.
Conclusion: Patients with DAI and autonomic dysregulation had a longer ICU stay and a poorer outcome compared to patients without autonomic dysregulation. The PSH-AM is a potential valuable tool to determine the likelihood of autonomic dysregulation.

1. Introduction

Diffuse axonal injury (DAI) is present in 72% of the patients with moderate or severe traumatic brain injury (TBI) and is caused by angular or rotational acceleration-deceleration forces which results in stretching and deformation of the brain tissue [17,40]. The axonal injury is diagnosed by means of characteristic deep microbleeds on magnetic resonance imaging (MRI) of the brain [18].

In a subgroup of patients with DAI symptoms of sympathetic overactivity, often referred to as paroxysmal sympathetic hyperactivity (PSH), can develop. PSH is a syndrome that is characterized by a paroxysmal transient increase in blood pressure, heart rate, respiratory rate, body temperature, sweating, and/or motor (posturing) activity [7]. PSH can occur after any type of brain injury, though it is mainly observed after TBI (79.4%) [32]. The presence of DAI after TBI is a risk factor for developing PSH [3,19,29]. In patients with TBI, PSH is associated with a longer stay in the intensive care unit (ICU), higher healthcare costs and a poorer outcome [3,5,16,28].

In clinical practice, after TBI symptoms of sympathetic overactivity do not always meet the criteria of classical PSH definition. This is mainly caused by of the lack of paroxysmal features, or the lack of simultaneity of the symptoms. The diagnosis of PSH is based on a high clinical suspicion and exclusion of alternative diagnoses [26]. Generally, to diagnose PSH there has to be simultaneous occurrence of at least five paroxysmal features, occurring for at least three consecutive days, without other possible causes [33]. However, this definition varies between studies [33]. Because the diagnosis is challenging, Baguley et al. described the development of the consensus based 'PSH Assessment Measure (PSH-AM)' to assign the probability of PSH as 'unlikely', 'possible', or 'probable' [7]. This assessment measure has two components, one to assign the probability of the diagnosis with a 'Diagnosis Likelihood Tool

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(DLT)', and another to assign the severity of the clinical features with the 'Clinical Features Scale (CFS)' (Table 1). All features scored are clinically easy to obtain, therefore the PSH-AM is easy to apply in everyday practice. This scoring method provides the opportunity to assess the probability and severity of PSH, providing clinical relevant information and to score and standardize symptoms for scientific research. If patients with PSH are not recognized this can have consequences for prognosis, since uncontrolled symptoms can lead to secondary brain injury and an increase in mortality [1,3,20]. To describe the symptoms that do not fit the criteria for PSH, but cannot be explained otherwise, we used the term 'autonomic dysregulation'.

Because it is difficult to diagnose, the syndrome is under-recognized and there is no generally accepted therapeutic strategy [4,20]. Moreover, even though autonomic dysregulation is associated with DAI [3,19,29], limited research has been performed on the incidence and the clinical consequence of autonomic dysregulation in this specific patient category [9,10].

The aim of this paper was to describe autonomic dysregulation in patients with DAI after TBI; referring to the incidence, how autonomic features are expressed, treatment and outcome.

A systematic review was performed to compare clinical practice with the literature. The second aim is to study the use of the PSH-AM to improve the recognition of this disorder.

2. Methods

2.1. Cohort study

2.1.1. Study population and design

This is a retrospective cohort study, involving patients with DAI recruited from a Dutch level I trauma centre (St. Elisabeth Hospital, Tilburg) in the period 2008–2014. Patients were included if they had TBI, were aged 16 or older at trauma, and were diagnosed with DAI on a brain MRI within six months after trauma. DAI was defined as microbleeds on MRI with T2 Stir Gradient Echo Resonance (T2*GRE) or Fast Field Echography (FFE) sequence. Exclusion criteria were large cerebral infarction, artefacts on the MRI impairing the diagnosis or grading of DAI, pre-existent mental retardation and other neurological conditions that affect long-term follow-up.

In this retrospective cohort study we focused on the patients with DAI, who were clinically diagnosed with autonomic dysregulation. Autonomic dysregulation was diagnosed by the intensivist and/or neurologist. This could consist of unexplained sustained hypertension, tachycardia, tachypnea, or fever, in which diagnostics provided no other explanation.

Follow-up was obtained prospectively and consisted of the Glasgow Outcome Scale Extended (GOSE). The GOSE is a global scale for functional outcome that rates the patient status in eight categories, 1 indicating death and 8 indicating good recovery, a score of 6 or higher was considered a favourable outcome [45].

2.1.2. Magnetic resonance imaging

The MRI of the brain was performed on a 1 Tesla (T), 1.5 T or 3 T system (Philips Medical System). Three stages of DAI were classified on MRI of the brain: 1) lesions in the lobar white matter, 2) lesion in the corpus callosum, and 3) lesions in the brainstem [18]. MRI images were reviewed on T2*GRE/FFE sequence by a neuroradiologist and reassessed for DAI grading by a researcher (ME). In case of discrepancy a neuroradiologist was consulted. Images were assessed by the researcher and consulting neuroradiologist together and consensus was reached through discussion.

2.1.3. Treatment of autonomic features

No standardized protocol was available for the treatment of symptoms of autonomic dysregulation during the time period of inclusion. When symptoms occurred they were treated by the critical care physician who consulted the neurologist. A symptom specific therapy was started, among others the use beta blockers, sedatives, muscle relaxants and cooling with a cooling blanket.

2.1.4. Data collection and analysis

The clinical data were derived from ICU graphics and medical files, this included the symptoms and therapeutic interventions of autonomic dysregulation. In addition, the following parameters were collected as determinants: demographic parameters (i.e. sex and age), injury related parameters (i.e. Glasgow Coma Scale (GCS), Injury Severity Score, DAI grading) and ICU and hospital stay. A GCS score of 13 to 15 was considered as mild TBI, a score of 9 to 12 as moderate TBI, and a score of 3 to 8 as severe TBI. The PSH-AM was calculated for patients diagnosed with autonomic dysregulation. As discussed in the introduction, the PSH-AM consists of two components the CFS and the DLT. In the CFS a score is awarded for clinical symptoms (heart rate, respiratory rate, systolic blood pressure, temperature, sweating, and posturing during episodes), 0 points resembles no abnormalities and 3 points the most severe expression of these features, a maximum of 18 points can be scored on the CFS. The DLT describes the clinical features of the symptoms (among others the paroxismality, duration, and frequency of symptoms, and the absence of other causes for the symptoms), each feature present scores 1 point (maximum of 11 points), a higher score indicates a higher likelihood the diagnosis is correct. When the scores of the CFS and the DLT are added, the scores can be divided in 'unlikely'(<8 points), 'possible' (8–16 points), and 'probable' (>17 points) PSH [7].

When data were missing 0 points were allocated for items on the CFS and DLT. When no severity for the features hyperhidrosis or hypertonia was recorded, 2 points (moderate) were assigned, since mild symptoms are often not reported in the patients records. The GOSE was collected prospectively by a structured telephone interview.

Table 1
The paroxysmal sympathetic hyperactivity - assessment measurement.

Clinical Feature Scale (CFS)					
	0	1	2	3	Score
Heart rate	<100	100–119	103–139	≥140	
Respiratory rate	<18	18–23	24–29	≥30	
Systolic blood pressure	<140	140–159	160–179	≥180	
Temperature	<37	37–37.9	38–38.9	≥39.0	
Sweating	Nil	Mild	Moderate	Severe	
Posturing during episodes	Nil	Mild	Moderate	Severe	
Subtotal					

Severity of clinical features		
	Nil	0
	Mild	1–6
	Moderate	7–12
	Severe	≥13

Diagnosis Likelihood Tool (DLT) (Score 1 point for each feature)
Clinical features occur simultaneously
Episodes are paroxysmal in nature
Sympathetic over-reactivity to normal non-painful stimuli
Feature persist ≥3 consecutive days
Feature persist ≥2 weeks post brain injury
Features persist despite treatment of alternative differential diagnoses
Medication administered to decrease sympathetic features
≥2 episodes daily
Absence of parasympathetic features during episodes
Absence of other presumed cause of features
Antecedent acquired brain injury
Subtotal
Total score (CSF + DLT)

PSH diagnostic likelihood		
	Unlikely	<8
	Possible	8–16
	Probable	>17

PSH: Paroxysmal Sympathetic hyperactivity.

Data analysis was performed using SPSS 24.0 (2016). The different variables were compared between patients with and without autonomic dysfunction using the Mann-Whitney *U* test for ordinal and continuous data. The nominal variables were analysed with the Chi square analysis or the Fisher exact test. A *p*-value of $p < .05$ was considered significant. The Odds ratio (OR) and associated 95% confidence interval (CI) were calculated with the binary logistic regression analysis.

2.2. Systematic review

A literature search was performed through MEDLINE on 28 March 2017 using the search terms 'paroxysmal sympathetic hyperactivity' or synonyms and 'traumatic brain injury' or 'diffuse axonal injury' or synonyms (Supplementary Table 1).

The obtained articles were screened on title and abstract using the following selection criteria:

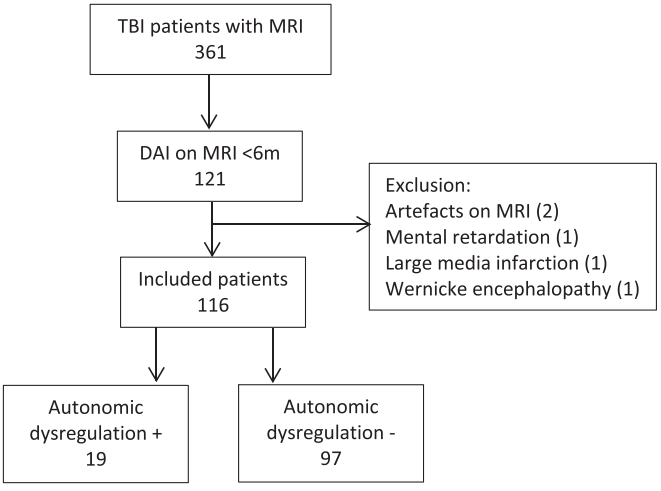
1) articles written in English, Dutch or German, 2) original data/patients, 3) patients with blunt TBI and autonomic dysregulation, 4) data of the subacute or acute phase of the injury, and 5) age 16 years or older. Animal studies and case series with five or less patients with TBI related autonomic dysregulation were excluded. The articles that remained after the title and abstract screening were reassessed on full text for inclusion and exclusion criteria. Articles without a definition of autonomic dysregulation were excluded. Discussion with a second researcher (ME) took place in case of doubt concerning in- or exclusion. If the same patient population was described in multiple articles and the same information about autonomic dysregulation was described, only the article providing the most relevant information was included, to reduce the risk of bias. After full text screening, additional papers were identified through cross-referencing.

The following information concerning autonomic dysregulation was subtracted from the selected articles: 1) Incidence of autonomic dysregulation in severe TBI patients in the subacute or acute phase, 2) Clinical characteristics, 3) Treatment, 4) Outcome (length of stay in the ICU and functional outcome on the Glasgow Outcome Scale (GOS) or GOSE). Data were pooled if the patient populations and definitions of autonomic dysregulation were comparable. Absolute risks and OR and associated 95% CI were collected if possible.

3. Results

3.1. Cohort study

In total, 116 patients with DAI were enrolled (Flowchart 1), 36 patients had a DAI grade 1, 30 a grade 2, and 50 a DAI grade 3 diagnosed on the 1 T ($n = 14$), 1.5 T ($n = 41$), or 3 T ($n = 61$) MRI. Of whom 16.4% ($n = 19$) were clinically diagnosed with autonomic dysregulation by the treating physicians. Patients with autonomic dysregulation had a median age of 23 years (range 17–54 years) and the majority (84.2%) were males. Of the patients with autonomic dysregulation, 11 patients (57.9%) scored 'probable' on the PSH-AM, 7 (36.8%) patients scored 'possible', and 1 (5.2%) patient scored 'unlikely' on the PSH-AM.



Flowchart 1. Patient selection process. Abbreviations MRI: Magnetic resonance imaging, TBI: Traumatic brain injury.

Table 2 presents the demographic and injury related data for patients with and without autonomic dysregulation. Patients with autonomic dysregulation were significantly younger than patients without autonomic dysregulation (OR 0.95, 95% CI 0.92–0.99). All patients with autonomic dysregulation had severe TBI ($p = .005$). Furthermore, patients with autonomic dysregulation had significantly more often DAI grade 3 compared to DAI grade 2 (OR 7.2, 95% CI 1.5–34.0), there were no patients with DAI grade 1 and autonomic dysregulation.

There was a large variance in the number of symptoms manifested in individual patients (varying from 5 or more ($n = 7$) to one symptom (n = 7), Table 3. Hyperthermia was most often the only symptom of autonomic dysregulation ($n = 6$) and it was also the most reported symptom ($n = 15$). Besides hyperthermia, tachycardia ($n = 13$), tachypnea ($n = 11$), and hyperhidrosis (n = 11)) were often reported. In the majority of the patients, the symptoms developed in the first two weeks after trauma ($n = 12$). The total duration of the symptoms varied from one week to two months. Ten patients (52.6%) received pharmacological treatment for the autonomic dysregulation, mainly opioids ($n = 9$), benzodiazepines ($n = 4$), metoprolol (n = 4) and clonidine (n = 4). Seven patients were treated for hyperthermia by initiating cooling until normothermia was reached.

Patients with autonomic dysregulation had a significantly longer ICU and total hospital stay ($p < .001$) (Table 4). The GOSE was obtained in 18 patients (94.7%) with autonomic dysregulation and in 74 patients (76.3%) without autonomic dysregulation, with a median follow-up of 52 months. The reasons for lost to follow-up were refusal to participate or impossibility to obtain contact by telephone or by post. An unfavourable outcome was seen in 83.3% ($n = 15$) of the patients with autonomic dysregulation and 47.3% ($n = 35$) of the patients without autonomic dysregulation (OR 5.6, 95% CI 1.5–20.9).

A comparable effect, although not significant, was found if we included only patients who were classified as probable PSH on the PSH-AM, of whom 90.9% ($n = 10$) had an unfavourable outcome (OR 4.0, 95% CI 0.3–55.5). Additionally, patients with hyperthermia as a single symptom also tended to have an unfavourable outcome on the GOSE (80.0%, $n = 4$), although this effect was less strong (OR 3.6, 95% CI 0.4–33.2). When the DAI grade was included in a multivariate logistic regression analysis, autonomic dysregulation remained associated with an unfavourable outcome (OR 4.4, 95% CI 1.1–18.2).

3.2. Systematic review

The search in MEDLINE provided 1180 articles. After screening on in- and exclusion criteria, on title/abstract and on full text, 28 relevant articles remained. A reference check provided two additional articles, resulting in a total of 30 articles (Flowchart 2). The data extraction of the 30 included articles is described in Supplemental Table 2.

3.2.1. Incidence of autonomic dysregulation

The incidence of autonomic dysregulation in TBI patients, reported in 15 articles, varied between 7.7% and 32.6% [5,9,13-16,19,21,22,28,31,34,36,42,44]. The majority of these studies included patients with severe TBI, two articles included patients with a vegetative status after TBI [13,34], three articles included patients with moderate-to-severe TBI [5,21,22], and one article included patients with TBI with any type of severity [36]. Two out of seven articles published after the introduction of the PSH-AM in 2014 applied the PSH-AM, either as an inclusion criterion [31], or as scoring method [41].

Table 2
Demographic and injury related data for patients with and without autonomic dysregulation.

	With autonomic dysfunction (n = 19)	Without autonomic dysfunction ($n = 97$)	p-value	Odds ratios (95% CI)
Age, years (median, range)	23 (17–54)	33 (16–78)	0.02	0.95 (0.92–0.99)
Male (number, %)	16 (84.2%)	70 (72.2%)	0.39	2.1 (0.6–7.6)
Severity TBI (number, %)			0.01	–
GCS 13–15	0 (0%)	15 (16.1%)		
GCS 9–12	0 (0%)	16 (17.2%)		
GCS 3–8	18 (100%)	62 (67.7%)		
Injury Severity Score (median, range)	38.0 (16–54)	29.5 (4–75)	0.03	1.0 (1.0–1.1)
DAI grade (number, %)			<0.001	7.2 (1.5–34.0)[a]
Grade 1	0 (0%)	36 (37.1%)		
Grade 2	2 (10.5%)	28 (28.9%)		
Grade 3	17 (89.5%)	33 (34.0%)		

Abbreviations: CI: Confidence Interval, DAI: Diffuse Axonal Injury, GCS: Glasgow Coma Scale, TBI: Traumatic Brain Injury.
[a] DAI grade 3 compared to DAI grade 2.

Three articles with a comparable study population were pooled which included in total 251 patients with severe TBI, autonomic dysregulation was present in 13.5% ($n = 34$) [19,28,42].

One article described the incidence of autonomic disorders in patients with DAI, of the 124 included patients with DAI, neurovegetative disorders were reported in 24.2% ($n = 30$) [10].

Five articles described the presence of DAI on Computed Tomography (CT) or MRI, DAI was reported in 21.1% to 91.4% of the patients with autonomic dysregulation [3,5,19,29,30]. In three of these studies a statistically significance difference in DAI lesions was reported between patients with and without autonomic dysregulation [3,19,29]

3.2.2. Clinical characteristics of autonomic dysregulation

In total, 15 studies were included in the analysis of clinical characteristics of autonomic dysregulation (Supplemental Table 3) [3,5,11,13,15,16,19,22,23,29-31,34,38,39]. The observed individual symptoms of autonomic dysregulation were described in 11 articles. All studies reported hypertension as a clinical feature, observed in 5.3% to 100% of the patients [3,5,15,16,22,23,29-31,38,39]. Hypertonia, although reported in only four articles [3,15,16,29], occurred most often with an incidence of 94% to 100%, followed by tachycardia, which occurred in 50.6% to 100% of the patients (six articles) [5,23,29-31,38].

The median or mean onset of the first episode of autonomic dysregulation was in the first week (range 4–6 days) [15,16,19,30]. However, the mean total duration of autonomic dysregulation ranged widely with a minimum duration of 10.7 days and a maximum of 162 days [13,19,29,31,34].

Mathew et al. described the number of simultaneous symptoms, in 44.8% of the 29 patients all six symptoms were presented, in 34.5% five symptoms and in 20.7% four symptoms [31].

Hyperthermia was described as a major symptom in a couple of studies. Elevation of temperature was the most predictive component of the modified Clinical Feature Severity Scale for the development of autonomic dysregulation in the study of Hinson et al. (OR 2.0, 95% CI 1.1–3.4) [22]. In addition, a prospective cohort study that included neurological ICU patients with fever showed that autonomic dysregulation was associated with a prolonged duration of fever (mean 10.5 ± 7 days versus 5.1 ± 3 days) [36].

3.2.3. Treatment of autonomic dysregulation

Six articles reported information concerning the treatment of autonomic dysregulation [4,6,16,30,38,41]. Supplemental Table 4 summarizes the four articles that described the number of the different type of medications given for patients with autonomic dysregulation [4,6,16,38]. Of the 20 different medications prescribed in 72 patients, opiates and benzodiazepines were most prescribed with a frequency of 59.7% (range 18.8–87.5%) and 44.4% (range 16.7–87.5%) respectively. All four articles reported the use of beta blockers, which were prescribed to 12.5–33.3% of the patients.

The effect of the treatment was described in six patients, they reported a full response on morphine ($n = 2$), and a partial response on bromocriptine (n = 2) and dantrolene ($n = 1$) [38].

Tang et al. studied the effectiveness of prevention with dexmedetomidine, an α2 adrenergic agonist that may block norepinephrine release, in 50 patients and 40 controls [41]. The overall PSH-AM scores in the dexmedetomidine group were significantly lower compared to the control group, which corresponds with a lower probability of the diagnosis autonomic dysregulation.

3.2.4. Outcome

Four articles described the outcome of patients with autonomic dysregulation after severe TBI measured with the GOS at 12 months [15,16,28,44]. An unfavourable outcome (GOS 1–3) was found in 55.9% ($n = 33$) of the 59 included patients.

Of these four articles, three articles compared the outcome of the severe TBI patients with and without autonomic dysregulation [15,16,28]. Of the patients with autonomic dysregulation 46.2% (18/39) had an unfavourable outcome on the GOS at 12 months, compared to 35.4% (46/130) of the patients without autonomic dysregulation (OR 1.6, 95% CI 0.8–3.2).

One article included patients with autonomic dysregulation who were in a vegetative state after TBI, an unfavourable outcome (GOS 1–3) was seen in 61.7% ($n = 68$) of these patients [13]. Another article described the outcome in patients with DAI and reported an unfavourable outcome (GOS 1–3) in 70% of the 30 patients with autonomic symptoms [10].

The mean ICU stay in patients with severe TBI was reported in four articles, 89 patients with autonomic dysregulation were compared with 227 patients without autonomic dysregulation with a mean ICU stay of 26.9 days (11.9–60.6 days) and 13.4 days (9.1–23.0 days) respectively [3,16,28,31].

4. Discussion

In our cohort study, autonomic dysregulation was present in 16.4% of the 116 patients with DAI and 57.9% ($n = 11$) of these patients had a probable PSH according to the PSH-AM. Furthermore, our study showed that patients with autonomic dysregulation after DAI were younger, had more severe brain injury, had a longer ICU and hospital stay, and had a higher chance of an unfavourable outcome than patients without autonomic dysregulation. In our systematic review, patients with autonomic dysregulation and severe TBI also had a longer ICU stay and an unfavourable outcome compared to patients without autonomic dysregulation, although this difference was not significant.

Limited research has been published concerning the incidence and outcome of autonomic dysregulation in patients with DAI [9,10]. In a

Table 3
Clinical characteristics of the patients with autonomic dysregulation.

Patient No.	Age (years)	DAI grade	Tachycardia	Tachypnea	Hypertension	Hyperthermia	Hyperhidrosis	Hypertonia	Onset after trauma (days)	Total duration (days)	CFS maximum score	DLT score	PSH-AM probability	Treatment	First M6 (days)	ICU stay (days)	GOSE (follow-up in months)
1.	33	3	+	−	−	−	−	−	20	17	3	8	Possible	Me	28	55	6 (16)
2.	22	3	+	+	+	+	+	+	8	♦	15	7	Probable	Mo, Ba	−	13	5 (26)
3.	27	3	+	+	+	−	+	+	0	♦	13	10	Probable	Pr, Mo, Fe, Lo, Cl, Zo	30	43	4 (29)
4.	23	2	+	+	+	−	+	+	4	53	14	9	Probable	Pr, Fe, Lo, Cl, Mi, Ve, Da, Le	38	64	3 (23)
5.	23	3	+	+	+	+	+	+	6	30	16	10	Probable	Ba, Fe, De	18	35	6 (35)
6.	21	2	+	+	+	−	+	+	3	51	14	8	Probable	Mo, Fe, Cl, De, Se, Pr, Di	31	68	5 (29)
7.	32	3	+	+	−	+	+	+	12	38	14	8	Probable	Mo, Ba, Fe, Cl, Da	−	40	3 (49)
8.	17	3	+	+	−	+	+	−	7	♦	11	7	Probable	Me	−	59	3 (54)
9.	19	3	+	−	−	+	−	−	27	♦	5	3	Possible	−	21	40	5 (47)
10.	54	3	−	−	−	+	−	−	6	22	3	5	Possible	−	−	24	1 (6)
11.	41	3	+	+	−	+	+	−	14	♦	11	7	Probable	Me	−	64	4 (61)
12.	26	3	+	+	+	+	+	−	18	♦	15	9	Probable	Me	−	61	3 (65)
13.	22	3	−	−	−	+	−	−	13	6	3	5	Possible	−	18	25	♦
14.	28	3	+	+	−	+	+	−	23	♦	11	7	Probable	−	56	48	5 (63)
15.	18	3	+	+	−	+	+	−	10	♦	12	7	Probable	−	−	72	3 (61)
16.	51	3	−	−	−	+	−	−	15	♦	3	5	Possible	−	−	35	1 (1)
17.	22	3	−	−	−	+	−	−	11	22	3	7	Possible	−	32	41	7 (82)
18.	25	3	−	−	−	+	−	−	64	♦	3	5	Possible	−	−	100	3 (87)
19.	18	3	−	−	−	+	−	−	♦	♦	2	3	Unlikely	−	−	49	3 (92)

Abbreviations: Ba: baclofen, CFS: Clinical Feature Scale, CL: clonidine, DLT: Diagnosis Likelihood Tool, Da: dantrolene, DAI: Diffuse Axonal Injury, De: dexmedetomidine, Di: diazepam, Fe: fentanyl, GOSE: Glasgow Outcome Scale Extended, ICU: Intensive Care Unit, Le: levomepromazine, Lo: lorazepam, Me: metoprolol, Mi: midazolam, Mo: morphine, M6: motor score on Glasgow Coma Scale of 6, No: Number, Pr: propofol, PSH: Paroxysmal Sympathetic Hyperactivity, Se: seroquel, Ve: vecuronium, Zo: zopiclon.
+symptom present, − symptom or treatment absent or not reported in the patient record, ♦: Missing.

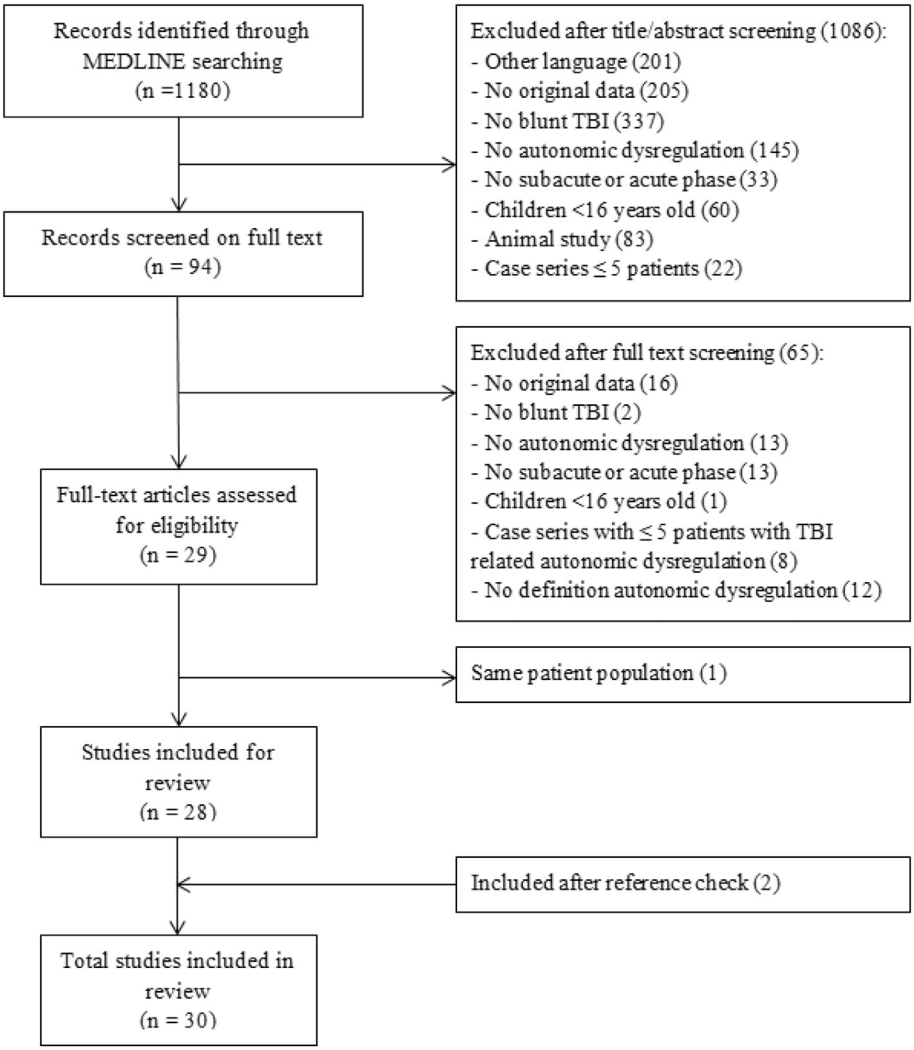
Table 4
Outcome data for patients with and without autonomic dysregulation.

	With autonomic dysregulation (n = 19)	Without autonomic dysregulation (n = 97)	p-value	Odds ratios (95% CI)
ICU stay, days (median, range)	48 (13−100)	7 (0–64)	<0.001	–
Hospital stay, days (median, range)	57 (22–179)	25 (1–91)	<0.001	–
GOSE at follow-up (number, %)			0.01	5.6 (1.5–20.9)
Unfavourable (GOSE 1–5)	15 (83.3%)	35 (47.3%)		
Favourable (GOSE 6–8)	3 (16.7%)	39 (52.7%)		
Follow-up, months (median, range)	52.0 (19–92)	52.0 (14–96)		

Abbreviations: CI: Confidence Interval, GOSE: Glasgow Outcome Scale Extended, ICU: Intensive Care Unit.

retrospective analysis of Gonzalez et al., the incidence of autonomic dysregulation in patients with DAI was 19% and the presence of the syndrome was associated with a poor prognosis [9], although they did not provide a comparison between patients with and without autonomic dysregulation. Chelly et al. concluded that autonomic dysregulation in patients with DAI was associated with a higher mortality, however they reported only the incidence of neurovegetative disorders (hypertension, hypotension, bradycardia, tachycardia or thermal deregulation without infectious or thromboembolic conditions), which was 24.2% [10]. In line with prior research, the incidence of autonomic dysregulation in our study was 16.4% and it was associated with a higher chance of an unfavourable outcome.

In accordance with our results in patients with DAI, previous studies in patients with TBI showed that patients with autonomic dysregulation were significantly younger, had a longer ICU stay, and had a poorer outcome [3,5,15,16,28,29]. However, in our cohort study, patients with autonomic dysregulation and DAI after TBI had a higher chance of an unfavourable outcome (GOSE 1–5) than patients with autonomic dysregulation and severe TBI in the systematic review (GOS 1–3), respectively 83.3% and 55.9%. Patients with DAI but without autonomic dysregulation in the cohort study had an unfavourable outcome in 47.3%, while in the systemic review 35.4% of the patients with severe TBI without autonomic dysregulation had an unfavourable outcome. Perhaps, the disparity in severity of the brain injury and the presence of DAI, has influenced the difference in outcome. Patients with DAI had a higher chance of an unfavourable outcome than patients with severe TBI without DAI [25] and patients with autonomic dysregulation had more severe DAI than patients without autonomic dysregulation.



Flowchart 2. Article selection process. Abbreviation: TBI: traumatic brain injury.

Another explanation is the outcome measure used, the GOSE or GOS. We considered 'lower moderate disability' (GOSE 5) an unfavourable outcome and 'upper moderate disability' (GOSE 6) a favourable outcome, while in the less extensive GOS 'severe disability' (GOS 3) is considered an unfavourable outcome and 'moderate disability' (GOS 4) a favourable outcome.

For many years there was no diagnostic test for autonomic dysregulation [2]. In 2014 Baguley et al. presented the PSH-AM, a scoring method by which the severity and likelihood of PSH can be determined. When the PSH-AM is used, patients can be scored as having probable PSH, independent of the number and simultaneity of autonomic symptoms.

In the original definition of PSH, patients have to have at least five out of seven autonomic features to diagnose PSH [3]. However, there is no clear evidence that a certain number, frequency or duration of autonomic symptoms has to be present to diagnose autonomic dysregulation [33]. A higher number of different autonomic features did raise the specificity in prior research [3]. As observed in our study, patients with only one item on the CFS ($n = 6$) can have possible PSH according to the PSH-AM. Because in the PSH-AM the severity of the feature and the score on the DLT are considered. Only one patient was diagnosed by the treating physicians with autonomic dysregulation, while this was unlikely according to the PSH-AM. Therefore, we find that the PSH-AM correlates with the clinical diagnosis of autonomic dysregulation in patients with DAI. Using the PSH-AM prevents the exclusion of patients because of partial expression of autonomic features [2,35], which can be harmful, since uncontrolled symptoms can induce complications and even death [8,20]. Besides, delayed recognition leads to repetitive and expensive testing (e.g. sepsis workups) and unnecessary medication administration [8,12,20,37]. Hence, the PSH-AM can be seen as valuable tool in diagnosing PSH.

Hyperthermia seems to be an important feature of autonomic dysregulation and is the most reported symptom in our study and in the literature. Moreover, hyperthermia was frequently observed as a single autonomic symptom in our study, this observation could be explained by sedation for ventilation and pain management, which suppresses other autonomic symptoms [3,8]. These patients had an increased risk of an unfavourable outcome (OR 3.6, 95% CI 0.4–33.2). Previous studies also showed that untreated hyperthermia can lead to secondary brain injury and a higher mortality [3,24,43]. Even though it is obscure whether hyperthermia as only feature may be diagnosed as autonomic dysregulation, it remains important to recognize and treat patients with unexplained hyperthermia as soon as possible to minimize complications.

Some limitations should be addressed. First, this is a single-centre study performed in a Level I trauma centre with a Level I Intensive Care Unit. Results may not generalize to other institutions with other patient populations. The retrospective character of the cohort study, limited the possibility to study the daily number and duration of episodes, the total duration of autonomic dysregulation, and the effectiveness of the treatment. The patients in the cohort were scored according to the PSH-AM. Since missing variables were scored as 0 points, it is possible that the likelihood of PSH was underestimated. Also, we could have missed patients when autonomic dysregulation was not recognized by the neurologist or intensivist and the presence of autonomic features was not reported in the file. Second, the MRI scans were performed on a 1 T, 1.5 T and 3 T scanner. A 3 T MRI scan is almost twice as sensitive for microbleeds (on T2 STIR Gradient Echo) in comparison to a 1.5 T MRI [27]. The MRI field strength may have influenced the diagnosing and grading of DAI, resulting in an underestimation of DAI in the patients scanned on the 1 T or 1.5 T MRI. Third, medication administered on the ICU, such as sedatives and antipyretic drugs influence clinical features such as described in the CFS. It was not possible to correct for these medications, however it is possible that the severity or presence of clinical features was masked by these drugs, resulting in an underestimation of the presence or severity of the autonomic dysregulation.

Further research should be performed to investigate the influence of various autonomic symptoms on the outcome and the clinical applicability of the PSH-AM.

5. Conclusion

Autonomic dysregulation occurred in 16.4% of our patients with DAI, and in 57.9% of them a probable PSH was found according to the PSH-AM. Patients with TBI and DAI and autonomic dysregulation were younger, had more severe brain injury, had a longer ICU and hospital stay, and had a poorer outcome than patients without autonomic dysregulation. The PSH-AM is a potential valuable tool to determine the likelihood of the diagnosis PSH-AM. Early recognition and treatment of autonomic dysregulation is necessary and further research should be performed to develop evidence-based treatment protocols.

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Conflict of interest statement

The authors have no conflicts of interest to report.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.10.018.

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