Dysautonomie

H.Binder

Wachkomatagung

2015

Wien

J Neurol Neurosurg Psychiatry 1999;**67**:39±43

Dysautonomia after traumatic brain injury: a forgotten syndrome?

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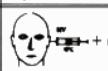
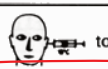
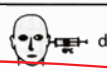
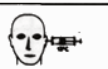
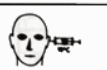
- **Definition:**

- **Ein Syndrom mit vielen Namen:**

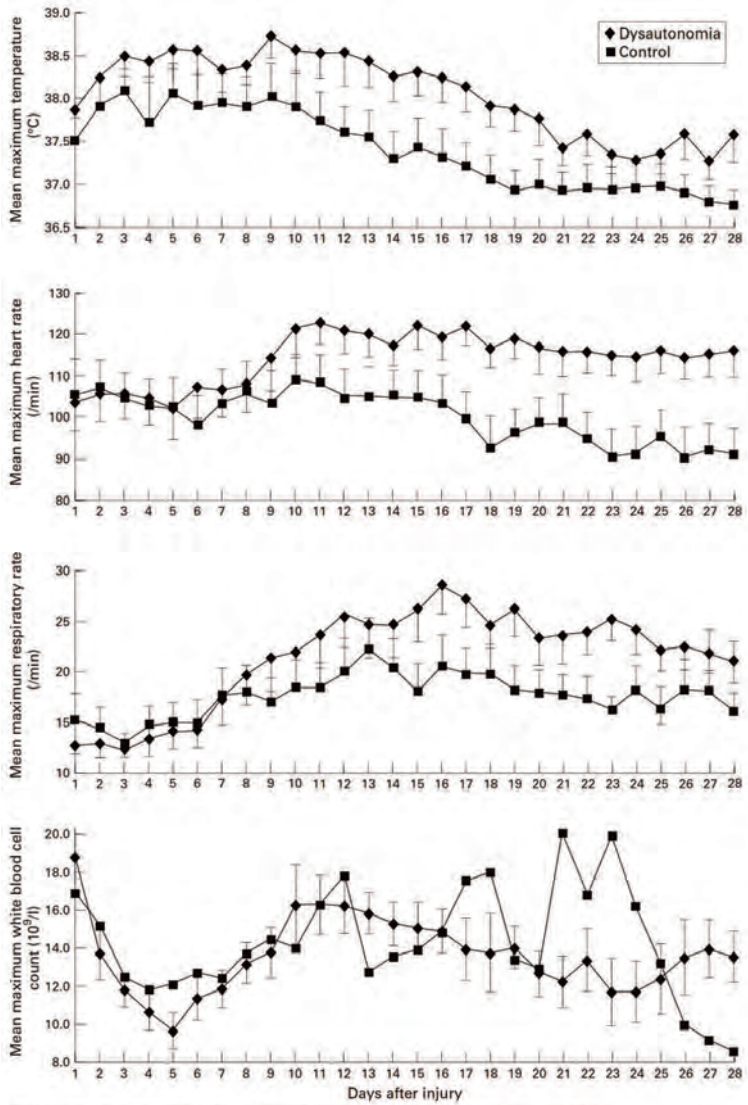
  - **Paroxysmal Sympathetic Hyperactivity**
  - **Autonomic storms**
  - **Sympathetic storms**
  - **Diencephalic seizures**
  - **Brainstem attack**
  - **Autonomic dysfunction syndrome**
  - **Dysautonomia**
  - **Paroxysmal autonomic instability with dystonia**
  - **Hyperpyrexia associated with muscle contraction**
  - **Hypothalamic-midbrain dyrsregulation syndrome**
  - **Acute midbrain syndrome**

- **Symptomatik:**

Das kennen wir alle in der Akutsituation

Phasen der Hirnstammeinklemmung	Mittelhirnsyndrom				Bulbärhirnsyndrom	
	1	2	3	4	5	6
Vigilanz	leichte Somnolenz	tiefe Somnolenz	Coma	Coma	Coma	Coma
Reaktivität auf sensorische Reize	verzögert	vermindert	fehlend	fehlend	fehlend	fehlend
Spontane Motorik						
Motorische Reaktion auf Schmerzreize						
Muskeltonus	normal	erhöht (an d. Beinen)	erhöht (generalisiert)	stark erhöht	normal – schlaff	schlaff
Pupillenweite	 mittelweit	 verengt	 eng	 mittelweit-erweitert	 erweitert	 maximal weit
Pupillenreaktion auf Licht	 normal	 verzögert	 träge	 vermindert	 angedeutet – fehlend	 fehlend
Bulbusbewegungen	pendelnd	dyskonjugiert	fehlend	fehlend	fehlend	fehlend
Oculo – cephaler Reflex	 °	 +	 ++		 °	 °
Vestibulo – okulärer Reflex	 + (normal)	 ++	 tonisch	 dissoziiert	 °	 °
Atmung						
Temperatur						
Pulsfrequenz						
Blutdruck	normal	normal	leicht erhöht	deutlich erhöht	vermindert	stark vermindert

Gerstenbrand und Lücking



Physiological indices over the first 4 weeks. Error bars indicate the 95% CI for each index identified.

Aber wie lange??

Baguley IJ, Nicholls JL, Felmingham KL, et al: **Dysautonomia after traumatic brain injury: a forgotten syndrome?** ***J Neurol Neurosurg Psychiatry 1999;67:39±43***

- **Diagnostische Kriterien:**
  - **Episodisches Auftreten von 4 der unten stehenden 6 Kriterien unter Ausschluss anderweitiger Ursachen:**
    - **- Fieber (> 38° C)**
    - **- Tachycardie (>120 x' or > 100 x' unter Beta-Blocker)**
    - **- Hypertonie (SBP > 160 or PP > 80)**
    - **- Tachypnea (RR > 30)**
    - **- Exzessives Schwitzen**
    - **- Massive Dystonie**

New consensus criteria: Assessment tool – Part 1

Paroxysmal Sympathetic Hyperactivity - Assessment Measure					
Clinical Feature Scale (CFS)					
	0	1	2	3	Score
heart rate	< 100	100 - 119	120 - 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	
			CFS Subtotal		
Severity of Clinical Features			nil	0	
			mild	1 - 6	
			moderate	7 - 12	
			severe	≥ 13	

A. A. Rabinstein and E. E. Benarroch, "Treatment of paroxysmal sympathetic hyperactivity," *Current Treatment Options in Neurology*, vol. 10, no. 2, pp. 151–157, 2008

New consensus criteria: Assessment tool – Part 2

Diagnosis Likelihood Tool (DLT)			
clinical features occur simultaneously			
episodes are paroxysmal in nature			
over-reactivity to normally non-painful stimuli			
features persist ≥ 3 consecutive days			
features persist ≥ 2 weeks post brain injury			
features persist despite treatment of 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			
(Score 1 point for each feature present)	DLT subtotal		
Combined total (CFS + DLT)			
PSH Diagnostic Likelihood	unlikely	< 8	
	possible	8 - 16	
	probable	> 17	

TABLE 1: Features of Paroxysmal Sympathetic Hyperactivity and Mixed Autonomic Hyperactivity

Category	Clinical Features	Paroxysmal Sympathetic Hyperactivity	Mixed Autonomic Hyperactivity
Sympathetic	Increases in HR, RR, BP, temperature, sweating, and pupillary dilation	Yes	Yes
Parasympathetic	Decreases in HR, RR, BP, temperature, and pupillary contraction	No	Yes
Motor features	Decerebrate posturing, decorticate posturing, spasticity, hypertonia and/or dystonia, teeth-grinding, agitation	Yes	Variable
Other	Hiccups, lacrimation, sighing, yawning	No	Yes

HR = heart rate; RR = respiratory rate; BP = blood pressure; Yes = clinical features present in syndrome; No = clinical features not present; Variable = variable presentation of features.

Perkes I et al.: Ann Neurol 2010;68:126–135

- **Verlauf und Dauer:**

- **Dysautonomie – Phasenhafter Verlauf**
  - Phase 1
    - Aufnahme an ICU
    - Sedierung, Relaxation – Differenzierung schwierig
  - Phase 2
    - Nach Beendigung von Sedierung, Relaxation
    - In der **Frühphase**
      - vegetative Basisaktivität erhöht
      - häufige und langdauernde dysautonomer Episoden mit und ohne erkennbarem Trigger,
      - Parallel dazu Tonus- und Haltungspathologie
    - In der **Spätphase**
      - Ruhewerte des Vegetativums normalisiert
      - an Häufigkeit und Intensität abnehmende “dysautonome Attacken”
      - Motorik bestimmt von Primär- und Sekundärläsionen
  - Phase 3
    - Dysautonome Paroxysmen nur mehr getriggert (>1 Jahr)

Table 1 Injury related variables and dysautonomic features at admission to rehabilitation

Subject No	Time to rehab admission (days)	Initial GCS	CT findings	Dysautonomic features					
				HR	RR	BP	Temp	Sweat	Post
1	89	4	R frontal lobe laceration, R SDH with midline shift, L temporal contusions, cerebral oedema, #BOS	−	−	−	+	+	+
2	66	3	Multiple petechial haemorrhages c/w DAI, R SDH with midline shift, pontine contusion, #L orbital floor	−	−	−	+	+	+
3	38	5	L SDH with midline shift, widespread petechial haemorrhages c/w DAI	+	+	?	+	?	+
4	42	4	L parietal contusions, R sided brainstem contusions, #BOS	+	+	?	+	+	+
5	29	3	L frontotemporal contusion with midline shift, L midbrain contusion, DAI, traumatic SDH	+	+	+	+	+	+
6	20	3	R frontoparietal SDH with midline shift, DAI, cerebral oedema	+	+	+	−	+	+

#, fracture; BOS, base of skull; c/w DAI, consistent with diffuse axonal injury; GCS, Glasgow Coma Score; L, left; R, right; SDH, subdural haematoma.
+/−, presence or absence of tachycardia (HR), tachypnoea (RR), hypertension (BP), unexplained fever (Temp), increased sweating (Sweat) or posturing (Post).

Baguely I et al.: Gabapentin in the management of dysautonomia following severe traumatic brain injury: a case series. J Neurol Neurosurg Psychiatry 2007;78:539–541

Alter

Monate

Table 1 Summary of literature cases of dysautonomia

Author	Case No in Study	Age, Sex	GCS	Temp °C	Heart Rate /min	BP mm Hg	Resp Rate /min	Posturing	Sweating	Outcome (GOS)	Time of Assessment	CT
Rossitch *et al*[2]	1			Y	Y	Y	Y	Y	Y	≤3		
	3			Y	Y	Y	Y	N	Y	≤3		
	5			Y	Y	Y	Y	Y	Y	5		
Rossitch *et al*[2 11]	2	24, M	6	39.6	165	160/100	52	Y	Y	4	6	CC, blocked cisterns
	4	24, M	<8	39.6	103	170/80	60	Y	Y	≤3	3	Normal
Boeve *et al*[5]	1	17, F	<8	42	190	170/–	40	Y	Y	3	8	SAH, IVH, CC
Strich *et al*[7]	1	28, M	5					Y	Y	3	8	
	2	32, F	<8	Y			Y	Y	Y	3	4	
	4	27, M	<8	Y		Y		Y	Y	3	6	
Pranzatelli *et al*[9]	2	7, M	<8	39.3	160	150/105	45	Y	Y	≤3		Diffuse SAH
	3	19, M	<8	40	140	160/115	40	Y	Y	≤3		SAH, generalised oedema
Chiloero *et al*[13]	1	26, M	6		155			Y		1	6	SDH, CC
Sandel *et al*[14]	1	17, M	8	Y	130	170/120	N	Y	Y	4	3	SAH, CC
Silver *et al*[15]	1	27, M	6	Y	Y	Y	Y	Y	Y	2-3	12	CC
	2	25, F	4	Y	Y	Y	Y	Y	Y	3		SAH, IVH
Meythaler *et al*[16]	1	20, F	3	38.9				Y	Y	3		Normal
	3	15, F	4	40.6	Y				Y			IVH, DAI

GCS=Glasgow coma scale; BP=blood pressure; GOS=Glasgow outcome score; SAH=subarachnoid haemorrhage; IVH=intraventricular haemorrhage; SDH=subdural haemorrhage; CC=cortical contusion.

When available, the values of the various indices are reported. Y=the reporting, but not the severity, of hyperthermia, tachycardia, hypertension, tachypnoea, posturing or sweating. N=absence of the symptom. Blank ®elds are included when data were not reported. Age is in years, time of assessment in months after injury.

Baguley I et al.: Dysautonomia after traumatic brain injury: a forgotten syndrome? *J Neurol Neurosurg Psychiatry 1999;67:39±43*

- **Ursachen:**

TABLE 2: Conditions Preceding Paroxysmal Sympathetic Hyperactivity Onset

Etiology	No.	%	Cases Contributing to Subtotal
Traumatic brain injury	277	79.4	$n < 5$[28,32-35,38,43,49,63,69,74,75,77,86,88-97]; $n < 10$[3,13,15,68,87]; $n < 20$[6,11,98]; $n = 20$[45]; $n = 35$[7]; $n = 42$[5]; $n = 68$[29]
Hypoxia	34	9.7	$n < 5$[6,14,28,46,71,73,81-83,89,92]; $n < 10$[29,45]
Stroke	19	5.4	$n < 5$[6,34-36,72,88,92,99]; $n = 8$[29]
Hydrocephalus	9	2.6	$n < 5$[34,37,51,78,79,100]
Tumor	2	0.6	$n < 5$[31,49]
Hypoglycemia	1	0.3	$n = 1$[70]
Infectious	1	0.3	$n = 1$[29]
Unspecified	6	1.8	$n < 5$[28,45,101]
Total	349	100	

Unspecified = original article did not state etiology; No. = total number of reviewed cases; n = number of cases in individual studies.

Perkes I et al.: Ann Neurol 2010;68:126–135

- **Pathophysiologie:**

- **Pathophysiologie:**
  - **Diskonnektion**
  - **Exzitatory-inhibitory ratio model**

  - **gesteigerte Aktivität zentraler sympathisch aktiver diencephaler und/oder Hirnstamm-Regionen als Folge von**
    - **direkter Aktivierung oder Enthemmung**
    - **fehlender Kontrolle höherer Zentren**
  - **Allodynie-Konzept**

Baguley I et al.: A Critical Review of the Pathophysiology of Dysautonomia Following Traumatic Brain Injury. Neurocrit Care (2008) 8:293–300

Organ and organ system	Activation of parasympathetic nerves	Avtivation of sympathetic nerves
Heart muscle	Decrease of * heart rate * contractility (only atria)	Increase of * heart rate * contractility (atria, ventricles)
Coronary arteries		Vasoconstriction
Urinary bladder * Detrusor * Internal sphincter	 Contraction 0	 Small relaxation Contraction
Tracheo-bronchial muscles	contraction	Relaxation

CHJ Mathias, R Bannister: Autonomic Failure, 2002

Organ and organ system	Activation of parasympathetic nerves	Activation of sympathetic nerves
Liver	0	Glycogenolysis Gluconeogenesis
Fat cells	0	Lipolysis (free fatty acids in blood increased)
Beta-cells in islets of pancreas	secretion	decrease of secretion
Adrenal medulla	0	Secretion of adrenaline and noradrenaline
Lymphoid tissue	0	Depression of activity (e.g. of natural killer cells)

CHJ Mathias, R Bannister: Autonomic Failure, 2002

- **Trigger-Faktoren:**
  - **Schmerz**
  - **Überdehnung der Harnblase**
  - **Katheter-Manipulation**
  - **Körperbewegungen**
  - **Absaugen**
  - **spontan**

- **Warum ist es wichtig die richtige Diagnose zu stellen?**

- **Differentialdiagnose:**
  - **Sepsis**
  - **ICP ↑**
  - **Anfälle**
  - **Nachblutung**
  - **Atemwegsobstruktion**
  - **Pulmonalembolie**
  - **Serotonin-Syndrom/ NMS / Maligne Hyperthermie**

- **Therapie:**

Table 1. Medications used for the treatment of PSH

Medication	Mechanism	Mode of action	Starting dose	Frequency	Symptoms treated
Propranolol	Nonselective β-blocker	Peripherally decreasing effect of catecholamines	40 mg	Every 12 h	Hypertension, tachycardia, fever
Morphine	μ-Opioid receptor agonist	Centrally at medullary vagal nuclei and peripherally	1–8 mg	According to the onset of PSH	Tachycardia, peripheral vasodilation, allodynic response
Baclofen	$GABA_B$-specific agonist	Centrally	5 mg	3 times/day	Pain, clonus, rigidity
Gabapentin	GABA agonist	Centrally	300 mg	3 times/day	Spasticity, allodynic response
Benzodiazepines	GABA receptor agonist	Centrally	Depending on the drug used		Agitation, hypertension, tachycardia, posturing
Bromocriptine	Dopamine D_2 agonist	Centrally at hypothalamus	1.25 mg	Every 12 h	Dystonia, fever, posturing
Clonidine	α_2-Receptor agonist	Centrally decreased sympathetic outflow	0.1–0.3 mg	Every 12 h	Hypertension
Dexmedetomidine	α_2-Receptor agonist	Centrally decreased sympathetic outflow	2 μg/kg	Every 1 h	Hypertension, agitation, tachycardia
Dantrolene	Decreases muscle contraction	Peripherally	0.25–2 mg/kg	Every 6–12 h	Muscle rigidity, posturing

Table. Summary of Reports of Pediatric Paroxysmal Sympathetic Hyperactivity (PSH)[1,4-11]

					Treatments and Reported Effectiveness†	
Reference	**Age*(Sex)**	**Injury Type**	**Onset of PSH**	**Duration of PSH**	**Ineffective**	**Effective**
Krach et al[1] (31 patients)	9.3 ± 5.3 (NR)	Trauma (n=20) Anoxia (n=9) Other (n=2)	Within 1 mo (=28)	<6 mo (n 22)	Effect not reported: Bromocriptine, chlorpromazine, antihypertensives, muscle relaxants	
Boeve et al[4]	17 (F)	Traumatic	5 days	15 mo	Anticonvulsants, midazolam 1-3 mg IV PRN	Propranolol, 3 mg IV once; morphine, 10 mg, G-tube every 4 hr; acetaminophen, 650 mg, G-tube every 4 hr; bromocriptine, 1.25 mg, G-tube twice daily
Goh et al[5]	7 (M)	Resection of midbrain glioma	Within 1 wk	6 mo	Phenytoin, 100 mg twice daily	Diazepam, 1 mg every 6 hr; lorazepam, 1 mg IV PRN; clonidine, 100 mcg every 8 hr
Russo et al[6]	10 (F)	Traumatic	5 days	5 days	Morphine, midazolam, diazepam, 0.1 mg/kg/dose IV PRN; clonidine, 1 mcg/kg/dose IV every 6 hr	Bromocriptine, 0.025 mg/kg/dose every 12 hr
Cuny et al[7]	17 (M)	Traumatic	~60 days	48 days		Intrathecal baclofen, 96-432 mcg/day
Rodriguez et al[8]	6 (M)	Traumatic with cardiac arrest	~6 days	<76 days	Phenytoin Effect not reported: diazepam, morphine	Midazolam, baclofen
	12 (F)	Traumatic	1 day	>65 days		Diazepam, clorazepate, baclofen
Mehta et al[9]	14 (F)	Hypoxic-ischemic	1 wk	8 wk	Anticonvulsants, atenolol, clonidine, hydralazine, morphine, fentanyl, methadone, bromocriptine, intrathecal baclofen	Baclofen pump
Woo et al[10]	12 (M)	Traumatic	1 day	3 wk (spastic at 3 mo)		Midazolam, morphine
Singh et al[11]	1 (F)	Intracranial tuberculoma	Not stated	>1 mo		Benzodiazepines, β-blockers, clonidine
Lv et al[12]	8 (M)	Traumatic	10 days	~40 days	Midazolam, propranolol, bromocriptine	Morphine, hyperbaric oxygen therapy
Deepika et al[13]	6 (F)	Right middle cerebral artery infarction with Moyamoya	3 days	Until death at 28 days post-infarction	Dexmedetomidine, 1 mcg/kg/hr IV; metoprolol, 50 mg/day; clonidine, 0.1 mg/day	

IV, intravenous; NR, not reported; PRN, as needed

* age in years

† Doses and route included when reported.

- **Prognose:**

Table 4 Outcome data for dysautonomia group and control groups

	Dysautonomia group	*Control group*	*Significance*
Mean hospital DOS (days)	267.9	69.2	$F(1,64)=38.6$, p=0.000**
Mean ICU DOS (days)	13.3	11.6	$F(1,64)=0.413$, p=0.58
Mean rehabilitation DOS (days)	206.8	44.1	$F(1,58)=42.9$, p=0.000**
Mean PTA duration (days)	124.4	36.6	$F(1,43)=50.4$, p=0.000**
Median GOS score	3	2	$U(1,67)=84$, p=0.000**
Median discharge FIM	60	119	$U(1,48)=16$, p=0.000**
Mean FIM change score	44.4	51.8	U(1,48)=232, p=0.41
Persistent amnesia (yes/no)	21/12	2/33	$\chi^2=25.3$, p<0.005**

DOS=Duration of stay; ICU=intensive care unit.
**p<0.005.

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TABLE 3: Sample Characteristics of Paroxysmal Sympathetic Hyperactivity Cases

Characteristic	Value
Age, mean yr ± SD	24.2 ± 11.8
Sex, No. (%)	
Male	112 (78)
Female	31 (22)
GCS severe injury [<9], No. (%)	199 (100)
GOS, No. (%)	
1: Death	22 (18)
2: PVS	37 (30)
3: Severe disability	56 (45)
4: Moderate disability	7 (5)
5: Good recovery	3 (2)
Clinical setting, No. (%)	
ICU	139 (45)
Rehabilitation	119 (39)
Combined	48 (16)

Available data varied (total, n = 349; age, n = 279; sex, n = 143; GCS, n = 199; GOS, n = 125; clinical setting, n = 306). SD = standard deviation; GCS = Glasgow Coma Scale[66] at emergency department admission; GOS = Glasgow Outcome Scale[8]; PVS = persistent vegetative state; ICU = intensive care unit.

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Outcomes for children with and without dysautonomia

Outcome	Dysautonomia (n=33)	No dysautonomia (n=216)	p
Length of stay, d			<0.001
Mean (SD)	114 (66)	47 (56)	
Range	16–301	0–463	
Length of stay corrected[a], d			<0.001
Mean (SD)	106 (64)	43 (46)	
Range	16–287	0–259	
Number of re-admissions to acute care facilities			<0.001
Mean (SD)	1.52 (1.33)	0.32 (0.80)	
Range	0–5	0–5	
Disposition, n (%)			0.002
Home	22 (67)	189 (88)	
Procedure, then home	2 (6)	7 (3)	
Alternative rehab facility	0 (0)	6 (3)	
Long-term nursing care	3 (9)	2 (1)	
Hospitalization	6 (18)	12 (6)	

[a]Corrected for days spent away from The Children's Institute during acute care re-admissions.

Kik KA, Shoykhet M, Jeong JH et al.: dysautonomia after pedIatric brain injury.Dev Med Child Neurol. 2012 August ; 54(8): 759–764.

- **Zusammenfassung:**

- **Bei bis zu 1/3 der Patienten nach schweremSHT**
- **Bei hypoxischer Encephalopathie**
- **Besonders häufig bei jüngeren Patienten**

- **Häufig Fehldiagnosen**
- **Unklare Nomenklatur und diagnostische Kriterien**

- **Wichtige Diagnose – Warum?**
  - **gesteigerte sekundäre Morbidität**
  - **Hypermetabolism (Gewichtsabnahme)**
  - **langdauernde Hyperthermie**
  - **Dehydratation**
  - **Myocardiale Schäden**
  - **Erhöhter Hirndruck(?)**
  - **Kontrakturen**
  - **Heterotope Ossificationen**

  - **unnötige Untersuchungen und Therapien**
  - **Verlängerter ICU-Aufenthalt**

ENDE