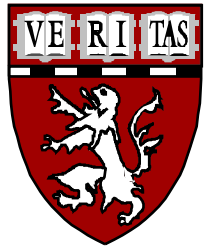
Autonomic Dysfunction in the Intensive Care Unit

Roy Freeman, MB ChB

Center for Autonomic and Peripheral Nerve Disorders
Beth Israel Deaconess Medical Center
Harvard Medical School



Case

- A 29-year-old healthy male was thrown from his motorcycle while riding without a helmet in wet weather
- He was admitted in a comatose state.
- He showed asymmetric extensor posturing to painful stimuli
- CT scan showed bilateral frontal contusions, diffuse edema and right subdural hematoma
- 6 days later he developed a paroxysmal episodes of hypertension (170/100 mmHg), sinus tachycardia, tachypnea, diaphoresis and dystonic posturing
- EEG showed no epileptiform activity, sepsis work-up negative, no hypoxia.

Nomenclature

- Paroxysmal sympathetic hyperactivity
- Sympathetic storms
- Autonomic storms
- Mid-brain dysregulatory syndrome
- Paroxysmal autonomic instability (with dystonia)
- Diencephalic seizures

Nomenclature

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- Diencephalic seizures

Characteristic features

- Lability of:
  - Blood pressure
  - Heart rate
  - Respiratory rate
  - Body temperature
- Other features
  - Agitation
  - Diaphoresis
  - Flushing
  - Piloerection
  - Pupillary dilatation
  - Muscle tone changes
    - § Generalized hypertonia
    - § Focal dystonias

Proposed diagnostic criteria

- Presence of *several* of the following :
  - profuse sweating
  - agitation
  - tachycardia (>120 bpm)
  - hypertension (SBP > 160 mmHg)
  - tachypnea
  - fever (> 38.3°C),
  - rigidity, extensor posturing or severe dystonia

Clinical setting

- Severe traumatic brain injury
  - diffuse axonal injury
  - focal intraparenchymal lesions
- Severe hypoxic encephalopathy
- Subarachnoid hemorrhage
- Acute hydrocephalus
- Intracerebral hemorrhage

Clinical setting

- Typically occurs 5-7 days after inciting event
- Episodes occur several times a day
- May last up to 12 hours
- Can persist for weeks or several months after the inciting event
- Rarely first appear in the subacute or even chronic stage

Provocative factors

- Pain
- Bladder distention
- Foley catheter manipulation
- Bowel evacuation
- Body turning
- Spontaneous (without obvious provocation)

Pathophysiological mechanism

- Unknown
  - Activation of diencephalic or brainstem excitatory regions and/or
  - Disinhibition of subcortical structures
- Specific mechanisms
  - Baroreflex failure
  - Catecholamine release
  - Increased sympathetic nerve traffic

Differential Diagnosis

- Neuroleptic malignant syndrome
- Serotonin syndrome
- Malignant hyperthermia
- Sepsis
- Pulmonary embolus
- Seizures
- Encephalitis
- Cushing response

Treatment

- First line:
  - Morphine (or other opioids)
    - 2-8 mg as prn boluses
  - Non-selective beta blockers e.g., propranolol
    - 20-60 mg q 4-8 hour via enteral route
- Other agents
  - Dopamine agonists
  - Benzodiazepines
  - Gabapentin
  - Clonidine
  - Dantrolene
  - Baclofen

Diencephalic Epilepsy

- Symptoms of paroxysmal flushing, diaphoresis, mydriasis, hypertension, lacrimation, shivering, hiccupping, and respiratory changes
- Cholesteatoma at foramen of Munro impinging on thalami

Penfield W. Diencephalic autonomic epilepsy

Arch Neurol Psychiatry 1929; 22: 358-374

Diencephalic Epilepsy

- Heterogeneous etiologies including head trauma, neoplasms, neuronal degeneration, hydrocephalus, agenesis of the corpus callosum and without obvious pathology
- Reported therapy - morphine sulphate, bromocriptine and benzodiazepines.
- Not responsive to anticonvulsants
- Possible activation or release of central sympathoexcitatory regions

Autonomic Epilepsy

- Anatomical approach
- Semiological approach

Causes of Death in Epilepsy

- Mortality in epilepsy – 2-3 times the general population
- Causes:
  - Concomitant diseases
  - Status epilepticus
  - Seizure related
    - Suffocation
    - Drowning
    - Head trauma
    - Burns
    - Aspiration
  - Treatment related
  - Suicide

Epilepsia 2003; 44 (Suppl 6): 19-20

Sudden Unexplained Death

- Age related
- Normal subjects
  - <45 years – 5 per 100,000
  - Elderly – 300 per 100,000
- Epilepsy (SUDEP)
  - All patients – 1 per 1,000
  - “Severe” epilepsy – 1 per 250

Epilepsia 2003; 44 (Suppl 6): 19-20

SUDEP

- Incidence:
  - 7-17% of deaths in all patients with epilepsy
  - 0.35 - 6 per 1000 person years
  - 24 times the general population
  - 1 in 10 of deaths in adults aged 15 to 44

SUDEP

- Risk Factors:
  - Young, male (> 3:1)
  - History of GTC seizures
  - Low anti-convulsant levels
  - Treatment non-compliance
  - Black
  - History of alcohol abuse
  - Anatomic brain lesions

Based on multiple studies including medical examiner data

SUDEP

- Prospective cohort study
- 4,578 patients followed for 16,463 patient-years.
- Incidence of SUDEP was 1.21/1,000 patient-years
- Higher among women (1.45/1,000) than men (0.98/1,000)
- SUDEP accounted for 18% of all deaths.
- Independent risk factors:
  - Occurrence of tonic-clonic seizures
  - Treatment with more than two anticonvulsant medications
  - Full-scale IQ less than 70
  - Subtherapeutic anticonvulsant levels at the last visit equally common
  - No particular anticonvulsant appeared to be associated with SUDEP

Walczak et al. Neurology 2001;56:519–525

Sudden Unexplained Death

- Proposed Mechanisms
  - Cardiac arrhythmia
  - Cardiac ischemia
    - Perivascular or interstitial fibrosis
    - Myocyte vacuolization
  - Ictal or post-ictal apnoea
  - Neurogenic pulmonary edema

Sudden Unexplained Death

- Mechanism
  - Cardiac arrhythmia
  - Ictal or post-ictal apnoea
  - Neurogenic pulmonary edema
  - Intrinsic cardiac pathology
    - § Perivascular or interstitial fibrosis
    - § Myocyte vacuolization
  - Heavier than normal heart, lung and liver weight

Diencephalic Epilepsy

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Autonomic Epilepsy

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- Semiological approach

Autonomic Epilepsy

- Anatomical approach
  - Central autonomic network
    - Insula
    - Amygdala
    - Prefrontal cortex
      - Ventromedial prefrontal cortex
      - Anterior cingulate cortex
- Semiological approach

Central Autonomic Network

- Interconnected areas throughout neuraxis
- Involved in tonic, reflex and adaptive control of autonomic function
- Receives and integrates visceral, humoral and environmental information
- Produces site specific changes in autonomic nervous system and visceral activity

Insular Cortex

- Primary viscerosensory cortex
- Contains organotopic viscerosensory map

  Taste - anterior insula

  General visceral - posterior insula
- Afferent input from NTS, parabrachial nucleus, thalamus and lateral hypothalamus
- Topographically organized descending visceral sensory and motor projections

Prefrontal cortex

The “autonomic premotor cortex”

- Ventromedial prefrontal cortex
- Anterior cingulate cortex

Ventromedial Prefrontal Cortex

- Role in high level emotional and cognitive function
- Convergence and integration of processed exteroreceptive and viscerosomatic information
- Extensive cortical, hypothalamic and brainstem connections
- Role in the control of emotional, behavioural and autonomic efferent responses

Anterior Cingulate Cortex

- The initiation, motivation and execution of emotional and goal directed behaviour
- Divided into “affective” and “cognitive” components
- Modulates autonomic responses associated with affective behaviour and response selection

Anterior Cingulate Cortex

- Affective component

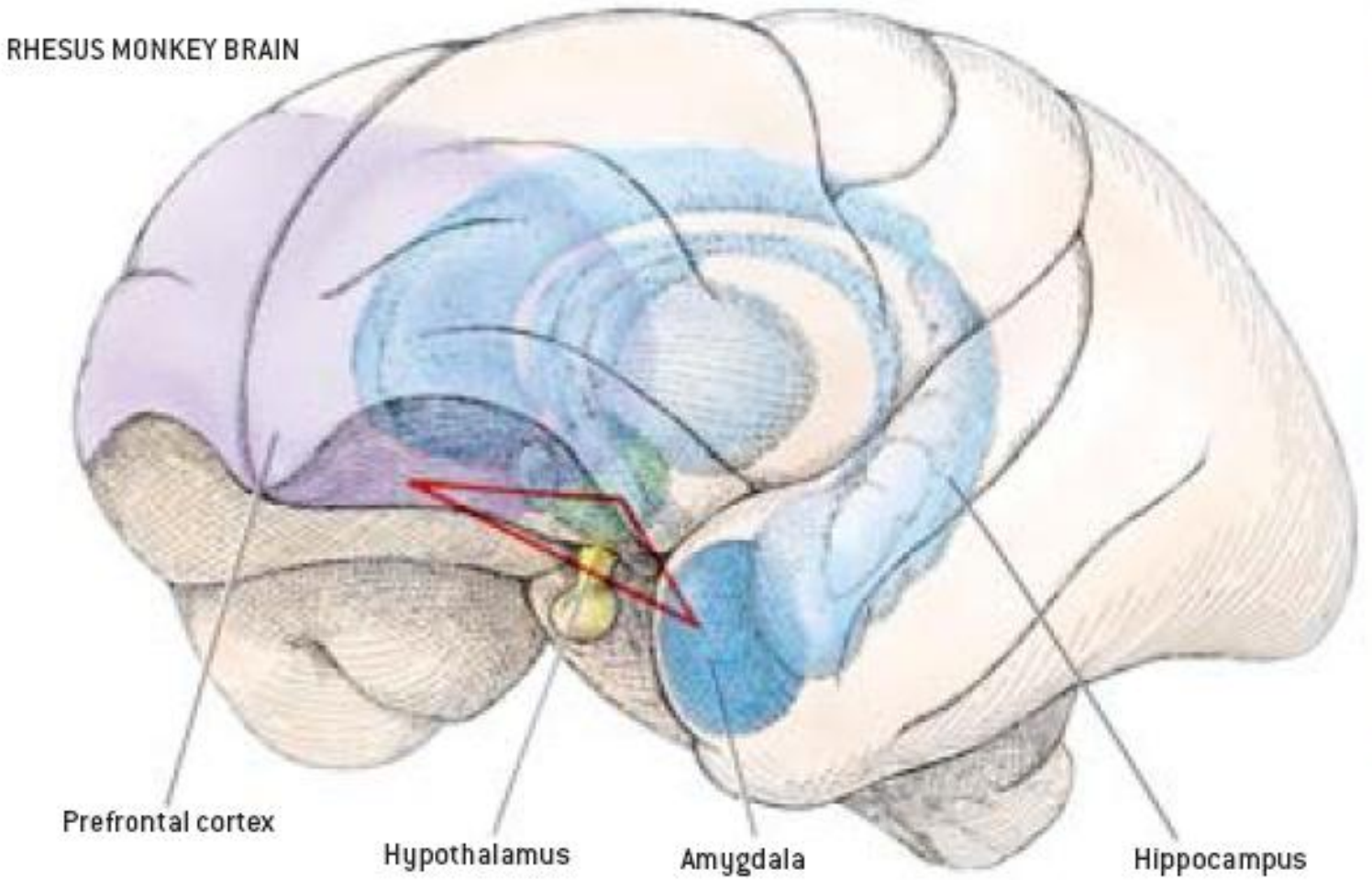
  Amygdala, hypothalamic and brainstem connections

  Visceromotor region - modulates autonomic activity and internal emotional responses

  High level regulation of autonomic and endocrine function, conditioned emotional learning, vocalization, and assessment of emotional valence of internal and external stimuli

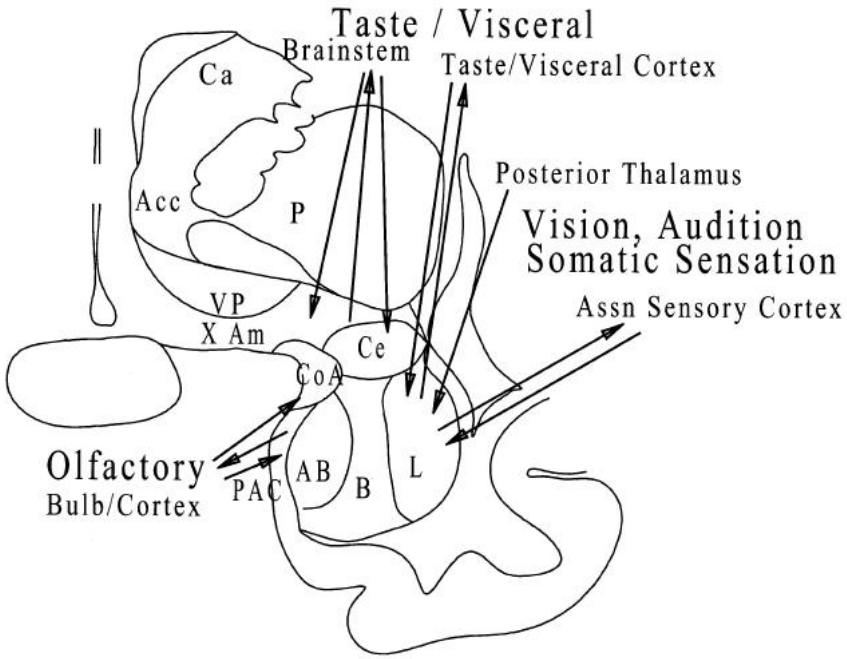
Central Nucleus of the Amygdala

- The amygdala interprets affective significance of afferent sensory information
- Generates appropriate autonomic, behavioural, motor and endocrine responses
- Basolateral nucleus receives afferent input from cortex, thalamus and brainstem
- Central nucleus projects to hypothalamus and brainstem autonomic nuclei



The neurobiology of fear
Kalin N www.sciam.com 2002

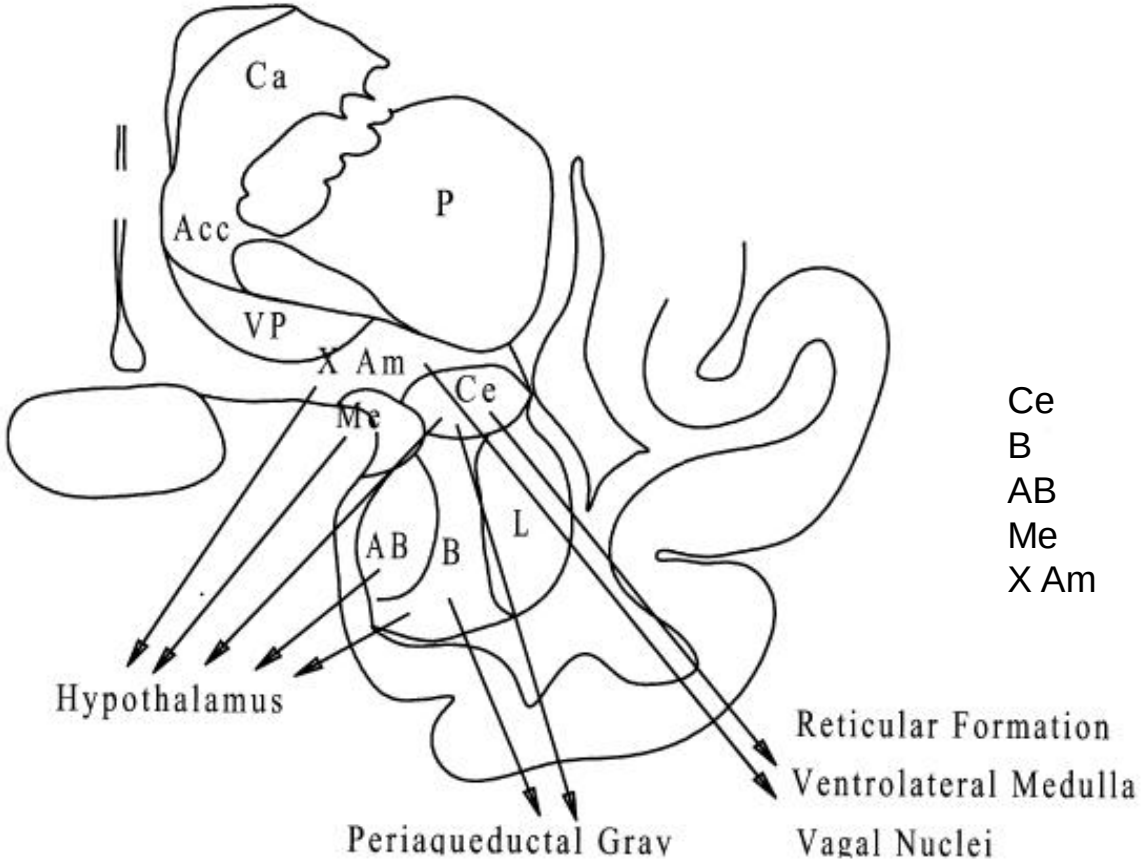
Summary of sensory inputs to amygdala



Ce	Central amygdaloid nucleus
B	Basal amygdaloid nucleus
AB	Accessory basal AN
Me	Medial AN
X Am	Extended amygdala
CoA	Ant. cortical amygdaloid nucleus
PAC	Peri-amygdaloid cortex

Comparative aspects of amygdala anatomy
Price J.L. *Ann. N.Y. Acad Sci* 2003; 985;50-58

Summary of outputs from amygdala to brainstem



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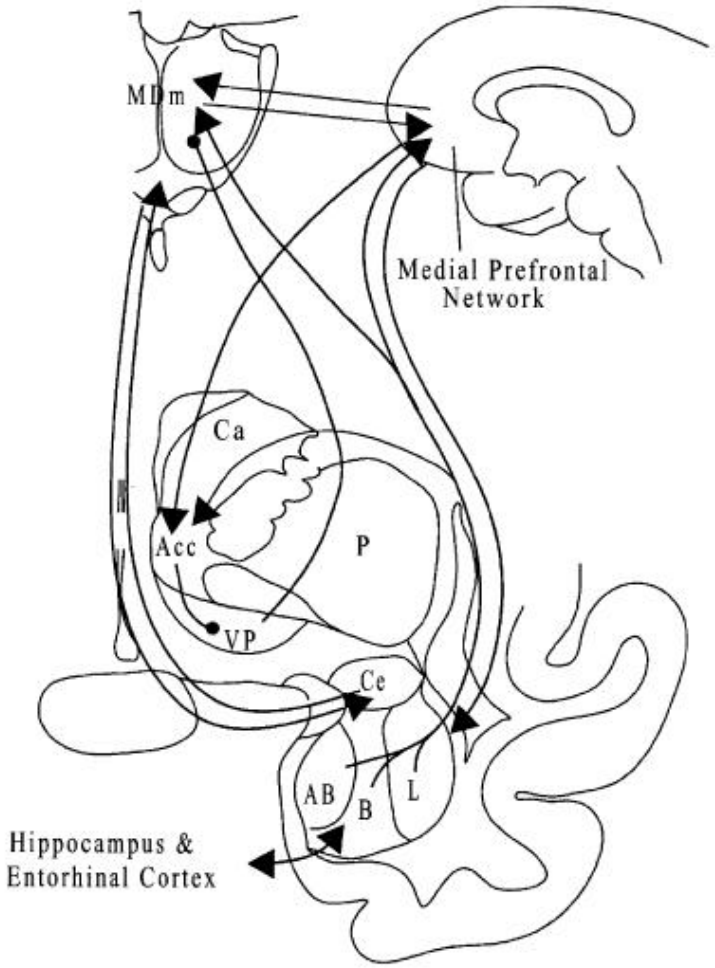
Summary of forebrain amygdala connections



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PAC	Peri-amygdaloid cortex
CA	Caudate
Acc	Accumbens
VP	Ventral Pallidum

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Sudden Unexplained Death

- Proposed Mechanisms
  - Cardiac arrhythmia
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  - Ictal or post-ictal apnoea
  - Neurogenic pulmonary edema

Autonomic Epilepsy

- Anatomical approach
- Semiological approach
  - Cardiovascular
  - Pulmonary
  - Gastrointestinal
  - Cutaneous
  - Urogenital

Cardiovascular Manifestations

- Heart rate
- Heart rhythm
  - Tachyarrhythmias
  - Bradyarrhythmias
- Blood pressure
- Cardiac ischemia
- Chest pain

Sinus tachycardia

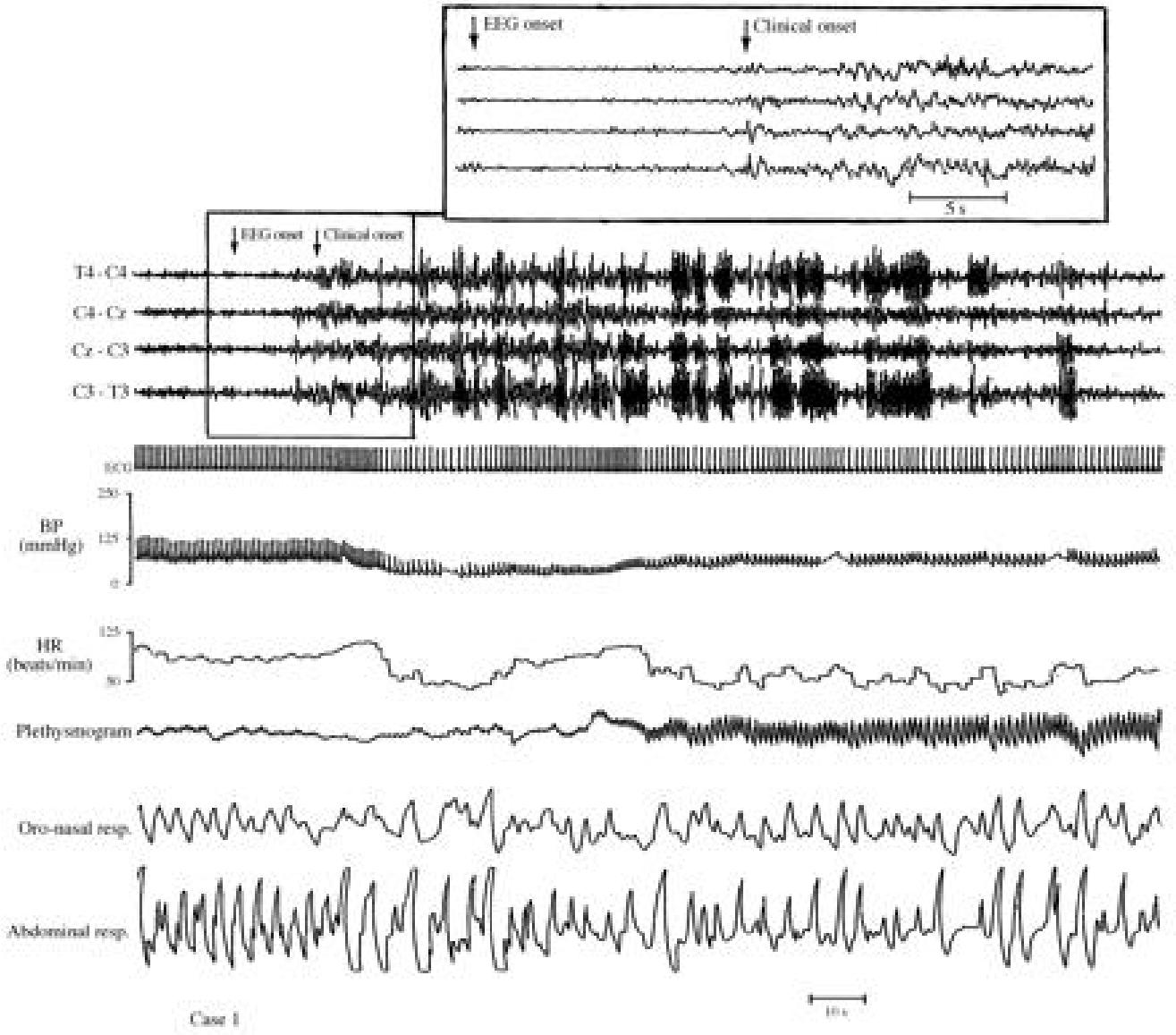
- Ambulatory cassette monitoring of the EKG and EEG
- 70 spontaneous seizures in 26 patients.
- 92% percent of the seizures were associated with an increase in heart rate.
- Maximum documented heart rate was 201 b.p.m.
- 67% of the seizures the heart rate > 120 b.p.m.
- The increase in heart rate was more common in younger and untreated patients

Blumhardt LD et al. Electrocardiographic accompaniments of temporal lobe epileptic seizures. *Lancet*. 1986;1:1051-1056

Bradycardia

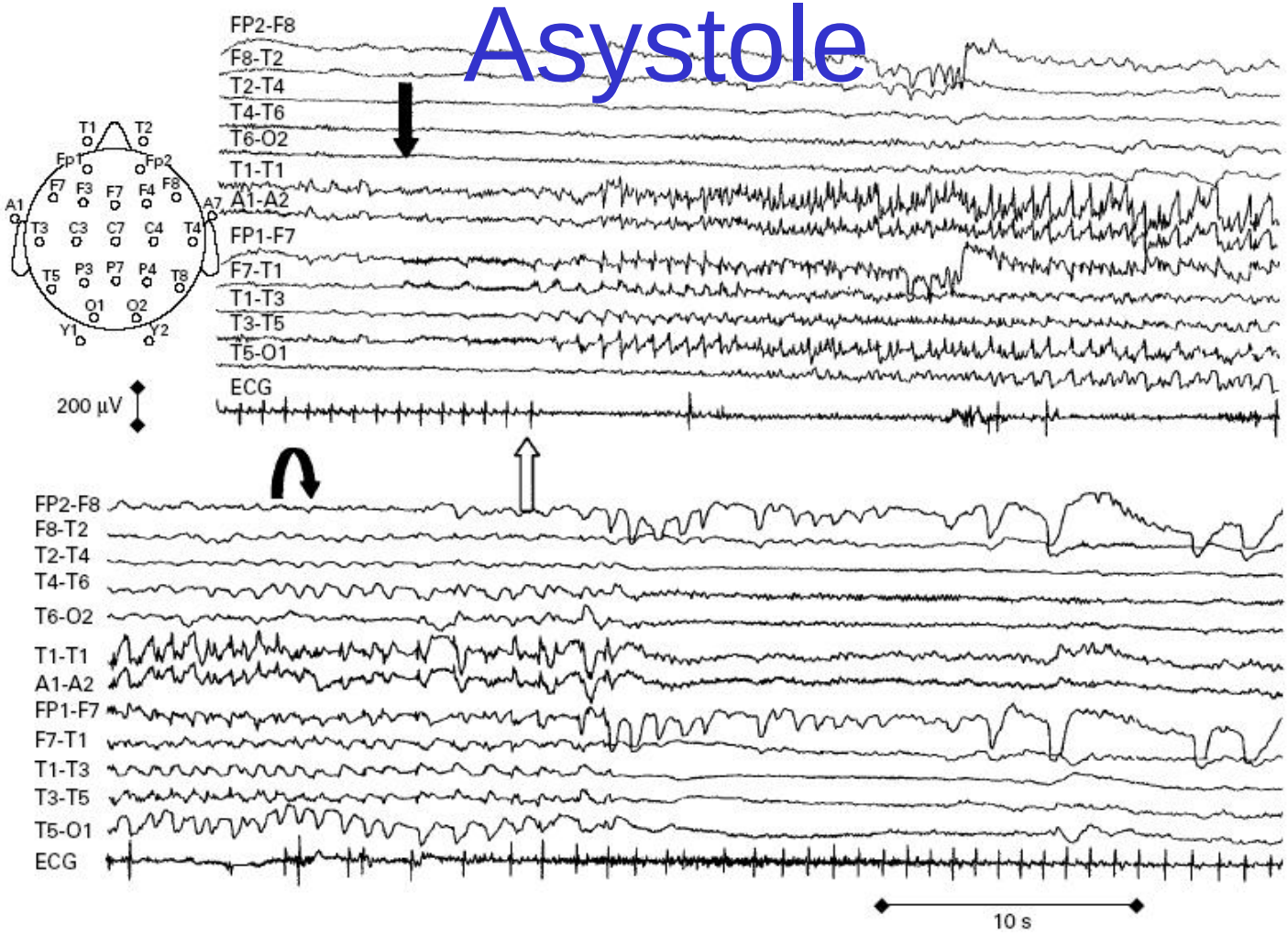
- 63 cases (3 new)
- 47 with simultaneous EEG
- 76% could be localized to fronto-temporal and temporal regions
- Ratio left to right localization – 26:19
- Role of carbamazepine

Tinuper et al. Ictal bradycardia in partial epileptic seizures
Brain 2001; 124:2361-2371

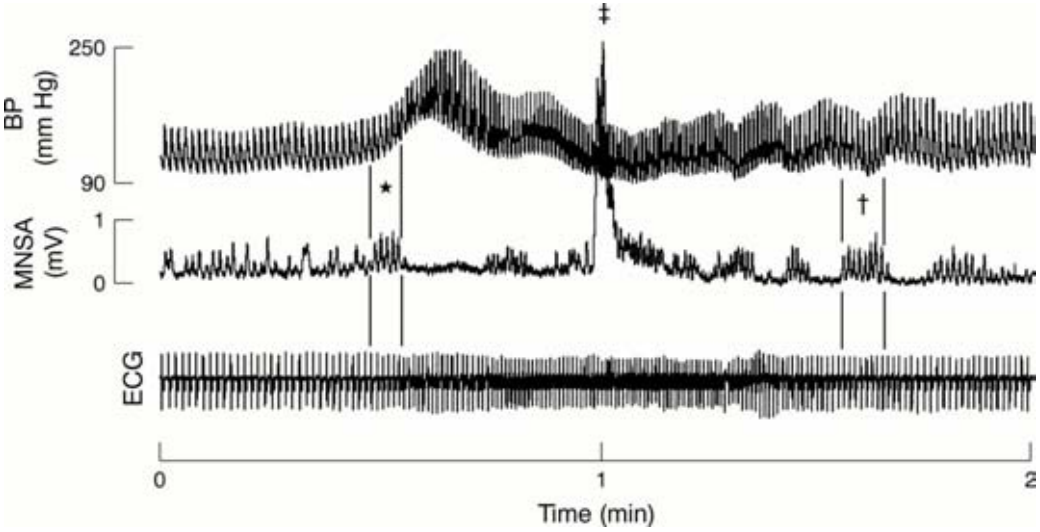


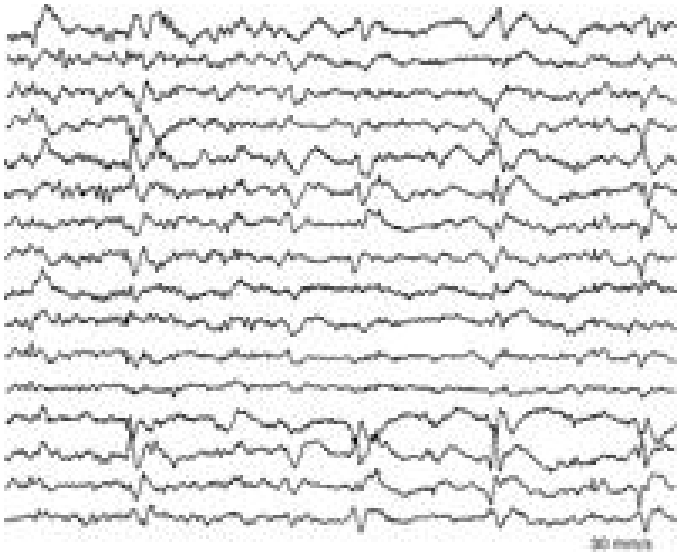
Tinuper et al. Ictal bradycardia in partial epileptic seizures
Brain 2001; 124:2361-2371

Asystole



Lim ECH et al. Brain seizes, heart ceases: a case of ictal asystole
J Neurol Neurosurg Psychiatry 2000;69:557–559





- Tilt table
- Absence seizure
- Increase MSNA
- Increase HR and BP

- Sleep EEG
- Left fronto-temporal spikes

Paroxysmal hypertension during a complex partial seizure
Jardine DL et al. J Neurol Neurosurg Psychiatry 2001;71:132-133

Cardiovascular Manifestations

- "Phaeochromocytoma like presentation"
  - Headache
  - Fear and anxiety
  - Tachycardia
  - Hypertension
  - Tremor
  - Flushing and sweating

R. W. Brown and W. R. McLeod. Sympathetic stimulation with temporal lobe epilepsy. *Medical Journal of Australia* 2:274-276, 1973.

Chest pain

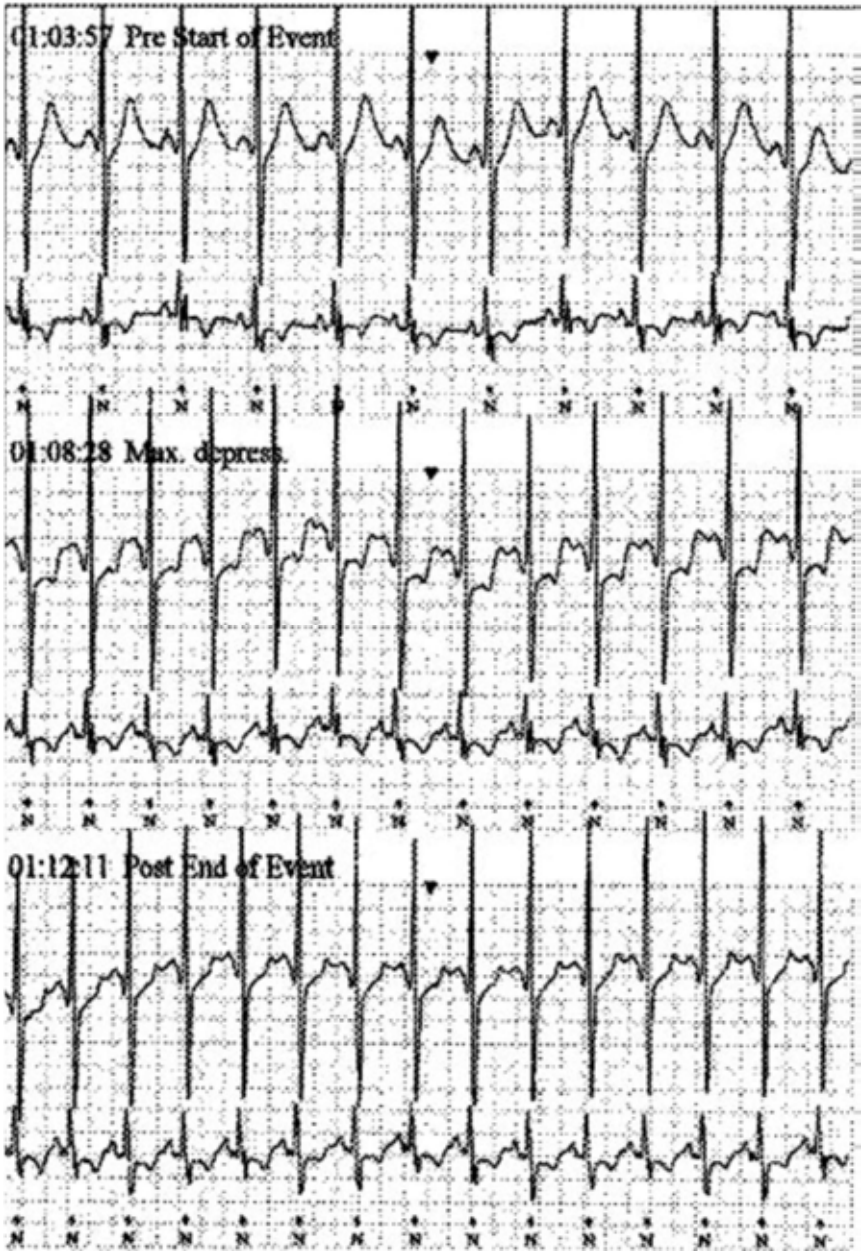
- 5 patients with documented epileptiform activity presented with chest pain
- 3 patients admitted to a coronary care unit.
- Features characteristic of angina pectoris
  - Radiation of the pain to jaw or left arm
  - Diaphoresis
  - Shortness of breath
  - Nausea.

Devinsky O et al. Cardiac manifestations of complex partial seizures. Am J Med. 1986;80:195-202.

Cardiac Ischemia

- Twenty-three subjects with drug refractory epilepsy
- Cardiovascular evaluation before and during video-EEG monitoring.
- ST-segment depression occurred in 40%
- Associated with a higher maximum heart rate during seizures.

Evidence of cardiac ischemia during seizures in drug refractory epilepsy patients
S. Tigaran et al. Neurology 2003;60:492–495



Evidence of cardiac ischemia during seizures in drug refractory epilepsy patients

S. Tigaran et al.
Neurology 2003;60:492–495

Respiratory Manifestations

- Apnoea
- Stridor
- Coughing
- Choking
- Hyperventilation
- Neurogenic pulmonary oedema

Gastrointestinal Manifestations

- Nausea and vomiting
- Abdominal bloating
- Abdominal pain
  - Periumbilical
  - Right upper quadrant
  - Rectal
- Bowel hypermotility and diarrhoea

Gastrointestinal Manifestations

- Ictus emeticus
  - Episodic vomiting
  - Usually associated with other seizure manifestations
  - Alteration in consciousness
  - Not recalled by patient
  - Non-dominant temporal lobe focus

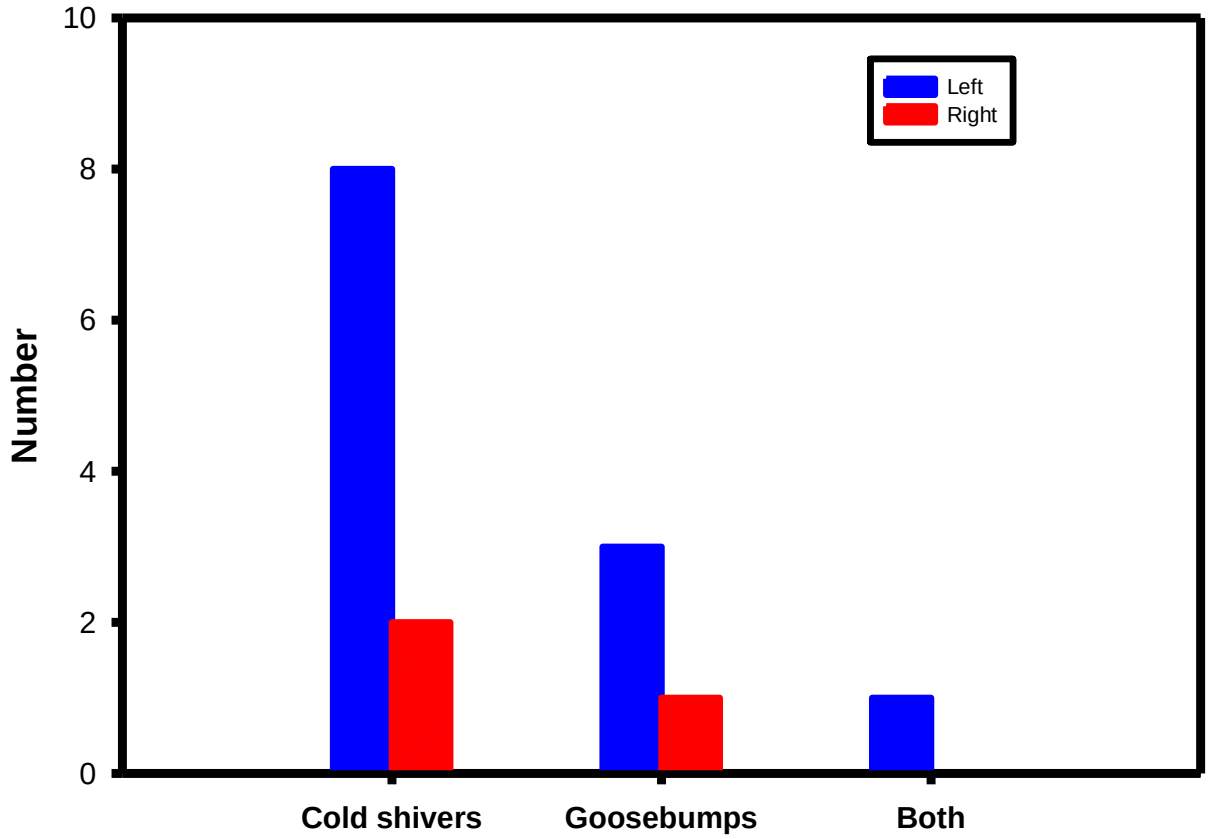
Early benign childhood occipital seizures (Panayiotopoulos syndrome)

- Newly recognized, high prevalence
- Children present at 3–6 years of age (13% prevalence)
- Seizures begin with pallor, sweating and irritability.
- Ictal vomiting most common symptom (86%)
- Eye deviation
- May progress to LOC, hemi or generalized convulsions
- Usually last >10 min (1/3 last hours)
- Seizures are infrequent (median 3)
- Remission in 1-2 years

Lada et al. Epilepsia 2003;44: 81-88

Cutaneous Manifestations

- Flushing
- Pallor
- Piloerection
- Diaphoresis
- Associated sensory phenomena



Stefan et al. Left hemisphere predominance of epileptic generators of cold shivers and goosebumps.

Epilepsia 2002; 41:43-45

Urogenital Manifestations

- Erotic thoughts
- Sexual arousal
- Orgasm and ejaculation
- Genital viscerosensory phenomena
- Sexual automatisms

Infectious diseases

- Botulism
- Diphtheria
- Tetanus

Case 5 – Clinical Course

- 69 yo woman with acute onset of dysphagia to solids and liquids, nausea and vomiting
- Generalized weakness and fatigue, dry mouth, a hoarse voice
- Constipation, urinary hesitancy and lightheadedness with standing

Cranial Nerves

Bilateral ptosis , decreased EOM, sluggish pupils

Facial weakness, dysphonia , dysarthria

Motor

Asymmetrical 4- to 4+ proximal weakness

Gait

Stands with assistance, unable to walk secondary to lightheadedness on standing

Orthostatic blood pressures not documented

Case

- 69 yo woman with acute onset of dysphagia to solids and liquids, nausea and vomiting
- Generalized weakness, dry mouth and hoarse voice
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Facial weakness, severe dysphonia and dysarthria

Motor

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Gait

Stands with assistance, unable to walk secondary to lightheadedness on standing

Orthostatic blood pressures

not documented

Case 5 - Diagnosis

A. Paraneoplastic autonomic neuropathy
B. AL amyloid neuropathy
C. Immune-mediated autonomic neuropathy
D. Diabetic autonomic neuropathy
E. Botulism

Case 5 – Investigations and Clinical Course

- Over 10 days
  - Worsening hypotension, ophthalmoplegia, dilated unreactive pupils
  - Elective intubation for airway protection
  - LP normal
  - Incremental response on repetitive stimulation

  Additional history

  Cans strawberry jam that she eats daily for breakfast

  Botulinum antitoxin A, B, and E administered on day#10

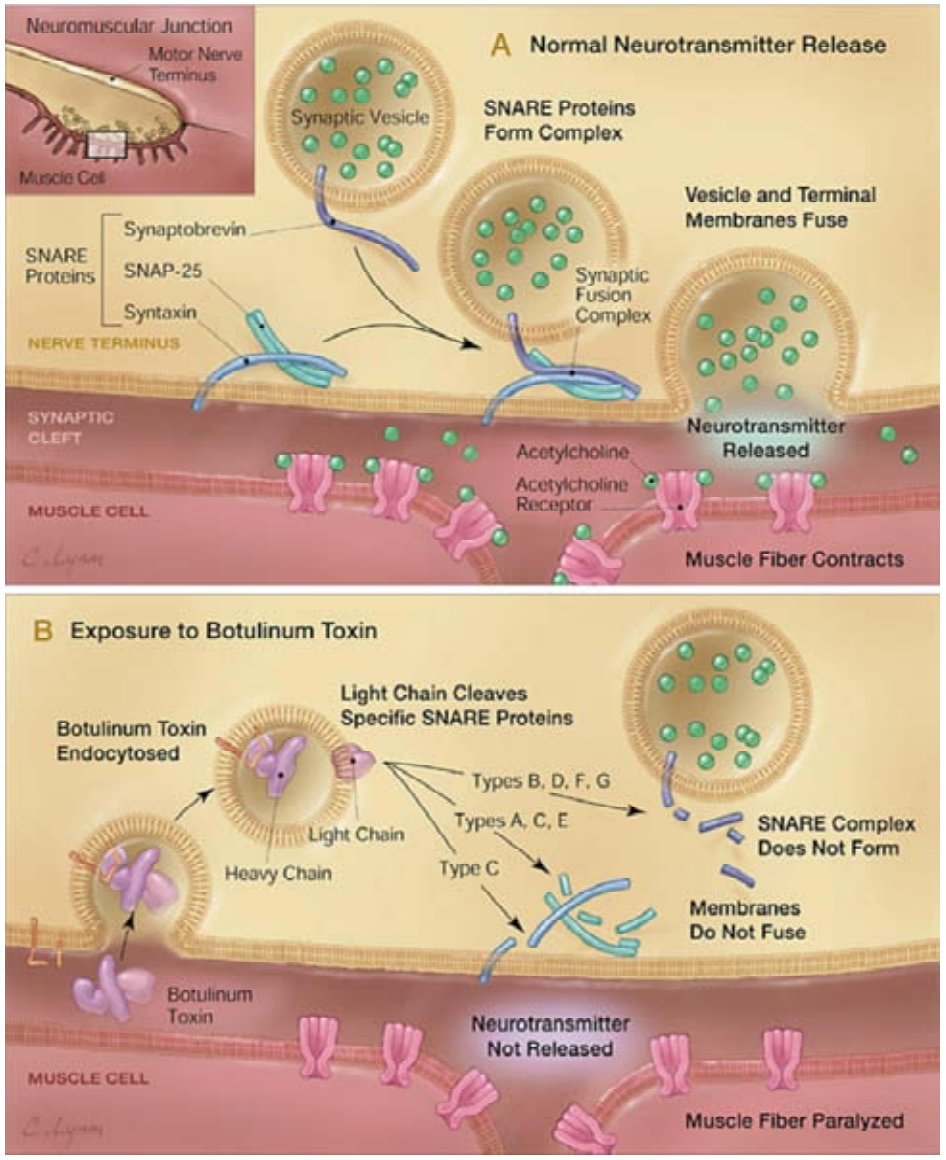
  Symptoms and signs improve dramatically over ~ 6 days

Botulism

- Paralytic disease caused by the neurotoxins of Clostridium botulinum
- Food borne, wound, infant, colonization, pharmaceutical botulinum toxin
- Types A, B, and E toxins most often responsible for disease in humans
- Light chain of toxin prevents assembly of synaptic fusion complex – blocking acetylcholine release
- Clinical diagnosis – laboratory confirmation delay
- Begin antitoxin therapy empirically

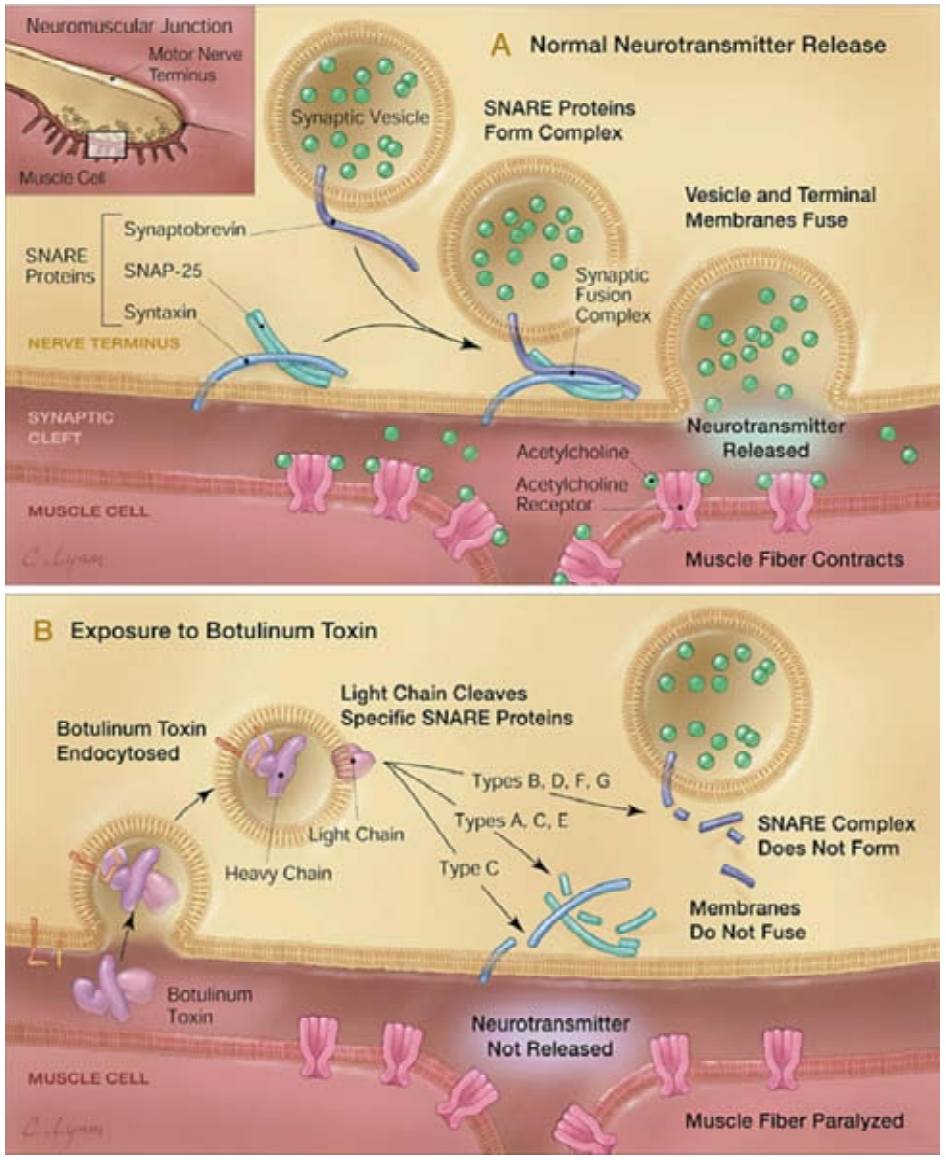
Neuromuscular

- Descending weakness
  - Ophthalmoplegia
  - Dysarthria
  - Dysphagia
  - Dysphonia
  - Neck and shoulder girdle
  - Diaphragm



Autonomic

- Xerostomia
- Xerophthalmia
- Mydriasis
- Gastrointestinal
  - Ileus
  - Gastric dilation
- Bladder
- Orthostatic hypotension



Immune mediated neuropathy
Autonomic Manifestations

- Inflammatory demyelinating polyneuropathy associated
- Acute (parainfectious) autonomic neuropathy
- Autoimmune autonomic ganglionopathy
- Paraneoplastic autonomic neuropathy
- Autoimmune disease associated autonomic neuropathy

Variations

- Tempo
  - Acute, subacute and chronic
- Distribution
  - Sympathetic
  - Parasympathetic
  - Small and large fiber sensory
- Topography
  - Organ system
  - Fiber length

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Sentinel case
Acute pan-dysautonomia

- Incapacitating orthostatic hypotension
- Severe bowel hypomotility
- Bladder atony
- Pupillomotor dysfunction
- Anhidrosis
- Albumino-cytological dissociation

R. R. Young, A. K. Asbury, J. L. Corbett, and R. D. Adams. Pure pan-dysautonomia with recovery. Brain 98:613-636, 1975

Cholinergic dysautonomia

- Gastrointestinal hypomotility
- Hypotonic bladder
- Secretomotor dysfunction
  - Xerostomia
  - Xerophthalmia
- Pupillomotor dysfunction
- Erectile failure

Sympathetic dysautonomia

- Sympathetic adrenergic dysfunction
  - Orthostatic hypotension
  - Ejaculatory dysfunction
  - Sphincter dysfunction
  - Horner’s syndrome
- Sympathetic cholinergic dysfunction
  - Hypohidrosis and anhidrosis
  - Hyperhidrosis

Para-infectious autonomic neuropathy

- Infectious Mononucleosis

  Yahr MD and Frontera AT. Acute autonomic neuropathy. Its occurrence in infectious mononucleosis.

  Arch Neurol. 1975; 32:132-133.

- Streptoccal infection

  Thomashefsky AJ et al. Acute autonomic neuropathy.

  Neurology. 1972;22:251-255.

- Coxsackie B

  Pavesi G et al. Acute sensory and autonomic neuropathy: possible association with coxsackie B virus infection.

  J Neurol Neurosurg Psychiatry. 1992;55:613-615.

Para-infectious autonomic neuropathy

- Rubella

  Summers Q, Harris A. Autonomic neuropathy after rubella infection. Med J Aust. 1987;147:353-355.

- Herpes simplex

  Neville BG, Sladen GE. Acute autonomic neuropathy following primary herpes simplex infection.

  J Neurol Neurosurg Psychiatry. 1984;47:648-650.

- Non-diagnosed ‘viral syndromes’

  Antecedent presumed viral infection is frequently present (although specific infectious agent not usually identified)

Acute inflammatory demyelinating polyneuropathy

- Autonomic manifestations common
- May be the presenting feature
- More prominent in patients with
  - Respiratory failure
  - Severe motor deficits
  - Significant axonal features

Acute inflammatory demyelinating polyneuropathy

- Autonomic manifestations
  - Sinus tachycardia (10-50%)
  - Sinus pauses and other tachy- and bradyarrhythmias
  - Blood pressure lability – sustained hypertension, paroxysmal hypotension and hypotension
  - Bowel and bladder dysfunction
  - Pupillomotor disturbances
  - Sudomotor dysfunction - hypohidrosis and hyperhidrosis
  - Vasomotor abnormalities

Chronic inflammatory demyelinating polyneuropathy

- Symptomatic autonomic features infrequent
  - Mainly gastrointestinal (19%) and genitourinary (17%)
- Abnormal autonomic test results: 21- 76%
- Typically mild
  - Predominantly cholinergic
    - Sudomotor abnormalities – 34%
    - Cardiovagal abnormalities – 21%
    - Adrenergic abnormalities – 9%

Ingall TJ, McLeod JG, Tamura N. Autonomic function and unmyelinated fibers in chronic inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve 1990;13:70–76.

Figueroa JJ et al. Autonomic dysfunction in chronic inflammatory demyelinating polyradiculoneuropathy. Neurology. 2012;78:702-8.

Chronic inflammatory demyelinating polyneuropathy

Mathis S, Magy L, Diallo L, Boukhris S, Vallat JM. Amyloid neuropathy mimicking chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 2012;45(1):26-31.

Plante-Bordeneuve V, Ferreira A, Lalu T et al. Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP). Neurology 2007;69(7):693-698

- Adrenergic abnormalities – 9%

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Figueroa JJ et al. Autonomic dysfunction in chronic inflammatory demyelinating polyradiculoneuropathy. Neurology. 2012;78:702-8.

Autonomic Manifestations –
Typical setting

- Rapidly progressing
- Severe motor deficits
- Ophthalmoplegia
- Respiratory failure
- Sensory prominent GBS
- But may occur with any degree of weakness
- Rare – Miller-Fisher syndrome and CIDP

Autonomic Manifestations

- Cardiovascular
- Bowel
- Bladder
- Pupillomotor
- Sudomotor and vasomotor
- Vasomotor
- Neurogenic pulmonary edema
- Posterior reversible encephalopathy

Differential Diagnosis

- Hypoxia
- Pulmonary emboli
- Sepsis
- Electrolyte disturbances
- Gastro-intestinal bleeding

Blood Pressure

- Spontaneous blood pressures fluctuations
- Hypertension in up to ~60%
- Sustained or spells
- Can reach well over 200 mmHg
  - RICP
  - hypertensive encephalopathy
  - papilledema
  - PRES
  - neurogenic pulmonary edema

Hypertension

- Mechanism:
  - baroreflex dysfunction, renin and catecholamine elevation
- Treatment
  - Cautious – can cause severe hypotension
  - Reverse Trendelenburg
  - Morphine
  - Beta - adrenoreceptor blockers
  - Nitroprusside for acute changes
  - Clonidine may stabilize fluctuations

Hypotension

- Occurs in up to 60%
- Alternates with hypertension
- Provoked by suctioning, intubation, bowel bladder distention or emptying
- May extend into rehabilitation
- Mechanism
  - Baroreflex dysfunction
  - Lower threshold for hypotensive-bradycardic response
  - Sympathetic denervation

Hypotension treatment

- Treatment
  - Minimalist approach
  - Avoid provocations
  - Volume expansion - fluids / albumin
  - Trendelenburg
  - Phenylephrine

Bradycardia

- Persistent or episodic
  - Sinus arrest
  - A-V conduction block
  - Asystole
  - ‘Vagal spells’
    - Provoked by vagotonic stimuli
    - May be a component of hypotensive-bradycardic response
- Treatment
  - Observation, atropine or pacemaker

Sinus tachycardia

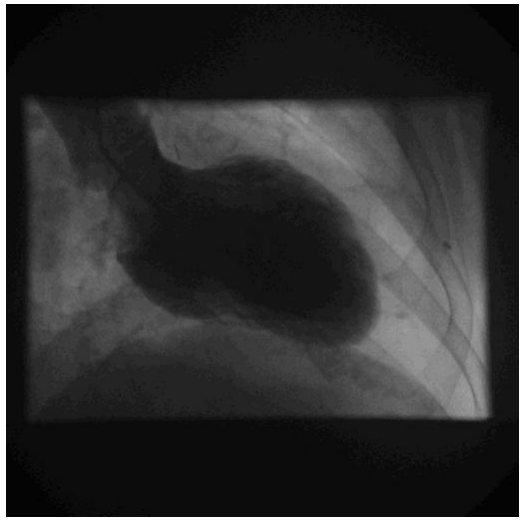
- Occurs in up to 80%
- May precede the onset of weakness
- Associated with reduced R-R interval variability – may predict subsequent arrhythmias (Flachenecher. Brain 1997)
- Treatment not necessary unless associated with myocardial ischemia

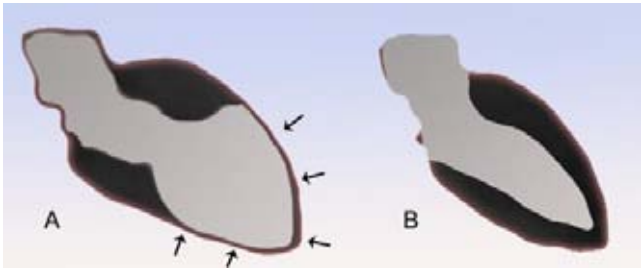
Other

- Atrial arrhythmias
  - Atrial fibrillation
  - Atrial flutter
  - Paroxysmal atrial tachycardia
- Ventricular arrhythmias
  - Premature ventricular contractions, bigemini,
  - Ventricular tachycardia and fibrillation
- Sudden cardiac death – rare

Takotsubo cardiomyopathy

- Stress myocardopathy, neurogenic stunned myocardium, broken heart syndrome
  - Myocardopathy associated with increased sympathetic activity following emotional stress
  - Unique pattern - akinesis or dense hypokinesis of the apical and midventricular segments, with sparing of the basal segments.





Takotsubo cardiomyopathy

- Stress myocardopathy, neurogenic stunned myocardium, broken heart syndrome
  - Myocardopathy associated with increased sympathetic activity following emotional stress
  - Unique pattern - akinesis or dense hypokinesis of the apical and midventricular segments, with sparing of the basal segments.
  - Presentations – chest pain, dyspnea, hypotension - symptoms of myocardial ischemia
  - Elevated troponin level
  - Several case reports in GBS
  - Associated with and possibly due to high levels of circulating catecholamines

Autonomic Manifestations

- Cardiovascular
- Bowel
- Bladder
- Pupillomotor
- Sudomotor and vasomotor
- Vasomotor
- Neurogenic pulmonary edema
- Posterior reversible encephalopathy