Autonomic Dysfunction: Autonomic Non-Epileptic Seizures and the Autonomic Epilepsies

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Introduction

- Myriad of Symptoms related to acute autonomic dysfunction: Syncope, Autonomic Epilepsia, and the Autonomic Semiology of Epilepsy
- What is a seizure, or non-epileptic seizure?

Definitions

- Seizure: a sudden attack (of an illness or disease); epileptic seizure: uncontrolled, hypersynchronous brain electrical activity
- Epilepsy: unprovoked, recurrent seizures
- Drop Attacks: any event in which the person falls
- Syncope/Transient loss of consciousness: short LOC and muscle strength
  - Usually fast onset, short duration, and fast recovery

Non-Epileptic Seizure

- Paroxysmal event that mimic an epileptic seizure but do not involve abnormal, rhythmic discharges of cortical neurons. Called a hypersynchronous neuronal discharge.
- May be caused by physiological (ie vagotonia) or psychological conditions.

Dx Epilepsy: Errors (adults)

- Psychogenic, non- epileptic seizures
- **Syncope**
- Hypoglycemia
- Panic attacks
- MovementDisorders
- Sleep Disorders (parasomnia, hypnic jerks)
- TIA
- Migraines (TGA)

Table 1 Functional Organization of Symptoms associated with Autonomic Disorders

System	Dysfunction	Symptom
Vasomotor	Hypertension	Headache
Cardiovascular	Hypotension	Dizziness, light-headedness, blurred vision, loss of consciousness or syncope
	Arrhythmia	Palpitations, loss of consciousness or syncope
	Vascular changes	Purple feet, mottled skin, acrocyanosis, blotching
Gastrointestinal	Oropharyngeal dysmotility	Feeding problems (poor suck, drooling, aspiration pneumonia)
	Esophageal dysmotility	Dysphagia (difficulty swallowing)
	Gastroesophageal reflux	Nausea, recurrent vomiting
	Bowel dysmotility	Bloating, profound constipation, or diarrhea
Ophthalmologic	Alacrima	Dry eye
	Nonreactive or sluggish pupil	Dark or light intolerance
	Eyelid weakness	Ptosis
Respiratory	Alveolar hypoventilation	Cyanosis with sleep
	Apnea	Breath holding spells
	Insensitivity to hypoxia	Syncope at high altitudes or plane travel
	Insensitivity to hypercarbia	Muscle twitches, hypertension
Sudomotor	Altered sweating	Hypohidrosis or hyperhidrosis, excessively dry skin, clammy hands and feet, unexplained fevers, heat intolerance
Urinary	Nocturia	Frequent awakenings to urinate or nocturnal enuresis >5 years
Central dysfunction	Thermoregulatory abnormalities	Decreased basal body temperature, unexplained high fevers
	Sleep-wake disturbance	Fractured sleep, insomnia, nocturnal enuresis > 5 years of age
	Altered affect and emotions	Poor socialization skills, increased anxiety, emotional lability, tics or phobias, panic attacks
	Learning disability	Poor school performance, poor executive planning, attention problems, hyperactivity

Case History (1)

- 10 year old girl status post posterior fossa craniotomy for tumor
- Developed post-operative epilepsy, treated with AEDs
- Presented to the ED with seizure exacerbation with several seizures in 1 day
- Admitted to the PICU

Case History (2)

- Consultation to the Neurocritical Care Service
- History: her current seizures all occurred in the upright position
- Orthostatic BPs: marked drop in BP when standing

Syncope

- Common: 15 to 25% of children and adolescents
- Peak incidence 15 to 19 years; females predominate

Syncope Definitions

- **Transient loss of consciousness (TLOC):** loss of consciousness with a rapid onset, short duration and a spontaneous and complete recovery.
- **Syncope:** TLOC due to cerebral hypoperfusion
- **Symptoms vary by rapidity of onset:**
- Very rapid onset:
  - may notice few features
- Slowly developing forms (autonomic failure):
  - Difficulty in thinking, light-headedness, followed by loss of color vision and blurring or darkening of vision, sounds seem from far away

Syncope: Major Categories

- Reflex (Neurally-mediated) syncope: vasovagal situational, carotid sinus, mechanical or hydraulic factors
- Syncope due to orthostatic hypotension: primary autonomic failure, secondary autonomic failure, drug-induced autonomic failure, volume depletion
- Cardiovascular mediated syncope: arrhythmias or structural disease
- Non-cardiovascular syncope

Table 1 Differential Diagnosis of Pediatric Syncope*

- Cardiovascular mediated syncope
- Neurocardiogenic syncope (vasodepressor vasovagal)
- Orthostatic hypotension
- Postural orthostatic tachycardia syndrome (POTS)
- Convulsive syncope
- Reflex syncope
- Psychogenic syncope/ panic attacks/ hyperventilation
- Situational syncope
  - Coughing
  - Sneezing
  - Micturition
  - Defecation
  - Deglutition (cold liquids)
  - Hair grooming
  - Trumpet playing
  - Suffocation
  - Weight lifting
  - Diving
  - Stretching
- Drug and toxin induced
- Metabolic
  - Hypoglycemia
  - Electrolyte disorder
  - Endocrine disorder

*Modified and reprinted with permission.[4]

Table 2 History of "Red Flags" Requiring Urgent Referral to Pediatric Cardiology

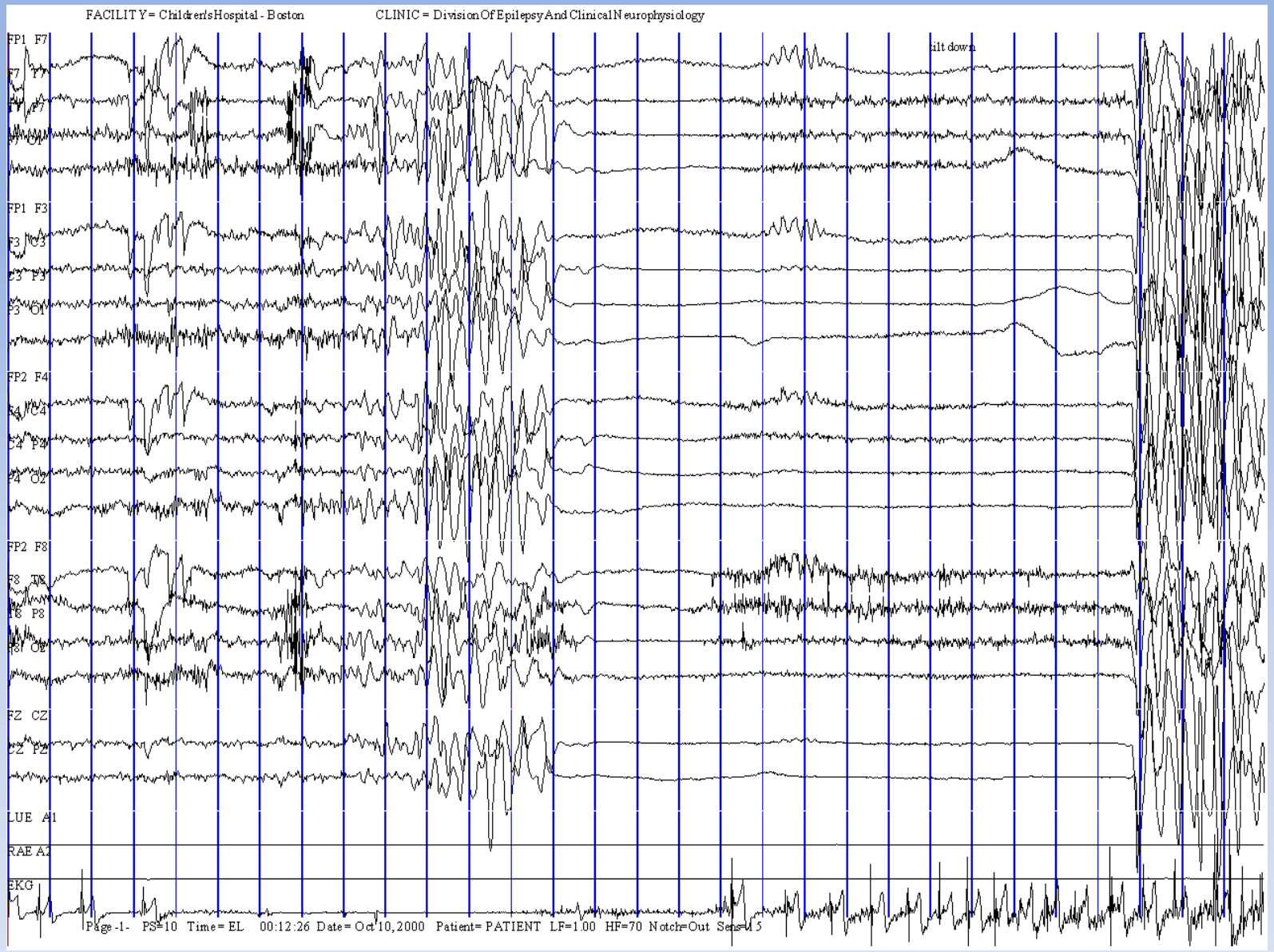
- History of heart murmur or congenital heart disease
- Acute attacks associated with hyperpnea or cyanosis
- Syncope during exercise, including swimming or with exertion
- Family history of early sudden cardiac death, long QT syndrome, sensorineural hearing loss, familial heart disease
- Medications that can result in long QT syndrome, arrhythmias
- Absence of usual premonitory symptoms or precipitating factors associated with neurally mediated syncope
- Unusual syncope triggers such as loud noises, fright, or extreme emotional stress

Table 5 Diagnostic Evaluation of Pediatric Syncope

1. Hematological—biochemical
   - CBC
   - Serum iron, TIBC, ferritin
   - CMP
2. Cardiac evaluation
   - EKG
   - Echocardiography
   - Holter or event monitor.
3. Autonomic evaluation
   - Neurocardio autonomic reflex testing with and without tilt table testing
   - Quantitative sudomotor axon reflex test (QSART)
   - Thermoregulatory sweat test (TST).
4. Miscellaneous
   - Urine specific gravity
   - Urinary sodium levels
   - Pregnancy test in all menstruating females.

EEG, CT, and MRI of the brain are not recommended unless the loss of consciousness is suspected not to be syncope.

CBC, complete blood count; CMP, complete metabolic panel; TIBC, total iron binding capacity



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ORIGINAL ARTICLE

Pediatric Syncope

Is Detailed Medical History the Key Point for Differential Diagnosis?

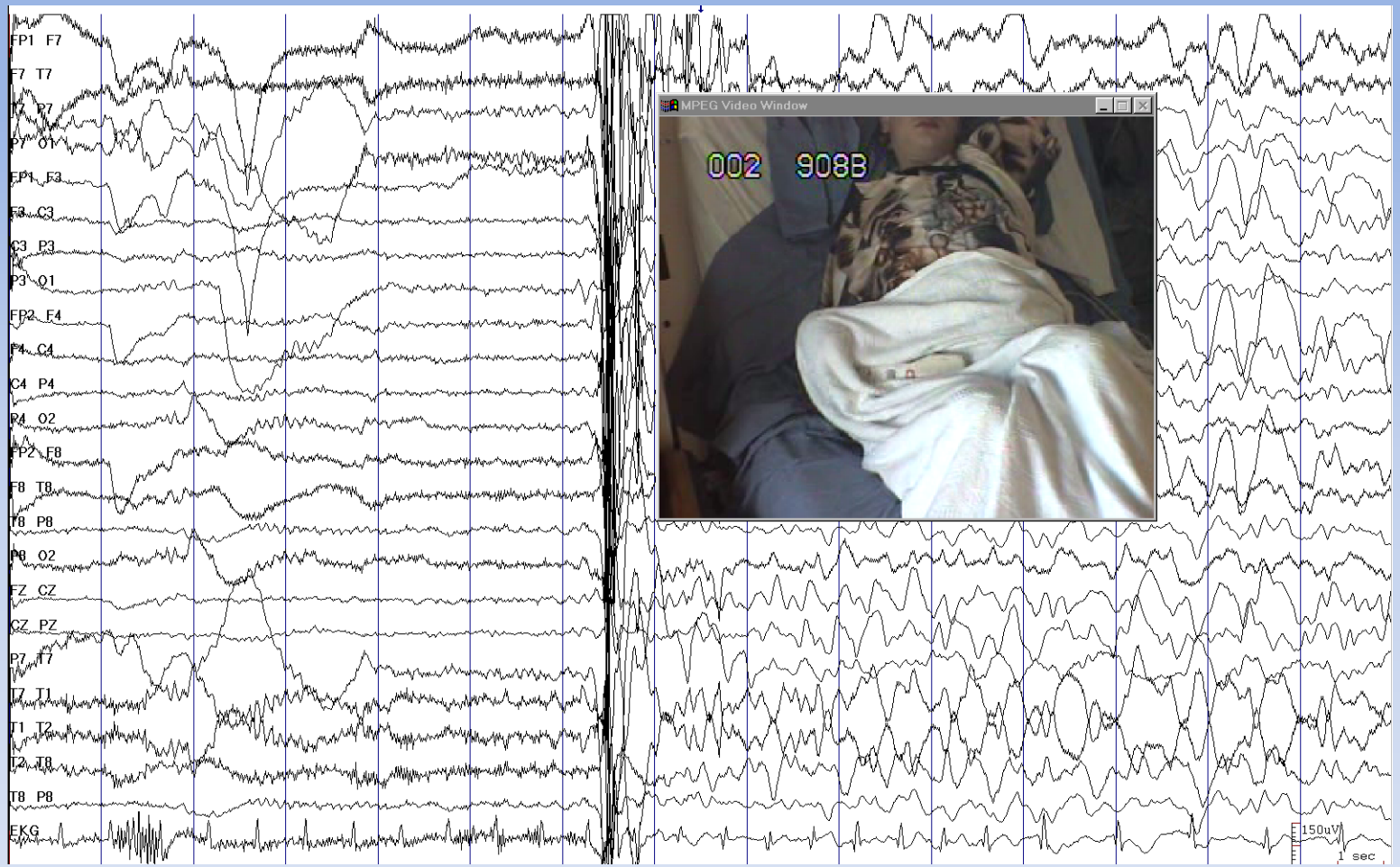
Mehmet Alper Ikiz, MD, Ibrahim Ilker Çetin, MD,† Filiz Ekici, MD,† Alev Güven, MD,‡ Aydan Değerliyurt, MD,‡ and Gülşen Köse, MD‡*

TABLE 1. Medical History Chart

Medical History	Family History	Position	Activity	Predisposing Factors	Prodromal Signs	During the Episode	After the Episode
Cardiac disease	Sudden death	Supine	Resting	Fear	Dizziness	Palpitation	Postictal stage
Epilepsy	Fainting	Sitting	Exercise	Excitement	Vision loss	Chest pain	Amnesia
Febrile convulsion	Cardiac disease	Standing	Position change	Pain	Paleness	Unconsciousness	Headache
Cardiac operation	Epilepsy		Mixation	Blood sampling	Nausea	Incontinence	Nausea
Syncope history			Defecation	Fasting	Sweating	Defecation	Neurologic deficit
Medical therapy			Coughing	Hot environment	Blurred vision	Involuntary movements	
Metabolic disease			Turning the head	Crowded area	Tinnitus	Jaw lock	Fatigue
Chronic disease				Long-standing time	Epigastric tenderness	Paleness and cyanosis	
				Hyperventilation		Injury	
				Menstruation			
				Infection			

Case History

- 15 year old boy referred for epilepsy monitoring for refractory drop attacks
- Failed three different antiepileptic drugs
- EEG had epileptiform features
- Also had migraines
- History: episodes only occurred when arms raised



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Stretch Syncope

Figure. The typical posture resulting in stretch syncope.

Case History (1)

- 7 year old girl referred for seizure
- While mother removing a braid from her hair, c/o stomach pain, arched back, had 2 to 3 minute GTC seizure
- No prior events, rare staring spells, and headaches
- Family history positive for migraines
- Examination, CT, EEG, AEEG normal

Case History (2)

- 2 weeks later, while hair combed, c/o stomach pain, screamed, lost consciousness for 45 seconds, post-event lethargy, and paresthesias in right foot
- No further episodes until she was taken off Pb 6 months later, event in morning, while hair was being combed, stomach pain, vision dimmed, lost consciousness, ocular supraversion, clonic movements right arm

J Epilepsy 1993;6:115–117

Hair-Braiding and Combing-Induced Syncope: A Paroxysmal Nonepileptic Event

James J. Riviello, Jr., and Stephen D. Rioux

Case History (1)

- 3 month old referred for diagnosis of epilepsy
- Episodes with tonic posturing occurred in the newborn period, especially with taking rectal temperature or with bowel movements
- EEG abnormal
- Episodes controlled after starting oxcarbazepine

Case History (2)

- Family history of vagotonia in mother, starting as a child

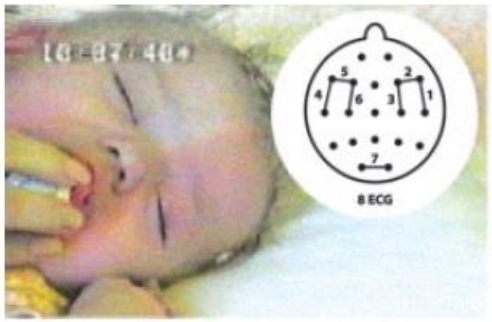
NEUROLOGY

Paroxysmal extreme pain disorder (previously familial rectal pain syndrome)

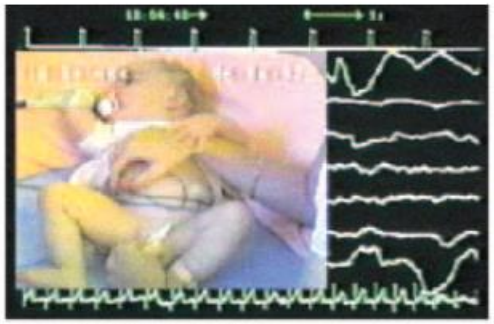
C. R. Fertleman, C. D. Ferrie, J. Aicardi, N.A.F. Bednarek, O. Eeg-Olofsson, F. V. Elmslie, D. A. Griesemer, F. Goutières, M. Kirkpatrick, I. N.O. Malmros, M. Pollitzer, M. Rossiter, E. Roulet-Perez, R. Schubert, V. V. Smith, H. Testard, V. Wong and J. B.P. Stephenson

Neurology 2007;69;586-595
DOI: 10.1212/01.wnl.0000268065.16865.5f

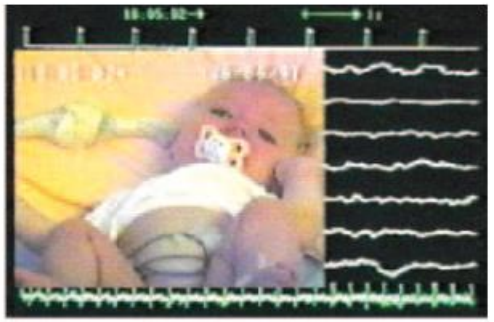
Figure 3 Frames from video-EEG of tonic attack in II:2, Family 9



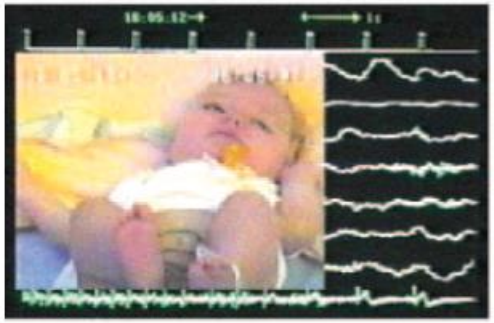
(i) **10:07:40** *EEG montage superimposed on frame showing harlequin colour change of face.*



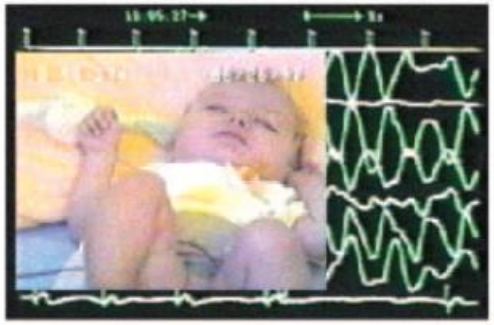
(ii) **18:04:48** *Wiping of vulval region.*



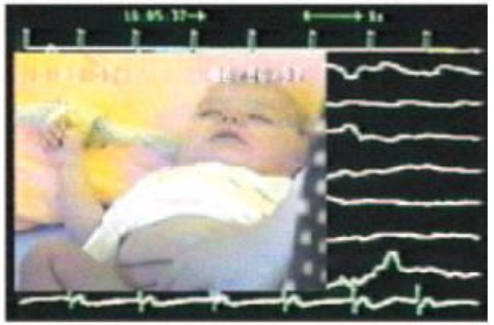
(iii) **18:05:02** *Tonic posturing. Facial flushing. Tachycardia with EMG on ECG channel.*



(iv) **18:05:12** *Hyperekplexia-like quivering, eyes closing. EEG beginning to slow. Transition from tachycardia to bradycardia, with EMG on ECG channel.*



(v) **18:05:27** *Stupor. Gross EEG slowing. Bradycardia with up to 4 seconds asystole.*



(vi) **18:05:37** *Doctor going to "resuscitate". EEG isoelectric. Bradycardia persisting.*

Low Iron Storage in Children and Adolescents with Neurally Mediated Syncope

IMAD T. JARJOUR, MD, AND LAILA K. JARJOUR, MB ChB, MPH

Objective To investigate whether neurally mediated syncope (NMS) is associated with low iron storage or serum ferritin (SF).

Study design 206 children evaluated between 2000 and 2004 for probable syncope at a tertiary care Pediatric Neurology Clinic were included in a retrospective study. Serum ferritin (SF), iron, total iron binding capacity, and hemoglobin were measured prospectively after initial history taking and physical examination, along with other diagnostic testing. We defined iron deficiency (ID) as SF <12 μg/L, and low iron storage as SF ≤25 μg/L.

Results Among 106 included patients with syncope, 71 had NMS and 35 had other causes of syncope. Patients with NMS, when compared with those with other causes of syncope, had a higher prevalence of low iron storage (57% vs 17%, $P < .001$) and lower mean values of SF (27 vs 46 μg/L, $P < .001$), transferrin saturation (23 vs 31 %, $P < .01$), and hemoglobin (13.3 vs 14 g/dL, $P < .05$). Only patients with NMS had ID (15%), anemia (11%), or ID with anemia (7%).

Conclusions Low iron storage or serum ferritin is associated with NMS and is a potentially pathophysiologic factor in NMS.

(J Pediatr 2008;153:40-4)

Relationship Iron to neurally mediated syncope (NMS)

- Abnormal catecholamine metabolism
- Iron dependent enzymes involved in synthesis and degradation of catecholamines

CAMERA STUDY

- **Cerebral abnormalities in migraine, an epidemiological risk analysis**
  - Infarcts in the posterior circulation territory in migraine
  - Migraine associated with increased risk of deep white matter abnormalities, subclinical posterior circulation infarcts, and brain iron accumulation
  - **Syncope in Migraine**
  - Syncope, orthostatic intolerance

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HIGH LIGHT
CME

Syncope in migraine

The population-based CAMERA study

R.D. Thijs, MD*; M.C. Kruit, MD*; M.A. van Buchem, MD, PhD; M.D. Ferrari, MD, PhD; L.J. Launer, PhD; and J.G. van Dijk, MD, PhD

Abstract—*Objective:* To examine the association between migraine and syncope-related autonomic nervous system (ANS) symptoms. *Methods:* A population-based study among migraineurs with and without aura (n = 323) and control subjects (n = 153) was conducted. A systematic questionnaire and cardiovascular measurements during rest, while standing, and after venipuncture addressed the prevalence of syncope, orthostatic intolerance, orthostatic hypotension (OH), and the postural tachycardia syndrome (POTS) in migraineurs and control subjects. *Results:* The lifetime prevalence of syncope in all participants was 41%, more often in women (45 vs 32%; $p = 0.02$). Compared with control subjects, migraineurs had a higher lifetime prevalence of syncope (46 vs 31%; $p = 0.001$), frequent syncope (five or more attacks) (13 vs 5%; $p = 0.02$), and orthostatic intolerance (32 vs 12%; $p < 0.001$). There was no association between ANS symptoms and the severity of migraine or migraine subtype. Cardiovascular measurements and the prevalence of POTS and OH did not differ significantly between migraineurs and control subjects. *Conclusion:* This population-based study demonstrated an elevated prevalence of syncope and orthostatic intolerance in migraineurs without clear interictal signs of autonomic nervous system dysfunction.

NEUROLOGY 2006;66:1034–1037

Seizures/Epilepsy
Differential Diagnosis

Syncope: A Videometric Analysis of 56 Episodes of Transient Cerebral Hypoxia

T. Lempert, MD, M. Bauer, MD, and D. Schmidt, MD

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56 episodes of transient cerebral hypoxia

- 20 seconds HV while squatting, fast rise to feet, 10 second Valsalva maneuver with forced expiration against closed glottis.
- Rapidly lowers cerebral perfusion combining hypocarbic cerebral vasoconstriction, orthostasis, and decreased venous return.
- Falls cushioned by foam, helper prevented falls.
- Video camera recordings, reviewed with attention to unresponsiveness, falls, myoclonus, non-myoclonic movements, eye movements, vocalizations.

Transient LOC

- 42/59 had LOC; 13 fell without losing consciousness completely, called incomplete syncope.
- Report only on the 42; onset marked by the incipient fall, verbal responsiveness indicated its termination.
- Duration: 12.1 +/- 4.4 seconds (4.5 to 21.7 s)
- 19 had partial response after 8.2 seconds, eye and head turning toward the voice

Myoclonus

- Myoclonus in 38/42 (90%); never preceded the fall.
- Starts 2.6 sec after LOC, lasting 6.6 sec.
- Outlasted partial responsiveness in 10 and verbal responsiveness in 4. Subjects remembered the twitching.
- Focal (16%), multifocal (52%), or generalized (3%); focal duration shorter than multifocal.
- Arrhythmic in 41.

Other Motor Movements

- Lateral head turns, +/- ipsilateral gaze deviation, lip-smacking, chewing, or fumbling (resembles automatisms)
- Righting movement in 45%
- Extensor posturing in 3 patients
- Lateral tongue bite in 1
- No urinary incontinence

Eye Movements

- Eyes open in 76%
  - 66% upper deviation, others either midposition or had a lateral deviation.
  - 50% subsequent change in eye position
- Blinking in 50%

Vocalizations

- 17/42 (40%), starting 2.1 seconds after LOC
- Continuous or intermittently accentuated moan of low pitch and voice

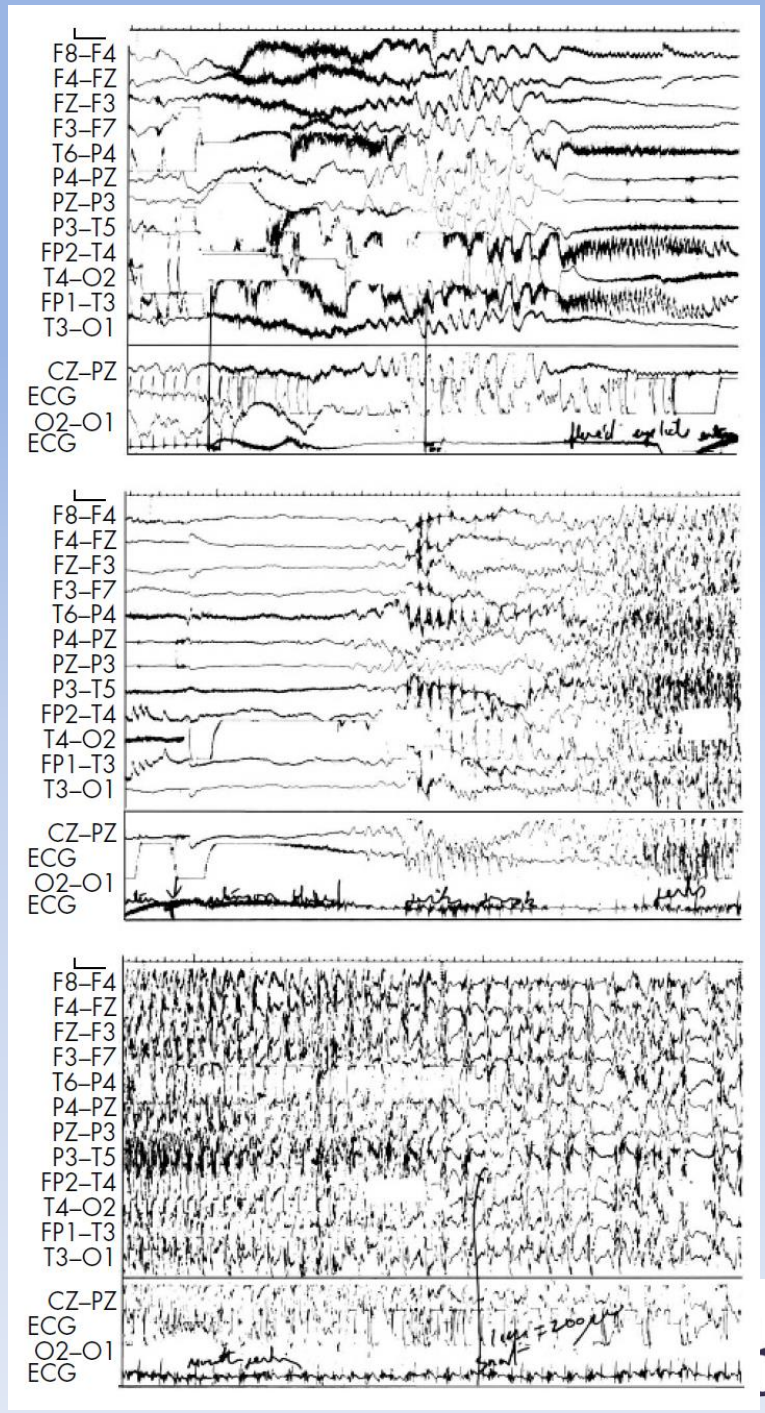
Experience of Syncope

- Visual and auditory hallucinations in 60%
- Perception of a gray haze, colored patches, or bright lights
- Realistic scenes, involving familiar places, situations, or persons
- 4 out of body experiences
- Auditory hallucinations in 36%; never in isolation, accompanied visual
- Rushing and roaring noises, screaming, or talking voices, but never intelligible speech
- Described weightlessness, detachment, and peace; 17% had negative feelings, with helplessness and disorientation

POTS and temporal lobe epilepsy

- Single case report, 20 year old with TLE and POTS

Anoxic-epileptic event



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Tongue Bite

Epilepsy

- Occurs in up to 41% of patients with GTC seizures
- Lateral tongue

Syncope

- 2-6% of patients with syncope
- Central tongue

ORIGINAL INVESTIGATION

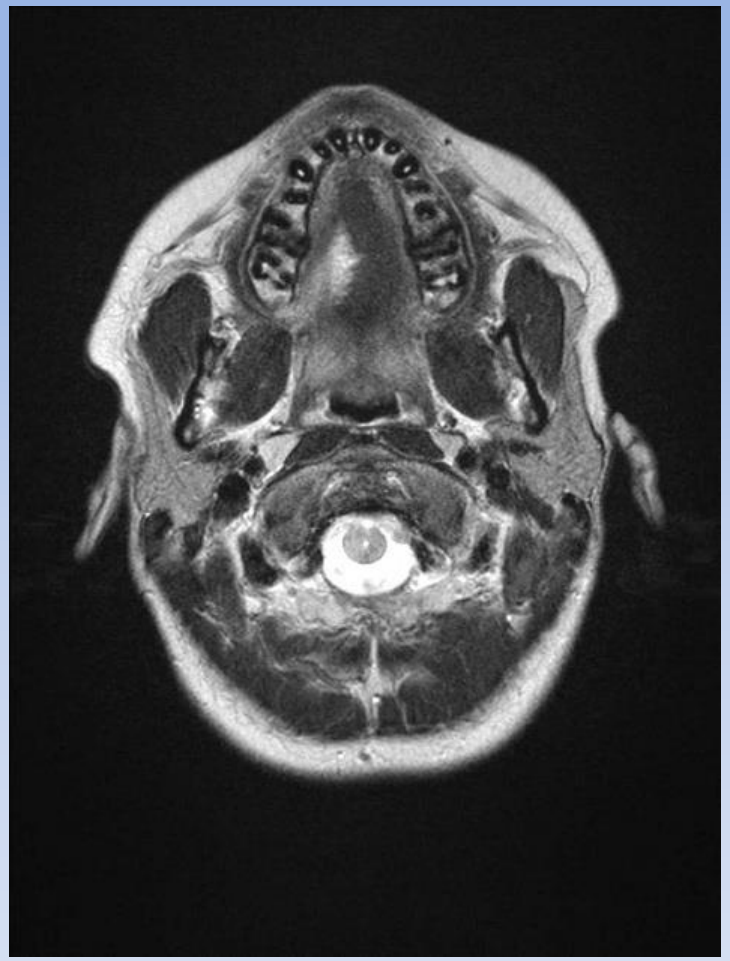
Value of Tongue Biting in the Diagnosis of Seizures

Selim R. Benbadis, MD; Barbara R. Wolgamuth, REEGT; Hershel Goren, MD; Sorin Brener, MD; Fetnat Fouad-Tarazi, MD

Table 1. Incidence of Tongue Biting in the Three Groups*

Patients' Group	Tongue Biting	No Tongue Biting	Total
Epileptic seizures	8	26	34
Pseudoseizures	0	29	29
Syncope	1	44	45
Total	9	99	108

*χ^2=15.11 (P=.001; exact χ^2 test).



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Epilepsia, **48**(6):1165–1172, 2007
Blackwell Publishing, Inc.

Autonomic Status Epilepticus in Panayiotopoulos Syndrome and Other Childhood and Adult Epilepsies: A Consensus View

*Colin D. Ferrie, †Roberto Caraballo, ‡Athanasios Covanis, §Veysi Demirbilek, #Aysin Dervent, ¶Natalio Fejerman, $Lucia Fusco, ‖Richard A. Grünewald, **Osamu Kanazawa, ††Michael Koutroumanidis, ‡‡Christina Lada, *John H. Livingston, ##Alessia Nicotra, ¶¶Hirokazu Oguni, $$Zarko Martinovic, ***Douglas R. Nordli,Jr., †††Pasquale Parisi, ‡‡‡Rod C. Scott, §§§Nicola Specchio, ###Alberto Verrotti, ¶¶¶Federico Vigevano, $$$Matthew C. Walker, ****Kazuyoshi Watanabe, ††††Harumi Yoshinaga, ††Chrysostomos P. Panayiotopoulos

Non-convulsive SE

- 50% of children with PS have NCSE (> 30 min).
- Seizures have predominantly autonomic symptoms, now called an “autonomic epilepsy” rather than an “occipital epilepsy.”
- Emesis, pallor, flushing, cyanosis, mydriasis, cardiac and temperature alterations, incontinence, salivation, intestinal motility.
- Initially awake, then develops altered awareness, gaze deviation, 50% brief hemi- or generalized convulsions.

TABLE 1. *Autonomic signs and symptoms during autonomic seizures and Aut SE*

System	Symptom / Sign
Gastrointestinal	Emetic symptoms: nausea, retching, and vomiting
	Abdominal (particularly epigastric) sensations of pain, hunger, or else vague unpleasant or uncomfortable feelings; may include a rising sensation
	Borborygmia
	Diarrhea
	Fecal incontinence
Cardiorespiratory	Palpitations/chest pain
	Sinus tachycardia
	Cardiac arrhythmias and bradycardia
	Blood pressure changes
	Apnea
	Hyperventilation
Vasomotor and pilomotor	Flushing
	Pallor
	Cyanosis
	Perspiration
	Goose flesh
Pupillary	Mydriasis
	Miosis
	Hippus
Genitourinary	Urinary incontinence
	Erotic feelings and genital sensations
	Erection and orgasms
Other	Lacrimation
	Increased bronchial secretion
	Fever

Syncope-like Epileptic Seizures in PS

- SLES defined as self-terminating events with sudden loss of postural tone and unresponsiveness, occurring with other ictal autonomic signs/symptoms (AS+SLES) or on their own (pure SLES).
- SLES in 17/33.
- With seizures, 53/74 (72%) had SLES (25 were AS+SLES and 28 had pure SLES.
- Pure SLES occurred in 7 children without premonition or triggers, did not resolve in the horizontal position, had no associated movements, even when longer than a few minutes.
- Concurrent autonomic symptoms: emesis, incontinence, mydriasis, miosis, cardiorespiratory abnormalities.

Autonomic Dysfunction in Epilepsy

- Ictal Dysautonomia
  - Ictal bradycardia, asystole
- Autonomic Nervous System and AEDs
- Autonomic Nervous System and VNS

Ictal Dysautonomia: Autonomic Manifestations of Seizures

- Pilomotor phenomenon: unilateral piloerection, ipsilateral temporal lobe; bilateral, no localiztion
- Ictal bradycardia, asystole: bilateral mesiotemporal (mesT) or insula
  - Ictal tachycardia: non-localizing
- Dyspnea: insula
- Hyperventilation: frontal and temporal, greater in mesial versus lateral temporal seizures
- Post-ictal cough: temporal, not right temporal as in adults
- Ictal spitting: non-dominant temporal lobe

Autonomic Manifestations of Seizures

- Ictal vomiting, nausea: anterior insula, non-dominant temporal
- Ictal laughing (gelastic): hypothalamic hamartomas, or tempora or frontal (cingulate)
  - Laughing with mirth: temporal
- Ictal smiling: non-dominant, posterior (T-P-O)
- Ictal crying (dacrystic): +/- non-dominant mesT
- Epigastric aura: TLE (mesial)
- Mydriasis, flushing: non-localizing [mesT, insula, frontal (para-saggital, orbitofrontal)]
- Urinary incontinence: frontal versus pressure

Epilepsia, **47**(3):584–588, 2006
Blackwell Publishing, Inc.

Autonomic Symptoms during Childhood Partial Epileptic Seizures

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**Epilepsie-Zentrum Bethel, Bielefeld, Germany; and †Bethesda Children's Hospital, Budapest, and ‡Department of Neurology, University of Pécs, Pécs, Hungary*

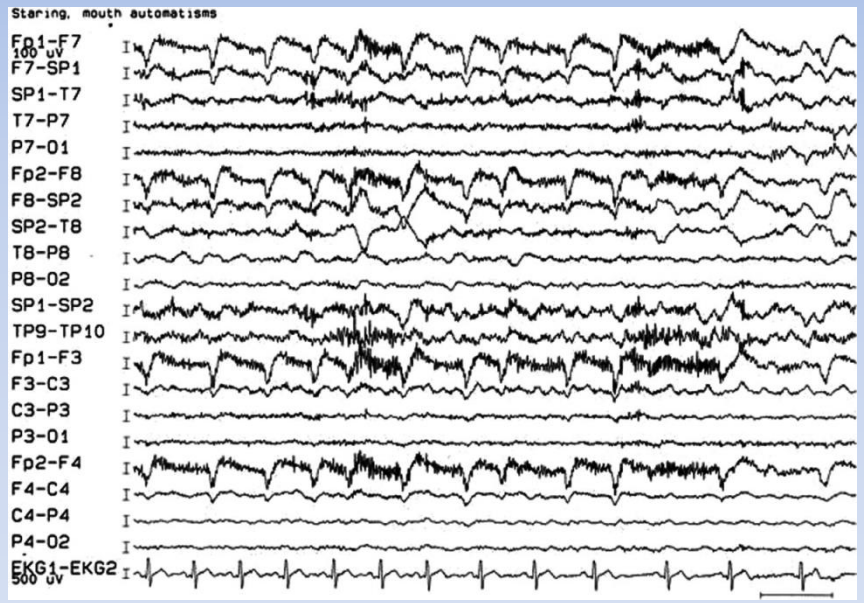
TABLE 1. *Frequency, localization, lateralization, and age dependence of autonomic signs observed in 100 patients 12 years or younger with partial epilepsy*

Autonomic symptoms	Total (n = 100)	Localization			Lateralization			Age dependence (p value)
		Temporal (n = 61)	Extratemporal (n = 39)	p Value	Left (n = 54)	Right (n = 46)	p Value	
Flushing	19	11	8	NS	7	12	NS	NS
Postictal coughing	16	15	1	0.004	10	6	NS	NS
Apnea, bradypnea	12	8	4	NS	7	5	NS	<0.001[a]
Epigastric aura	12	11	1	0.026	5	7	NS	NS
Hyperventilation	11	8	3	NS	6	5	NS	NS
Dyspnea	9	6	3	NS	3	6	NS	NS
Hypersalivation	5	4	1	NS	2	3	NS	NS
Vomiting	5	4	1	–	4	1	–	–
Nausea	3	3	0	–	0	3	–	–
Spitting	2	2	0	–	0	2	–	–
Miosis	1	1	0	–	0	1	–	–
Hiccup	1	1	0	–	1	0	–	–
Belch	1	0	1	–	0	1	–	–
Total	60	43	17	0.012	29	31	NS	NS

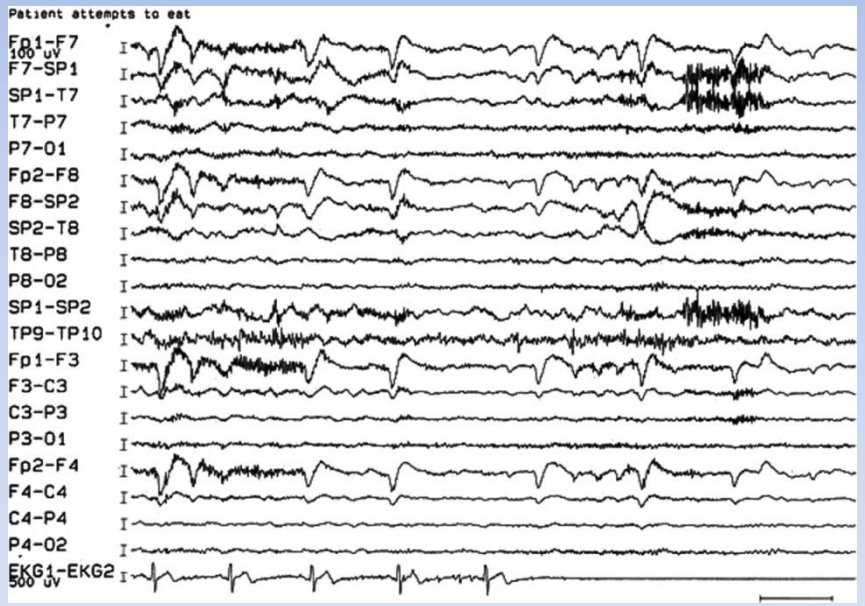
Very rare autonomic symptoms (observed in ≤5% of patients) were not assessed with statistical methods.
NS, no significant correlation ($p \geq 0.05$)
[a]Ictal apnea/bradypnea happened more frequently among younger patients ($p < 0.001$).

Ictal bradycardia, asystole

Bilateral rhythmic theta



Bradycardia followed by asystole



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Autonomic Nervous System and AEDs

- Cardiac rhythm changes:
  - Phenytoin, Carbamazepine, Oxcarbazepine, Lacosamide
- Carbonic anhydrase inhibition, impaired sweating, heat intolerance:
  - topiramate, zonisamide
- Respiration depression with benzodiazepines with ictal autonomic symptoms

Autonomic Nervous System and VNS

- Reduction in vagal tone during SWS
- Sympathetic predominance

- 4/26 (15%) developed obstructive sleep apnea after VNS

The END

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