Paroxysmal Events That Are Not Seizures: A Neurologist’s Perspective

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Anachronistic, Pejorative Terms

- Hysteroepilepsy
- Hysterical seizure
- Pseudoseizure
- Pseudoepileptic seizure
- Nonepileptic pseudoseizure
- Hysterical epilepsy
- Epileptic attack disorder
Terminology: The Continuing Debate

- NES or PNES has been the preferred term\(^1,\)\(^2\)
  - 59.7% use NES
  - 4.5% use ‘pseudoseizures’
  - 8.4% use ‘psychogenic seizures’
- NEE or nonepileptic attack\(^3\)
  - Confusion for patient and community about the diagnosis if ‘seizure’ used
  - Importance of acceptance of diagnosis for treatment

\(^1\)LaFrance WC, et al. *Epilepsy Behav.* 2008; \(^2\)LaFrance WC. *Neurology.* 2010; \(^3\)Benbadis SR. *Neurology.* 2010.
Nonepileptic Seizures

• Two subcategories
  • Physiologic
  • Psychogenic
    • Most common misdiagnosis of epilepsy
    • Over-interpretation of EEGs

Benbadis SR. *Epilepsy Behav.* 2005.
Physiologic NES

- Sleep disorders
- Nonepileptic myoclonus
- Syncope
- TIAs
- Paroxysmal movement disorders
- Non-toxic organic hallucinosis
- Paroxysmal endocrine disorders
- Paroxysm of neurological insults
Cardiac Arrhythmia

• Prolonged Q-T
• Precipitous loss of consciousness
• Average age = 10 +/- 7.6 years
• Mortality untreated = 0.5%/year
• Mean age of death in boys = 8 yo
Pediatric Physiologic NES

- Syncope – breath-holding spells
- Nonepileptic myoclonus – benign myoclonus of infancy, neonatal hyperekplexia
- Sleep disorders – night terrors
- Paroxysmal movement disorders – spasmus nutans, GE reflux – Sandifer’s, alternating hemiplegia, infantile masturbation, shuddering attacks, paroxysmal choreoathethosis

Benign Myoclonus of Early Infancy

- Onset 3-9 months
- Myoclonus of head, neck, and arms
- Multiple clusters per day
- EEG normal
- Development normal
- Resolves by 2 yo
Sandifer’s Syndrome

- Onset infancy
- Tonic posture to one side
- GER
- EEG normal
- May require treatment
Breath-holding Spells

- 4.6% of population
- Onset: 7-12 months
- Cyanotic or pallid types
- Always precipitated
- Normal EEG
- Resolves by 4 years of age
- Check iron; can be treated
Psychogenic NES terminology

- Undifferentiated somatoform disorder
- Factitious disorder
- Somatization disorder
- Malingering
- Panic disorders
- Reinforced disorders
- Conversion disorder*
- Hypochondriasis
- Depersonalization disorder
- Psychotic disorder
- Dissociative disturbances

*DSM 5 criteria
The Background of Pediatric and Adult Nonepileptic Events

<table>
<thead>
<tr>
<th>Psychosocial Factors</th>
<th>PEDIATRIC</th>
<th>ADULT</th>
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<tbody>
<tr>
<td>School difficulties</td>
<td></td>
<td>Physical abuse/trauma</td>
</tr>
<tr>
<td>Family adversity*</td>
<td></td>
<td>Sexual abuse/trauma</td>
</tr>
<tr>
<td>Bullying</td>
<td></td>
<td></td>
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<tr>
<td>Social immaturity</td>
<td></td>
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<tr>
<td>Solitary coping</td>
<td></td>
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</tr>
<tr>
<td>Psychiatric Comorbidities</td>
<td>Depression</td>
<td>Depression</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td>Somatization</td>
<td></td>
<td>Somatoform disorders</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td>Pain syndromes</td>
</tr>
</tbody>
</table>

*No difference from siblings in physical or sexual abuse

Psychogenic NES Comorbidities

- One large clinic found while reviewing patients with “refractory seizures” over a 5-year window, 27 (9%) of their 308 patients with NES had *chronic pain and/or fibromyalgia*
  - Positive predictive value of 75%, sensitivity 9%, specificity 99%
- For those who had an event (“seizure”) in the clinic:
  - Positive predictive value of 77%, sensitivity 3%, specificity 99%
Psychiatric Comorbidities

• Up to 70% have concurrent psychiatric disorder
• Personality disorders in Structured Interview: NES patients show paranoid/schizoid and borderline/antisocial/histrionic clusters compared to epilepsy patients with avoidant/dependent/obsessive clusters
• Severity of concurrent psychiatric symptoms worse in adolescents/adults than in children less than 13 years old
• Personality disorders are more common in adults than children
• Compared to siblings, children have more anxiety, depression, PTSD, adversities

Diagnosis and Treatment Delay

- Multiple and recurrent consultations between specialties
- Overutilization of expensive emergency resources
- Long delays with poorer psychosocial outcomes, unnecessary treatment and possible adverse events, and poor QOL

Cost of Psychological NES

- Lifetime cost estimated $100,000 for tests, procedures, medications
- Annual cost in Ireland $6809.66
- $100-900 million per year in medical treatment
- Aggressive treatment resulting in comorbidity
- 50% get disability, same rate as for epilepsy
- Study of 24 patients in private insurance HMO for 12 months before and after NES diagnosis (Ahmedani)
  - Decreased medical visits for ER, inpatient (50%), Neurology, other services
  - Marked decrease in total cost, inpatient costs ($1500 if no BHS referral versus $3700 if referral made), Neurology costs ($1587) and other costs
  - Increased behavioral health visits at increased but low cost

Coexistence of NES and Epileptic Seizures

- Various epilepsy centers have reported different rates
- Most tertiary centers grant 20% coexistence
- No formal epidemiologic study has been done
- Prevalence is 2-33 per 100,000

Epidemiology of NES

- True prevalence unknown
- 20% of epilepsy unit admissions
- 5% of outpatient epilepsy clinics
- This spectrum of disorders is common
- It is a heterogeneous population
- It is very costly to society to provide care for this diagnostic group
- NES can remain undiagnosed for many years
- Repeated studies in adults demonstrate a fairly consistent 4:1 female to male ratio for psychogenic NES
- Pediatric patients have a 2:1 female to male ratio
NES: % Mixed or Pure

- Pure NES: 42%
- Mixed: 58%
A precise description of event(s) of concern by patient and/or caretakers is vital.
Ictal Characteristics

Tonic-clonic Resembling Events

1. Out of phase UE and LE, Voc
2. Out of phase UE, LE and pelvic thrusting, no rigidity
3. Out of phase UE and LE, pelvic thrusting
4. No rigidity and pelvic thrusting

% Correct Classification

#1 #2 #3 #4
### Some Other Differentiating Factors

<table>
<thead>
<tr>
<th></th>
<th>Non-epileptic events</th>
<th>Epileptic events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing from sleep</strong></td>
<td>Awaken first</td>
<td>From sleep</td>
</tr>
<tr>
<td><strong>Affect</strong></td>
<td>Weeping</td>
<td></td>
</tr>
<tr>
<td><strong>Speech</strong></td>
<td>Stuttering</td>
<td>Absent, nonpurposeful</td>
</tr>
<tr>
<td><strong>Actions</strong></td>
<td>Irregular, side to side head, moves location</td>
<td>Continuous, unilateral to generalized</td>
</tr>
<tr>
<td><strong>Time course</strong></td>
<td>Start and stop</td>
<td>Progression, continuous</td>
</tr>
<tr>
<td><strong>Awareness</strong></td>
<td>Maintained</td>
<td>Confused to unresponsive</td>
</tr>
<tr>
<td><strong>Eyes</strong></td>
<td>Closed at onset</td>
<td>Open, may close later</td>
</tr>
</tbody>
</table>

Ictal Duration

TC EPILEPSY control (N=25)  NEE (N=25)

TC Mean=70s  NES Mean=134s
Is this an epileptic seizure?
Is this an epileptic seizure?
Safety
Semiology and NES

- 96% eye closure throughout events compared to epileptic events with eye open at onset and subsequent closure
  - Predictive value is 0.943 in NES, 0.987 in epilepsy
- Pelvic thrusting, bicycling, opisthotonus can be seen in frontal seizures as well
- Children tend to have non-motor events with resisting eye opening, guarding behaviors

# Prediction of NES by Semiology

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Epileptic Seizure</th>
<th>Non-epileptic Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Open or wide at onset or forced closure</td>
<td>Closed Flutter</td>
</tr>
<tr>
<td>Vocal/Audio</td>
<td>Guttural, expiratory cry</td>
<td>Weep, moan, cough</td>
</tr>
<tr>
<td>Onset</td>
<td>Abrupt</td>
<td>Wax/Wane; variable intensity with observer</td>
</tr>
<tr>
<td>Awareness</td>
<td>Altered</td>
<td>Preserved</td>
</tr>
<tr>
<td>Postictal</td>
<td>Confusion, sleep</td>
<td>Interactive, alert</td>
</tr>
</tbody>
</table>

48 signs were prospectively evaluated in 35 patients and validated in an additional subsequent 36 patients

Prediction of NES by Semiology

- Eyewitness reports were inaccurate and not statistically different from guessing
- Eyewitness report did not predict accuracy of VEEG diagnosis
- Blinded reviewers showed interrater reliability with VEEG at .94
- VEEG is gold standard for diagnosis

Recording *one* non-epileptic seizure is not sufficient for a definitive diagnosis.
Inducing non-epileptic seizures can be misleading and may be unethical and/or traumatic.

Induction of Psychogenic NES

• 51 patients at VA center received 5 ml NS followed by HV and PS for <15-20 minutes and all had 4 psychological tests
  • Dissociative Experience Scale, Structured Inventory of Malingered Symptomatology - SIMS, Test of Memory Malingering – TOMM, COPE
• 82% of suspected NES had an induced event
  • 93% on first attempt, 25% of remaining on 2nd
  • 92% of the hypermotor (N=26)
  • 65% of the hypomotor (N=20)
  • 100% of subjective group (N=5)

Ictal Characteristics: Prolactin Elevation

- Epileptic TC and PC seizures most reliably elevate prolactin levels at approximately 20 minutes post start of the event, but
  - NES with any nipple manipulation in females can also elevate prolactin
  - Convulsive syncope can elevate prolactin and have associated automatisms
  - Not all PC seizures consistently elevate prolactin
  - Psychotropics can elevate prolactin, including the newer agents
Requirements for Definitive NES Diagnosis

• Definitive video-EEG recording: video-EEG makes clear distinction which events are epilepsy or NES

• Record each type of reported event

• Multiple ictal events characteristic of the event(s) of concern have been recorded and it is clear which are non-epileptic and which are epileptic

Requirements for Definitive NES Diagnosis

A careful review of the patient’s history has transpired, and it is clearly documented whether there is or is not a history of epileptic events. Based on this information and the ictal/interictal video-EEG recording, a decision can be made to discontinue AEDs for pure NES, or continue usually only one AED because coexistent epilepsy is present.

Requirements for Definitive NES Diagnosis (cont.)

- A complete psychological, social, and psychiatric assessment and a definitive DSM-V diagnosis have been made.
- The full team (epileptologist, psychologist, social worker, nurses, neuropsychologist, +/- consulting psychiatrist) are in agreement with the diagnosis(es).
- Determine who will be present and how the diagnosis will be presented to the patient, +/- family or significant other.
Neuropsychological and Psychological Epidemiology of NES in Adults

• Females predominant – 80%
• Age at onset: 20s
• FSIQ ≤92 (average, but low, ~25 percentile)
• Neuropsychology: statistically significant lower function
• Role of depression, other emotional, affective factors
• Role of previous neuro insult
  • 80% by patient
  • 46% by physician

FSIQ = Full Scale Intelligence Quotient
Psychosocial Characteristics
Epidemiology

**Less than 55 years**
- Female
- Healthy
- Sexual abuse

**Older than 55 years**
- Male
- Health problems
- Less sexual abuse

History of fibromyalgia or chronic pain

Supportive Neuropsychological Data for Diagnosis

• PAI: conversion and somatization profile
• Overestimation of word finding difficulties
• Hypervigilance to angry faces on masked emotional Stroop task and higher baseline cortisol
• Increased avoidance with pictures of happy or angry faces

Cognitive and Psychosocial Functioning of the Pediatric NES Patient

- Sample sizes are small
- Male to female ratio: approximately 1:2
- Delay in diagnosis: weeks and up to 3.5 years
- Comorbid epilepsy diagnosis
  - This conference = 22%-38%
  - Previous studies = 16%-23%
- In NES
  - Below average IQ not uncommon
  - School problems >50%
  - History of sexual abuse = 13%-31%
  - Anxiety 81.8%, depression 39.4%, somatization common
    - >2.5 x the rate in siblings

Cognitive and Psychosocial Functioning of the Pediatric NES Patient (cont.)

- Parental somatization often present
- One or more stressors = 78%-94%
  - Marital discord
  - Parental psychopathology/EtOH
  - Parent-child conflict
  - Learning/attention problems
  - Lack of adequate peer support
  - Bullying
- No treatment studies
  - Acute therapy and parental education
  - May require intensive inpatient psychiatric care in some
  - As appropriate home/safety assessments
- Overall better prognosis than adults

Oh what to to, what to dooo?
Neurological Aspects

• Humility is prudent
• Epilepsy and NES can coexist – 15-20%
• Not all unusual epileptic events are frontal
• There are suggestive features to differentiate atypical epileptic seizures from NES
  • Brief
  • Frequent
  • Rapid recovery
Anatomical and Physiological Findings? Compared to Epilepsy Patients
Small N studies

- fMRI - ↑connectivity between insula, inferior frontal gyrus and, parietal cortex and precentral sulcus. Correlation with dissociation scores
- fMRI – abnormal Functional Connectivity Density in frontal, sensorimotor and occipital cortex, cingulate gyrus, insula
- MRI – cortical atrophy by voxel based kmorphometry and cortical thickness analysis of right hemisphere motor and premotor and cerebellum. Premotor atrophy associated with depression on assessment

Treatment of NES
“Cold water over the head is often successful if applied freely; in severe attacks a moderate quantity only excites redoubled violence, while a second gallon is more effectual than the first.”

Gowers (1885)
Gowers (1885)

“A much more convenient and effectual remedy than water is strong faradization to the skin; applied almost anywhere it will commonly quickly stop the attack.”
Telling the Patient

- Nonjudgmental, non-accusatory presentation
- Emphasize that “you don’t have epilepsy”
- Expected reaction to the presentation of the diagnosis is discussed and planned for (suicide risk, denial, “flight to health”)
- Aftercare is arranged with an identified therapist who clearly understands the diagnosis and a smooth transition is organized
- Treatment takes time; give the patient aegis

Presentation Points to the Patient

• These are real events
• Not under conscious control (dissociative, panic)
• Triggers may be unrecognized but may involve stress, depression
• Likely will get better but require psychiatric intervention and learning methods to help cope and control
• Epilepsy medications will not help these
• Will not be abandoned
• Multi-disciplinary team support
• Follow up will occur
• Problems arise: change in self image, defensive, paternalistic or categorical presentation destroys trust in MD

Presentation of the Diagnosis

• Goal: Acceptance of and understanding of the diagnosis
• There is not an agreement on how best to do this
• The patients are heterogeneous and one script does not suit all
• Understanding and acceptance may be easiest in those with a clear “trauma” and the most difficult for those who do not identify any stressors
Patient Reactions to Diagnosis

- “I thought so” – real relief
- Calm before the storm
- Disbelief but interested in exploring
- Frank denial
- Hostility and anger

This is why you need a team approach for diagnosis and treatment
Communication

• On Illness Perception Questionnaire
  – Neurologists viewed NEE as more treatable and amenable to personal control than patients and considered it a psychological disorder
  – Patients thought seizures were physical or partly physical

Treatment

• Predictors of response to Treatment:
  – Positive if Acceptance/Relief
  – Negative if Confused/Reluctant

• Acute Treatment
  – Usually measured after 12 sessions in trials of CBT or Mindfulness therapy

• Long term follow-up

What is the Treatment?

- Survey of what is being provided by neurologists at Epilepsy Programs
  - 93.34% recommended psychological therapy
  - 68.5% of neurologists followed the patient
  - 83% tapered AED
  - 79.9% provided education and educational materials
  - 33.6% started psychiatric mediation

What is Cognitive Behavioral Therapy?

- A form of psychotherapy in which the patient is an active participant
- 6-18 one hour sessions in 1-3 week intervals
- Performed face to face or over telephone although not as effective unless there is an on site supporter
- Most effective in combination with other treatment (anti-depressant)
- Six phases
  - Psychological assessment
  - Reconceptualization
  - Skills acquisition
  - Skills consolidation and application training
  - Generalization and maintenance
  - Post-treatment assessment follow up
Cognitive Behavioral Therapy (CBT)

- Confirmed efficacy in depression & anxiety
- Distorted somatic beliefs; develop dysfunctional repetitive illness behavior
- 21 outpatients with confirmed NES with median of 4 seizures per week
  - 14 met depression criteria, 11 anxiety including PTSD, 6 with obsessive compulsive disorder; 16 on psychiatry medication at start, 71% on AED
  - Multiple scales at baseline, end. F/up at 4, 8, 12 months
  - 17 completed 12 weeks of 1 hour sessions
  - 11 had no events by end of therapy
  - Seizures increased by 1st week of therapy

LaFrance WC, Syc S. Neurology. 2009.
Adult CBT Treatment Trial

- Pilot study: 38 pts (589 screened, 81 eligible)
- 3 centers, 16 week follow-up, not blinded
- Odds of seizure freedom 6.2x if CBT included
- 2\textsuperscript{nd} outcomes: depression, anxiety, dissociations, somatic symptoms
- Functional status and symptom scales significantly improved

<table>
<thead>
<tr>
<th>Treatment (N)</th>
<th>Reduction %</th>
<th>2\textsuperscript{nd} outcomes</th>
<th>ER visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT</td>
<td>51.4*</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Sertraline, max 200</td>
<td>26.5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>CBT + sertraline</td>
<td>59.3*</td>
<td>↓</td>
<td></td>
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<tr>
<td>Usual treatment</td>
<td>33.8</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

*P≤.05

## Outcome

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>On Disability</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>Return to Work</td>
<td></td>
<td>“low”</td>
</tr>
<tr>
<td>Event Free</td>
<td>80% ®</td>
<td>25-33%,*</td>
</tr>
<tr>
<td>Reduction of</td>
<td>®</td>
<td>40% RR -87 “improved”*</td>
</tr>
</tbody>
</table>

*With psych interventions of variable type and durations.

®No randomized controlled studies in children, ? Different psychopathology

Predictor of seizure cessation was being economically active at baseline and this correlation with shorter duration of event onset, lower seizure frequency, better QOL at onset

Intensive Short Term Dynamic Psychotherapy (ISTDP) and Health Care Utilization

- Data extraction 1 year prior and 1 year after for 28 patients with PNES
- Mean 3.6 sessions
- Ongoing 2-3 year follow up.
- No non-MD provider costs captured

Intensive Short Term Dynamic Psychotherapy (ISTDP) and Health Care Utilization

<table>
<thead>
<tr>
<th>Time Period</th>
<th>MD visits</th>
<th>MD costs</th>
<th>Hosp Adm</th>
<th>Hosp Days</th>
<th>Hosp Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>22.8</td>
<td>1083</td>
<td>1.43</td>
<td>17.4</td>
<td>21,856</td>
</tr>
<tr>
<td>Year 1</td>
<td>15.6 *</td>
<td>696.5*</td>
<td>0.46*</td>
<td>2.0</td>
<td>2684.1</td>
</tr>
</tbody>
</table>

2007 Canadian dollars. *P<0.05 t Test

Brief Symptom Inventory (BSI) and Inventory of Interpersonal Problems (IIP-32) – both significantly reduced

Prognosis

- Children/adolescents 81% free within 3 years
- Adults 29%-45% free within 5 years
  - Multidisciplinary team 50% free within 1 year
- Improved outcomes: social support; treatment through epilepsy center; young age; duration less than one year; motivation
- Negative outcomes: >2 years of symptoms; neurological and/or psychiatric disease
- Acceptance at presentation linked to 6-12 month prognosis being 2.85x more likely to be event free than non-acceptors. At 5-10 years this did not correlate

Is this an epileptic seizure?
NOW IT IS ALL VERY CLEAR – RIGHT!