Psychogenic Nonepileptic Seizures

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Disclosures

- None
- Written consent obtained for all patient images

Learning Objectives

- List the differential diagnosis of epilepsy
- Describe the features that distinguish psychogenic nonepileptic seizures from epileptic seizures
- Describe the treatment options and prognosis for psychogenic nonepileptic seizures
Case Presentation

- 26-year-old female referred from an outside provider for epilepsy surgery evaluation due to medically intractable seizures
- Seizures since high school, described as head turning to right followed by generalized shaking of extremities
- Initially, seizure free for 2 years on valproate, but for last 8 years they are intractable to antiepileptic medications (AEDs)
- Current AEDs: valproate ext release 1200 mg/d, carbamazepine ext release 1200 mg/d, topiramate 250 mg/d
- Past AEDs included gabapentin and lamotrigine—stopped due to risk of rash, dosage unknown

Case Presentation Continued

- 3 pregnancies on valproate: one miscarriage, one born with spina bifida who died shortly after birth, and third a healthy baby after being placed on folic acid supplementation
- Family history of epilepsy, no other risk factors
- Two routine EEGs were normal, MRI brain with and without contrast normal
- Exam: appeared sedated, otherwise normal
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Seizures & Status Epilepticus

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**Epilepsy**

- **Epileptic Seizure (ES):** clinical manifestation of abnormal and excessive synchronization of a population of cortical neurons

- **Epilepsy:** two or more recurrent seizures unprovoked by systemic or acute neurological insult

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**Epilepsy Continued**

- Affects 1% of US population
- Clinical Diagnosis: history, physical exam, electroencephalogram (EEG), MRI brain
- Goals of epilepsy treatment:
  - No seizures
  - No side effects
- Medications are first line therapy for epilepsy
  - 60-70% easily controlled with antiepileptic medications (AEDs)
  - 30-40% medically intractable
    - Requires non-medical treatment options such as epilepsy surgery, implantable stimulation devices, dietary therapies

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**Differential Diagnosis of Epilepsy:**
**Physiological Nonepileptic Paroxysmal Disorders**

- **Neonates**
  - apnea, benign sleep myoclonus, jitteriness, hyperkplexia

- **Infants**
  - breath-holding spells, shuddering attacks, Sandifer syndrome, benign myoclonus of infancy

- **Children**
  - breath-holding spells, vasovagal syncope, migraine, benign paroxysmal vertigo, staring spells, tics, parasomnias, rhythmic movement disorder, night terrors
Differential Diagnosis of Epilepsy: Physiological

- Adolescents and young adults
  - Vasovagal syncope, narcolepsy, periodic limb movements of sleep, tics, hemifacial spasm, stiff person syndrome, migraine
- Adults
  - Cardiogenic syncope, migraine, transient ischemic attack, transient global amnesia, tremors, REM sleep behavior disorder, narcolepsy, periodic limb movements of sleep, tics, hemifacial spasm, toxic-metabolic encephalopathy

Differential Diagnosis of Epilepsy: Psychological

- Children and adults
  - Psychogenic nonepileptic seizures
  - Conversion disorder
  - Panic attacks
  - Factitious disorder
  - Somatization disorder
  - Acute psychosis
  - Adjustment disorder
  - Personality disorder
  - Malingering

Psychogenic Nonepileptic Seizures (PNES)

- Episodes of altered movement, sensation, or experience resembling epileptic seizures but not associated with ictal epileptiform discharges in the brain, but which instead have a psychological origin
- Represent significant diagnostic challenge
PNES: Even the Name is Controversial

- Previously used terms:
  - Pseudoseizure, hysterical seizure, hystero-epilepsy, pseudoepileptic seizure, non epileptic attack disorder, stress-related seizures, functional seizures

- Definition of "seizure"
  - Experts propose a change to PNES "attacks", "episodes", "events", "spells", etc.

- 2003 study asked patients to rate the "offensiveness" of terms used
  - "Stress-related", "functional" seizures least offensive
  - "Symptoms all in the mind" and "hysterical" most offensive
  - "Non-epileptic attack," "pseudoseizure," "psychogenic" medium offensiveness

Epidemiology of PNES

- Estimated prevalence 2-33/100,000 in general population

- At a typical tertiary care epilepsy center, 20-40% of patients previously diagnosed with epilepsy are found to be misdiagnosed
  - PNES is the most common condition misdiagnosed as epilepsy
  - Of the 1% of US population presumed to have epilepsy, 5-20% may have PNES

Epidemiology of PNES Continued

- Prolonged PNES ("psychogenic status epilepticus") occur in one-third
  - More than one-quarter receive ICU care for presumed status epilepticus at least once

- Typically occurs between 20-30 years of age
  - Can occur in children and older adults

- Female predominance

Reuber M and Elger C 2003
de Timmer et al Seizure 2002
Carton S et al Seizure 2003
PNES: A Challenging Diagnosis

- 9 to 16 year delay from seizure onset to diagnosis of PNES on average
  - Broad diversity of presentations
  - Inadequate history
  - Reliance on clinical observation of event
  - Poor physician-patient rapport
  - Discomfort in making a psychiatric diagnosis

Consequences of Epilepsy Misdiagnosis

- Multiple AEDs
  - Toxicity, teratogenicity, cost, lab tests
- Repeated testing including EEGs, neuroimaging
  - $100,000 lifetime cost per patient
  - Estimated $100-900 million per year in medical services for PNES patients
- Iatrogenic complications for continuous PNES (status):
  - Oversedation requiring intubation, lines, etc.
- Vocational costs
  - Disability rates equal those with epilepsy
  - Employment difficulties
- Delay in access to appropriate psychological and psychiatric treatment

Factors Contributing to Misdiagnosis of Epilepsy

- Errors in EEG interpretation
  - Very few published studies
  - May be due to inexperience, biased opinion, overweighing importance of EEG
  - "overreading" vs. "underreading"
- Errors in EEG report interpretation of non-specific findings
- Epilepsy diagnosis “stamped” on patient and easy to perpetuate without questions
- Clinical features of ES and PNES similar
Diagnosis of PNES

- As detailed a description as possible of before, during and after events by patient and by witnesses
- Triggers, frequency, duration, stereotypy, response to previously tried medications, factors that attenuate event, etc.
- Often occur in front of witnesses
  - Episode occurring in doctor's office estimated to have 75% positive predictive value for PNES
  - Episodes occurring at time of electrode placement during video EEG monitoring more likely to be PNES
- PNES patients are more likely to have witnessed epileptic seizures in a friend or relative, or work in healthcare

Video EEG (VEEG)

- Gold standard in diagnosis of PNES
  - Absence of epileptiform activity on EEG before, during and after event and presence of semiological signs consistent with PNES on video
- Must record all habitual seizure types to make an accurate diagnosis, multiple of each type preferred
- In most cases, diagnosis of PNES with video EEG is clear and can be made with a high degree of confidence
Video EEG

- Limitations
  - Expensive, time-consuming
  - Not readily available in all centers
  - Experienced epileptologists required for accurate interpretation
  - Not all ES have epileptiform patterns on EEG
    - Frontal lobe seizures and simple partial seizures
    - Movement and muscle artifacts can obscure tracing

LaFrance W and Benbadis S 2011

Semiological Signs of PNES vs. ES

- No single sign that is pathognomonic for PNES
- Few prospective studies, most retrospective
- Many studies have other limitations: unblinded, single-observer, poorly defined signs, and evaluate individual patients and not individual spells
- Recent published reviews critiquing validity of reported clinical signs

Semiological Signs of PNES

- Eye closure
- Long duration
- Ictal weeping, stuttering
- Memory recall during ictal period
- Absence of postictal confusion
- Asynchronous limb and side-to-side head movements
- Waxing and waning
- Absence of postictal stertorous breathing
- Presence of postictal rapid, shallow breathing
- Frequent seizures (daily)
- “Teddy bear” sign

Avbersek A and Sisodiya S 2010
Ettinger AB et al. 1998
Hoerth M et al. 2008
Vossler DG et al. 2004
Burneo JG et al. 2003
Semiological Signs of PNES vs. ES

- Insufficient evidence in literature to distinguish PNES from ES:
  - Pelvic thrusting
  - Back arching or opisthotonus
  - Physical injury
  - Urinary incontinence
  - Tongue biting
  - Gradual onset
  - Fluctuating course
  - Thrashing movements
  - Non-stereotyped attacks

Avbersek A and Sisodiya S 2010
LaFrance W and Benbadis S 2011

Can Reports of Semiological Features Predict PNES?

- Overall the answer is no
  - Patients and witnesses can report clinical features that are discrepant from each other and from the review of video EEG recorded events

Syed TU et al. 2011
Reuber M et al. 2011

Frontal Lobe Seizures vs. PNES

- Represents diagnostic challenge due to nature of frontal lobe seizures and lack of ictal EEG patterns
- Frontal lobe seizures:
  - Typically brief (5-30 seconds)
  - Hypermotor behavior
  - Stereotypical events
  - Frequently occur out of EEG-verified sleep
- PNES never arises out of true sleep

LaFrance W and Benbadis S 2011
**Induction of PNES**

- Provocative approach to facilitate the diagnosis of PNES
- Remains controversial due to ethical concerns
  - Involves deception which may violate patient autonomy, undermine physician-patient relationship and may cause psychological harm
  - Benefit of timely diagnosis outweigh ethical concerns
- Can lead to incorrect diagnosis
- May be useful with “simple partial” seizures

Chen D et al. 2011

Benbadis S 2009
Serum Markers

- **Serum prolactin level**
  - Drawn within 15-20 minutes of seizure and 6 hours after seizure
  - Prolactin elevations (twice the baseline value) have a positive predictive value of 93-99% for generalized tonic-clonic and complex partial seizures
  - Lack of increase has 89% sensitivity to PNES
    - Limited usefulness for frontal lobe epilepsy vs. PNES
    - Elevated prolactin can be seen with syncope and use of certain dopamine agonists
- Other markers studied include CPK, neuron specific enolase, cortisol, WBC

Neuroimaging

- Structural abnormalities neither confirm nor exclude ES or PNES
- 10% PNES patients have structural abnormalities on MRI
- Small study looked at SPECT scans in PNES
  - No difference between ictal and interictal images

Neuropsychology Testing

- ES and PNES pts show no differences on tests of intelligence, learning and memory, but both score lower than healthy controls
- Some studies suggest pts with PNES put forth less effort on neuropsychological tests that ES pts
- Overall not useful in distinguishing ES from PNES
  - May be helpful after PNES diagnosis made
Psychopathology and PNES

- PNES are involuntary expressions of psychological stress and not willfully simulated events
- Exact psychological mechanism remains poorly understood
- Somatoform Disorder
  - Conversion disorder (most common)
  - Somatization disorder
  - Undifferentiated somatoform disorder
  - Pain disorder
  - Hypochondriasis

Psychopathology and PNES Continued

- Dissociative Disorder
- Post-traumatic Stress Disorder
- Personality Disorders
- Affective and Anxiety Disorders
- Common in context of social or family conflict and trauma
- History of sexual or physical abuse as child or adolescent
- Chronic pain symptoms of moderate to severe intensity occurred in 77% of all patients with PNES and in 96% of patients with persistent PNES (headache most common)

PNES in Children

- Can occur as early as age 5 or 6
- Cleveland Clinic Study
  - PNES was found in 7% of all pediatric VEEG performed between 1989 and 1995
  - Female predominance
  - All evaluated by pediatric psychiatry
  - Conversion disorder
  - Major depression
  - None with malingering or factitious disorder

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Ettinger A et al. 1999
Rueber M and Elger C 2003

Ettinger A et al. 1999
Rueber M and Elger C 2003

Wyllie E et al. 1999
PNES in Children Continued

- Severe family stress (divorce, parental discord, death) and sexual abuse most common psychosocial stressors
  - School failure, separation anxiety and school refusal less common
- PNES occurred months to years after stressor
  - Onset of PNES in adolescent girls following sexual abuse in early childhood

PNES in Veterans

- Recent study retrospectively reviewed VAMC EMU records over 10 year period (veterans and civilians admitted to same unit)
  - 25% PNES in veterans
  - 26% PNES in civilians
  - Average delay to diagnosis 60.5 months for veterans vs. 12.5 months for civilians
    - Lack of EMUs within VAMC system
    - Physicians less likely to challenge the diagnosis of epilepsy in patients with high rates of traumatic brain injury

How to Deliver the Diagnosis

- Treatment begins with clear communication and secure diagnosis
- Physician attitude and confidence
- Discuss how stress affects us in different ways, "body’s way of releasing stress or blowing off steam"
- "Good news"
- Acknowledge the episodes as real and disabling
- Acknowledgement that specific etiology is often not known
- Acknowledge feelings produced by diagnosis, such as anger
- Written material
- Clear follow-up plan to avoid patients feeling abandoned
Treatment of PNES

- Multidisciplinary approach
  - Neurological and psychiatric follow-up
- Withdrawal of AEDs considered safe
- Cognitive behavioral therapy
  - Recent randomized controlled trial
    - Statistically significant reduction in seizures with cognitive behavioral therapy versus standard medical care alone
- Pharmacologic therapy
  - Recent randomized double-blind, placebo-controlled trial
    - Flexible-dose sertraline vs. placebo over 12 weeks
    - 45% reduction in PNES with sertraline group
    - 8% increase in PNES in placebo group
  - Case reports and open-label trials

Driving and PNES

- Very few studies addressing this
  - Small review found PNES patients not at increased risk for car accidents
- Most physicians do recommend driving restrictions
  - Some experts recommend decision be individualized

Prognosis of PNES

- Variable
  - PNES can rarely resolve immediately after diagnosis explained
  - 28.8% of 164 patients free of PNES at 1-10 years after diagnosis
    - Improved outcome: social support, younger age, shorter duration, less dramatic features, higher education and socioeconomic status
    - Poor outcome: prolonged delay to diagnosis, significant psychiatric comorbidities
  - Significant decrease in ER visits and diagnostic tests
  - Better prognosis in children (70-80% seizure remission)
Case Presentation Continued

- Diagnosis of PNES made
- Patient’s AEDs not restarted at discharge
- Local psychiatric referral who began paroxetine and alprazolam
- New spell type began about 1 month after discharge
- Patient can tell difference between two types as she loses complete awareness with new type as compared to PNES
Co-Existence of PNES and Epilepsy

- Initial prevalence stated 10-50%
  - Previous studies included history as part of criteria for epilepsy diagnosis
- Benbadis 2001
  - Criteria used for PNES was generalized motor phenomena and loss of consciousness without EEG changes during the events and absence of postictal slowing
  - Only criteria for diagnosis of epilepsy was unequivocal epileptiform interictal or ictal discharges
  - 211 patients monitored in EMU in 1 year
    - 32 (15%) diagnosed with PNES
      - 3 (9.4%) had interictal epileptiform discharges on EEG
- Clinical features of ES and PNES in the same patient are different

Future Research

- How to limit EEG over interpretation
- More prospective, blinded studies focusing on accurate clinical symptoms or signs as VEEG remains a limited resource
- Insight into psychological mechanism of PNES to help guide treatment

Summary

- Some clinical signs are more suggestive of PNES vs. ES, though none are diagnostic
- Frontal lobe seizures can have atypical clinical features and a normal EEG, and can be confused with PNES
- VEEG is the gold standard for diagnosis of PNES
- The diagnosis of PNES should be presented to patients/families in a supportive and nonjudgmental fashion
- Prognosis of PNES is guarded, but a multidisciplinary approach to treatment may lead to better outcomes
Thank You