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Seizures and Tremor

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What is a Seizure? Epilepsy?

SEIZURE: a single event characterized by an abrupt change in behavior and accompanied by paroxysmal neuronal discharges…… either as a primary abnormal electrical excitability in an otherwise normal brain or secondary to another primary disorder

Paroxysmal- come and go in a burst, not always there

EPILEPSY:

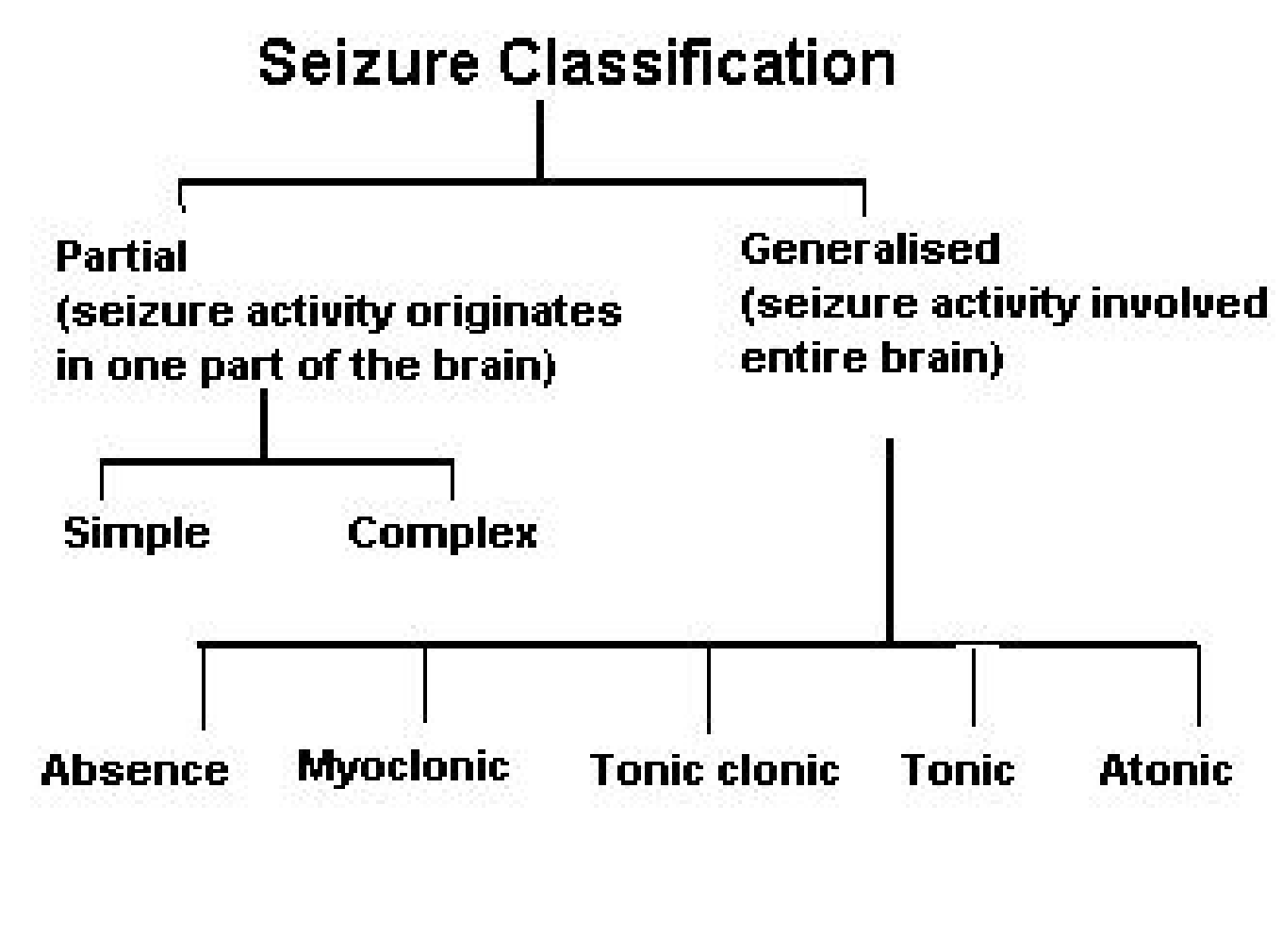
- Recurrent seizures
- Paroxysmal discharges from neurons (brain cells) are the primary disorder.

Causes of Seizures

- Acute response to an new condition (trauma, infection, stroke, toxin/drug, tumor, metabolic)
- Delayed effect due to a recent disease (trauma, infection, surgery)
- Permanent brain “scar” from an old disease (stroke, prenatal/perinatal insult, tumor, infection)
- Most common: Genetic brain hyperexcitability
  - Only hyperexcitability (seizures in otherwise normal person) – “idiopathic”
  - Other manifestations of brain dysfunction – eg. cognitive disorder, genetic syndrome, neurodegenerative disease, metabolic disease, neurocutaneous disorder, CNS malformation

Classification of Seizures:

International Classification of Epileptic Seizures



Partial Seizures

- Seizures in one area of brain - PARTIAL
  - Simple partial (patient awake – one localized seizure manifestation – eg. arm twitching)
  - Complex partial (alteration of consciousness plus localized movements, may be repetitive or odd movements like lip smacking)
    - simple at beginning, then alteration of consciousness (confusion to loss of consciousness)
    - impaired consciousness from beginning
    - with secondary generalization – as seizure progresses goes into generalized tonic-clonic seizure

Complex Partial Seizures

- AKA temporal lobe or psychomotor
- Impaired consciousness with complex symptoms, often partial seizure onset
- 20% of childhood epilepsy, old > young
- Focal brain problem can be present (eg. tumor, abnormal blood vessel)
- Partial seizures often part of genetic syndrome without specific area of brain abnormal
- Surgery can be treatment in severe cases

Generalized Seizures

- Seizures involving the whole brain at once - GENERALIZED
  - Absence (staring, eye blinking, old “petit mal”)
  - Generalized myoclonic (single or clusters of jerks)
  - Clonic (jerking)
  - Tonic (stiffening)
  - Tonic-clonic (stiffening followed by jerking, old “grand mal”)
  - Atonic (sudden loss of tone – head drops, falls)

Generalized Tonic Clonic Seizure

- most common seizure type in urgent care
- primary or secondarily generalized
- cause is found in about 25%
- 5-15% genetic factors
- 30-50% recurrence after one

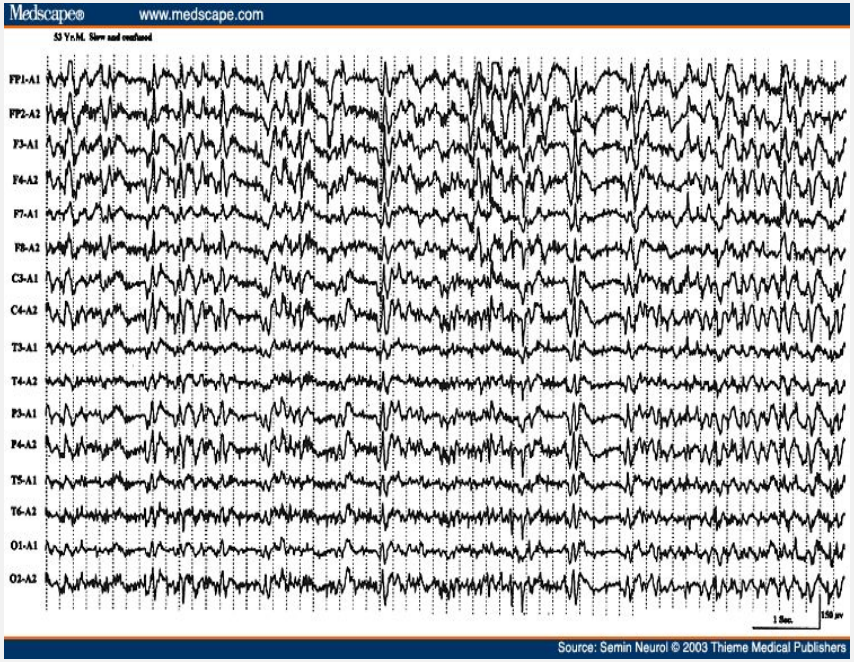
Generalized Tonic Clonic Seizure

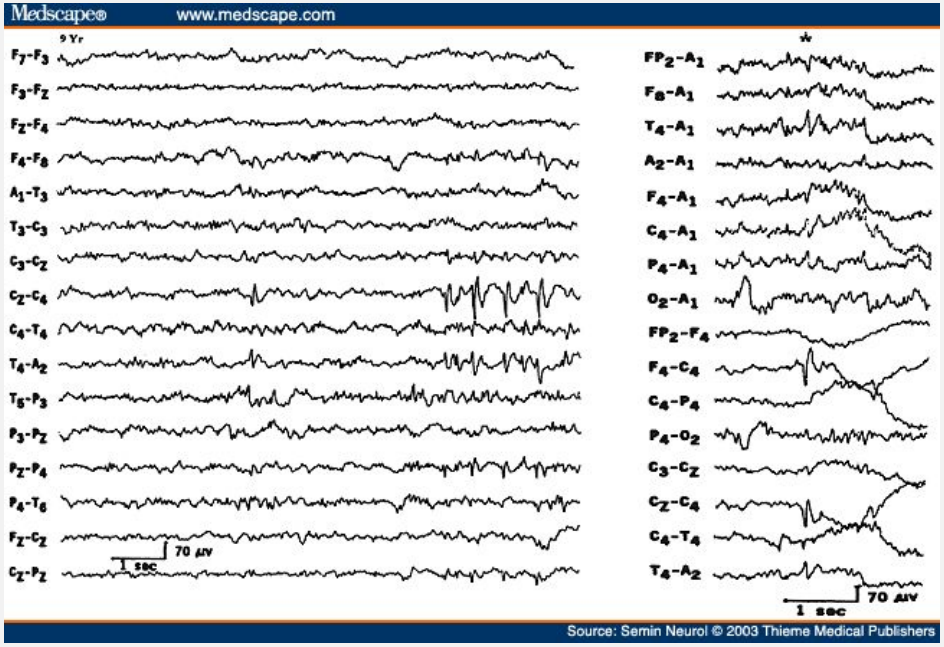
- Loss of consciousness + stiffening or clonic jerking
- Loud cry at onset , eyes roll up, noisy breathing, jaw clenched, oral secretions pool in mouth, incontinence, drowsiness after seizures
- Unwitnessed focal onset common

Status Epilepticus

- Single or repetitive seizure > 30 minutes
- Body changes
  - Poor breathing effort (shallow breathing)
  - Increased BP, pulse, and temperature
  - Increased blood measures: lactate, prolactin, and white blood cells
- Brain injury usually does not occur unless seizure is provoked by a brain damaging problem (like encephalitis)

Generalized and Partial Seizures





Febrile Seizures

- 2-5% of children will have at least one event
- Generalized
- Etiology: usually viral but any febrile illness possible
  - Genetic predisposition: family hx prognostic
- Criteria for diagnosis
  - Age: 6 months to 5 years
  - Fever present
  - <15 min
  - No evidence of CNS infection/other disease
  - No focal signs
  - Normal interictal EEG

Febrile Seizures – Prognosis and Treatment

- Most are “benign” and resolve by age 6
- 2-4% recur as non-febrile seizures in later life
  - The more febrile seizures a child has, the more likely he will develop epilepsy
- 20-40% will have recurrent febrile seizures
- Complexity of seizure important predictor for recurrence
- Control fever – Acetaminophen, Ibuprofen
- Treat infection (if present)
- Anticonvulsant treatment usually not needed, may use Diastat for longer episodes

Evaluation of Seizures

- Detailed moment by moment history of event (activity, body position, progression, duration, loss of sphincter tone, tongue biting, look for visual/auditory/olfactory auras)
- Note setting, last meal, provocative factors
- Birth and developmental status
- Head trauma and past CNS illness
- Family history
- Physical exam: Growth, optic fundi, skin (Wood's lamp), dysmorphisms, asymetries, organomegaly

Differential Diagnosis of Seizures
Non-Epileptic Spells

- Shuddering
- Neonatal Apnea
- Benign Noctural Myoclonus – when falling asleep
- Night terrors
- Migraine
- Panic Attacks
- Syncope (Fainting) – may end with brief convulsion
  - Breath-holding spells (kids<6y, start with cry/injury)
  - Hyperventilation
  - Neurocardiogenic Syncope
  - Prolonged QT (serious cause of fainting, may also have epilepsy)
- Can occur even in patient with syndrome known to be associated with seizures – need to be sure it's a seizure to treat right

Work-up of Initial Seizure

- Always: glucose, electrolytes, calcium
- If partial seizure: MRI > infused CT
- If acute fever or persistent mental status change: L/P
- EEG 2 wks later
- If slow development or <age 2 yrs: metabolic and genetic evaluation
- If already known to have syndrome associated with seizures, may just blood tests and EEG

Neurologic Referral for Seizures

- Diagnostic dilemmas
- Poor response to single drug treatment
- Doctor uncomfortable with seizure treatment
- High family anxiety
- Patient with complex mix of problems – eg. behavior, ID, seizures – that may involved a specialized approach

EEG in Seizure Disorders

- For diagnosis of epilepsy type
- To determine if episodes are actually seizures
- For specific epilepsy syndrome
- To help guide treatment decision
- After a major seizure:
  - slowing
  - suppression of seizure foci

Ambulatory EEG for Diagnosis (Neurotech, Digitrace)

Seizures in X Chromosome Disorders

- All cases 1992-2002 University of Siena, N=43
- 16 Turner, 17 Klinefelter, 7 XXX, 3 other
- Klinefelter
  - 2/17 partial complex seizures
  - EEG abnormal in 4/17 occipital or parietotemporal paroxysmal discharges
- Turner – no seizures
- XXX
  - 5/7 partial complex seizures
  - All 5 abnormal EEG with paroxysmal activity in temporo-parieto-occipital areas – characteristic pattern
  - Seizures associated with subnormal IQ
- Clinically seizures easy to control and many grew out of them

Grosso et al. J Clin Neurophys, 2004

Seizures in X Chromosome Disorders

- Klinefelters
  - 5 patients refered to epilepsy clinic, 4 seizures = 2 complex partial, 1 single GTC, 1 febrile, 1 EEG abnormal no seizures
  - All good prognosis, grew out of seizures
  - EEG occipital paroxysms in 2
  - Suggest generally good seizure outcome

Elia et al. Ital J Neurol Sci, 1995

- XXX
  - Patients recruited nationally 2005-2014
  - Compare prenatal diagnosis vs post-natal diagnosis
  - 16.2% of 74 have seizures (2.3% of 44 prenatal, 36.7% of 30 postnatal)
  - Generalized tonic clonic and partial complex
  - 6 abnormal EEG with paroxysmal discharges

Wigby et al. AJMG, 2015

Treatment of Seizures

What to Do for Seizure Acutely

- Don’t panic
- Put on side
- Make sure breathing
- Do not put anything in mouth – they will not swallow the tongue
- Do not give food or drink
- Let them sleep after event if needed
- If turning blue, not breathing at all, or seizure lasts >15 minutes – call paramedics
- Diastat if has it
- If first seizure – bring in for testing for underlying cause

Status Epilepticus Treatment

- Seizure that goes on for 30 minutes without patient becoming alert/responsive
- Routine Airway, Breathing and Circulatory management
- Metabolic Studies on blood
- Anticonvulsants
  - Diazepam (Valium IV, or Diastat rectally)
  - Lorazepam (Ativan IV)
  - Phenytoin (Dilantin) or fosphenytoin IV
  - Phenobarbital
  - Valproic acid (Depacon IV)
  - Keppra IV
- Refractory status
  - Intubation (and ventilation)
  - Pentobarbital, benzodiazepam drip, propofal

Anti-epileptic Drug Selection

- Define the syndrome
- Select medicine for syndrome
- Match medicine to patient characteristics

Basic Principles: Anticonvulsants in Children

- 1. start after 2 or more seizures
- 2. stop 2 to 4 years after last seizure
- 3. single drug regimen is best
- 4. use lowest effective dose
- 5. dose guide is effectiveness and toxicity
- 6. blood levels are less important
- 7. EEG is adjunct for deciding which drug, how much, and how long
- 8. more drug is not necessarily more effective

Traditional Anticonvulsants – Not First Line Choices Any More

- Phenobarbital – not used much any more
- Phenytoin (Dilantin) – not used much in children now due to long term side effects (gum swelling, facial changes, acne)
- Carbamazepine (Tegretol Carbatrol) – in past was first line anticonvulsant for partial seizures
- Valproic acid (Depakene, Depakote) – in past was first line treatment for generalized seizures (atonic, myoclonic, absence, GTC)

New Anticonvulsants: 1992-2011

- **Levetiracetam (Keppra) – now first line for most seizure types**
- **Oxcarbazepine (Trileptal) – partial seizures**
- Felbamate (Felbatol)
- Lamotrigine (Lamictal)
- Gabapentin (Neurontin)
- Vigabatrin (Sabril)
- Tiagabine (Gabatril)
- Topirimate (Topamax)
- Zonisamide (Zonagran)
- Fosphenytoin
- Pregabalin (Lyrica)
- Rufinamide (Banzel)
- Lacosamide (Vimpat)
- Fycampa

(Blood monitoring not required except Felbatol)

New Anticonvulsants: 1992-2011

New Drug	Main Treatment Focus
• Felbamate	partial; marrow & liver toxic
• Lamotrigine	partial, myoclonic, absence, LGS, may be used first for generalized seizures instead of valproic acid, slow to get on, watch for rash
• Gabapentin	partial; easy add on drug
• Vigabatrin	partial, infantile spasms, watch vision
• Tiagabine	partial
• Topirimate	partial, LGS, may be used instead of valproic acid, watch language and kidney stones
• Zonisamide	partial
• Fosphenytoin	less toxic: phenytoin pro-drug, use for status
• **Oxcarbazepine**	**less toxic than Tegretol (no epoxide) – now may be used fist line for partial seizures**
• **Leviteracetam**	**first line for generalized and partial – no major body side effects or drug interactions, watch for 15% increase in behavioral issues**

Ketogenic Diet

- Calorie restricted, high fat, low carb (very strict) – 90% calories from fat
- Causes ketosis, associated with seizure control
- About 20% good control rates in intractable patients
- Typically used when multiple anticonvulsants fail or when problems with anticonvulsant side effects
- Patient characteristics – works best under age 4, motivated older child, impaired older child
- Family characteristics – motivated, want to avoid meds if possible, capable with organized lifestyle
- Best for atonic and absence, but can work for all types

Vagal Nerve Stimulator

- Implanted by surgery at base of neck on vagal nerve
- Set to stimulate nerve at certain frequency
- Can adjust frequency to control
- About 10% rate of big improvement in control
- Work best for tonic seizures or when patient has aura and can activate device to abort full seizure
- Risks – hoarseness after surgery, infection

Epilepsy Surgery

- Types
  - Temporal Lobectomy
  - Other focal resection
  - Multiple sub-pial transection
  - Callosotomy
- Only for patients with partial epilepsy
- May be used in whole brain disorder if patient very intractable and appears to have dominant focus

Epilepsy: Seizure Recurrence Risks

- Non-compliance
- Too little sleep
- Intercurrent illness
- ? Stress
- Consider increasing, changing or adding medication
- Frequent recurrence with prolonged seizure or clusters – use rectal Diastat (valium) to stop at home

The Breadth of Epilepsy Care

- SEIZURE CONTROL -- Medication
- SIDE EFFECTS -- Lower or change drugs
- PSYCHOSOCIAL -- Support groups/ counseling
- EDUCATION -- IQ/LD testing; proper IEP
- BEHAVIOR -- Counseling, meds
- ADULT INDEPENDENCE -- Vocational counseling

When Can Seizure Medicines be Stopped?

- Consider stopping meds after 2 years seizure free, especially if EEG normal
- May treat longer if patient has an underlying condition associated with significant seizure risk or if EEG still shows strong epileptic activity
- If on multiple meds, may wean one after seizure free a year or two
- Always some risk of recurrence no matter how long wait past 2 years
- Can restart meds if recurrence

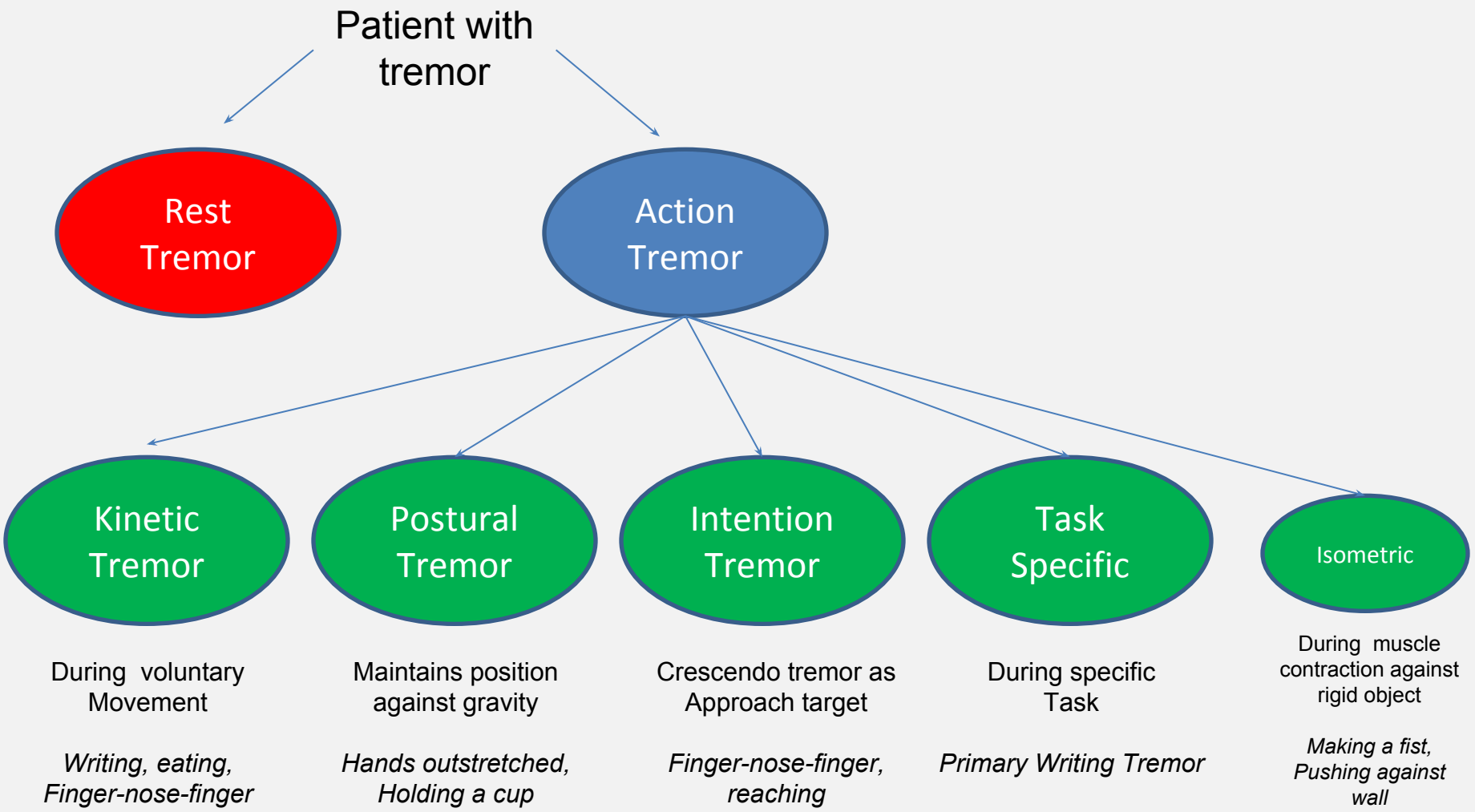
Tremor - Definition

- ✓ Rhythmic, sinusoidal, oscillation of a body part
- ✓ Alternating contractions of opposing muscle groups

Types of Tremor

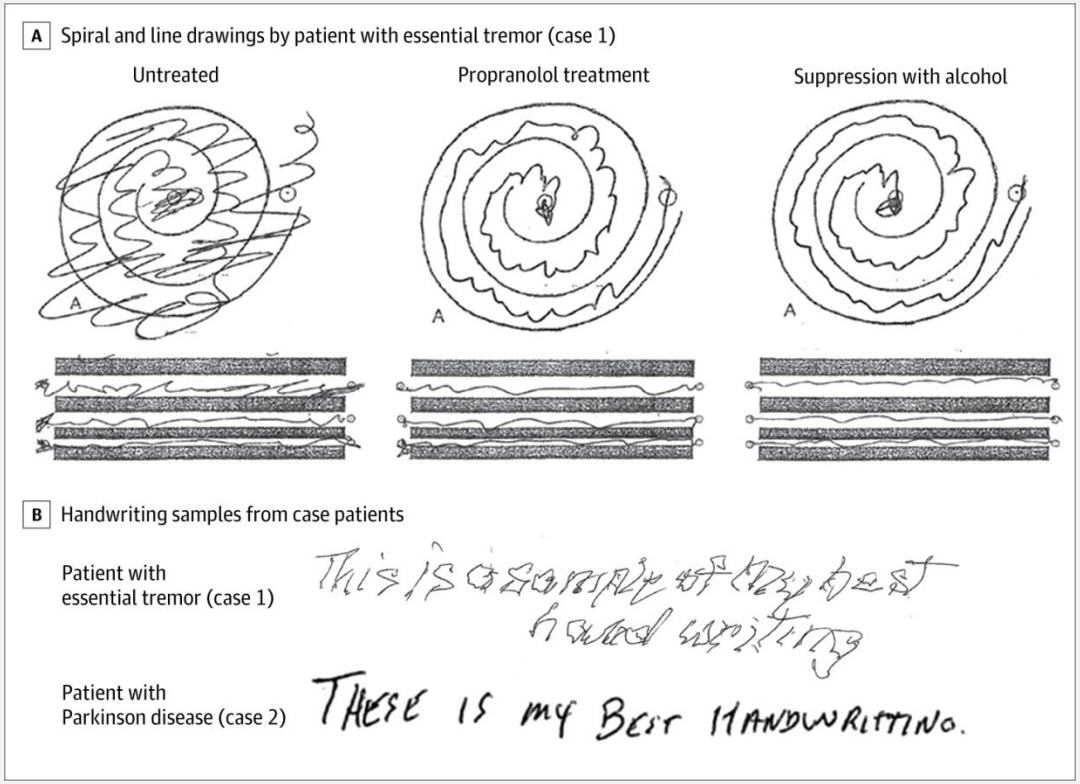
- Rest
  - Parkinsonian – at rest, “pill rolling”
- Action
  - Cerebellar – intention tremor can’t point directly to things, can have myoclonic tremor (jerky movements)
  - Kinetic – brought out by movement
  - Postural “Essential” – shaking when holding a posture
    - Most common type
    - “Benign”
    - More prominent in AM, after caffeine, when stressed
  - Enhanced physiological tremor – adrenalin release, can be side effect of mediations

Distinguishing Tremor Types



Deuschl et al. 1998

Writing and Essential Tremor



Tremor in X Chromosome Disorders

- Many case reports of tremor in KS literature
- KS case-control questionnaire study– University of Iowa
  - All patients in hospital database
  - Recruit 44 KS and 94 controls
  - 63% KS report tremor, 13% controls
  - 10% KS previously diagnosed with ET, 0% controls
  - KS tremor patients have tremor at earlier age
  - Also KS reported gait/balance problems more than controls (?apraxia vs ataxia – needs more study)
  - ET characteristics based on questionnaire responses
  - Essential and kinetic tremors are very common in KS: XXY and XXYY

Harlow and Gonzalez-Alegre, Parkinsonism and Related Disorders, 2009

Tremor in X Chromosome Disorders

- XXX – few case reports
- XXX national study
  - Exam: 23.6% of 72 – intention tremor or ET
  - History: 16.8% of 74 have tremor (11.4% of 44 prenatal dx, 22.3% of 30 postnatal dx)

Wigby et al.
AJMG, 2015

Essential/Kinetic Tremor Treatment

- Symptomatic – only when function is impaired
- Self medication with alcohol –makes tremor much less severe - diagnostic for ET in history
- Medications
  - Propranolol, other beta-blockers “olol”
  - Primidone
  - Less proven: gabapentin, leviteracetam, clonazepam and other benzodiazepines, topiramate, nimodipine
- Botox
- Deep brain stimulation

Treatment of X Aneuploidy-Associated Tremor

- ET and kinetic tremor – treatment same as general population
- A few reports of DBS with both positive and negative results
- Cases of KS with both alcohol-sensitive and -insensitive described