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West syndrome and Infantile Spasms: Breaking the ice


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West syndrome

- Infantile spasms: onset 3-12 months of life
- Characteristic EEG:

  interictal: hypsarrhythmia

  ictal: electrodecremental response
- Developmental arrest or regression
- Evolution into other types of epilepsies
- Multiple etiologies including genetic predisposition
- Unique treatments to control seizures and disease modifying effects

Causes of West Syndrome

- Unknown (Cryptogenic)

  Normal development/ examination prior to seizure onset

  Normal imaging

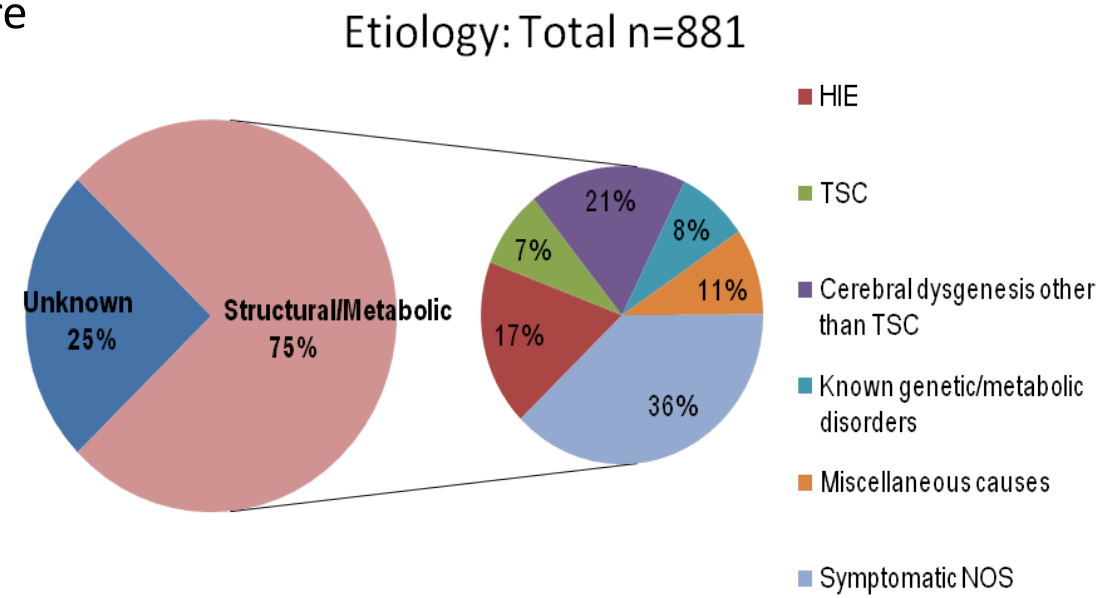
  No known etiology

- Structural/Metabolic (Symptomatic)

  Worst outcome

  Less responsive to treatments

- Genetic



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West syndrome: multiple etiologies and pathologies

Genetic

Mutations

- *TSC 1, TSC2, TUBA1A*
- *LIS1*
- *DCX*
- *ARX*
- *FOXG1 duplications*
- *MEF2C*
- *SLC25A22*
- *SPTAN1*
- *STXBP1*
- *FLNA (filamin A)*
- *CDLK5*
- *MAGI2*
- *PTEN*

- *Amino acidopathies: GLDC, GCST, GCSH, PAH*
- *KCNJ11*
- *Organic acidemias: MUT, BCKDHA, BCKDHB, DBT, DLD, PCCA, PCCB*
- *ATP7A (Menkes Disease)*
- *ARFGEF2*
- *MYH3*
- *SUCLA2*
- *MT-ATP6*
- *NF1*
- *SETBP1*
- *ST3Gal-III*

Chromosomal abnormalities

- *Down syndrome*
- *Deletion in 1p36*
- *Williams syndrome plus: Deletion in 7q11.23*
- *Pallister-Killian syndrome: Tetrasomy 12p*
- *Maternal Duplication 15q11q13*
- *Miller-Dieker syndrome: Deletion in 17p13*

Structural / metabolic

Malformations

- Cortical dysplasia
- Cerebral atrophy
- Polymicrogyria
- Microcephaly
- Hemimegalencephaly
- Lissencephaly
- Pachygyria
- Microdysgenesis
- Holoprosencephaly
- Corpus callosum agenesis
- And many more…

Other

Birth injury or Hypoxia
Degenerative diseases
- (Alper disease)

Infectious
- Meningitis/Encephalitis
- Congenital infections

Metabolic causes
- Disorders of carbohydrate, lipid or amino acid metabolism
- Storage diseases (Tay-Sachs)
- Metallopathies (kinky hair disease)
- Pyridoxine dependency

Mitochondrial diseases
Neoplastic (rare)
Toxins
Vascular (CVA, intracranial hemorrhage)
Autoimmune

Unknown etiology

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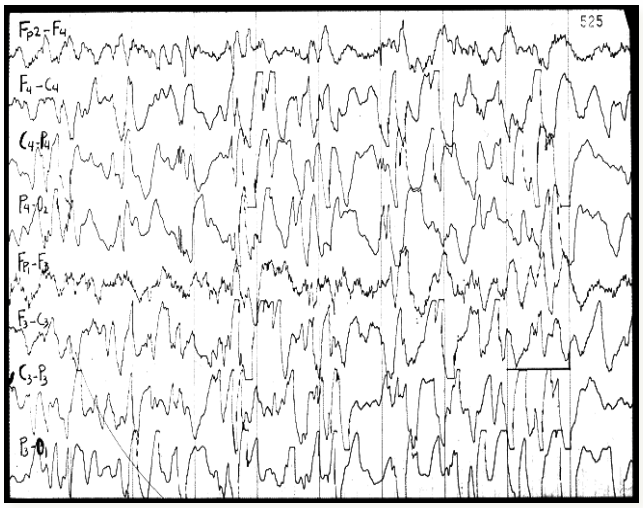
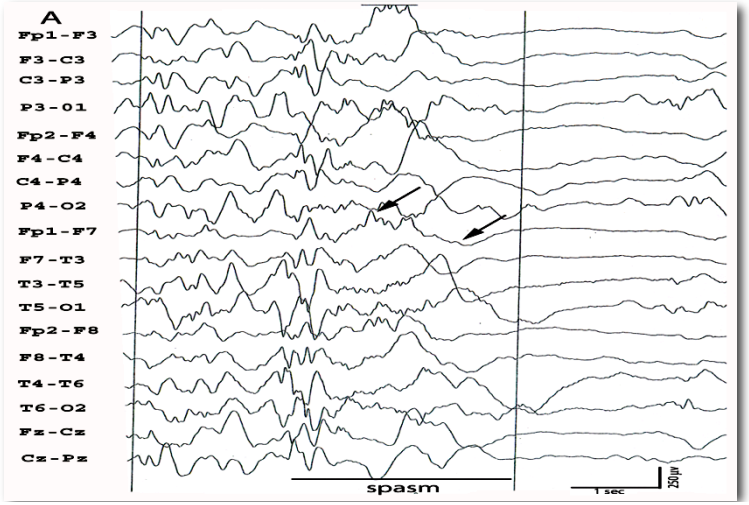
West syndrome

Hypsarrhythmia



Electrodecremental response



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Benign Non-Epileptic Infantile Spasms

- Age of onset: 3-8 months
- Features: Normal exam. Spasms during wakefulness. Remit by 2 years
- EEG: Normal
- Etiology: ? Reflux

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West syndrome (WS)

- WS is a non-specific syndrome, with spasms and characteristic EEG abnormalities that can result from lesions in widespread locations, cortical or subcortical, present at the appropriate maturational stage

- Some but not all patients with a disease (associated with spasms) will develop spasms

- There is unique common circuit that allows for the expression of spasms

- Unique treatments

Treatment choices

"Standard"

- Adrenocorticotropic hormone (ACTH)
- Corticosteroids
  - Hydrocortisone
  - Prednisolone
  - Prednisone
  - (Dexamethasone)
- Vigabatrin (VGB)
- Pyridoxine (vitamin B_6)

"Other (often after failure of standard treatment)"

- Benzodiazepines
- Valproic acid
- Topiramate
- Zonisamide
- Lamotrigine
- Felbamate
- Ketogenic diet
- Intravenous immunoglobulin
- Surgery

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Evidence-based guideline update: Medical treatment of infantile spasms

Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society

- ACTH or VGB may be useful for short-term treatment of IS, with ACTH considered preferentially over VGB
- Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to VGB in infants with cryptogenic IS, to possibly improve developmental outcome
- Low-dose ACTH should be considered for treatment of IS
- A shorter lag time to treatment of IS with either hormonal therapy or VGB possibly improves long-term developmental outcomes
- Etiology-specific?

Go et al., Neurology. 2012;78:1974-80

Side effects

- ACTH
  - Irritability
  - 'Cushingoid' facies
  - Hypertension
  - Myocarditis
  - Intracranial bleed
  - Infection
  - Cerebral atrophy
  - Costs
- Vigabatrin
  - Sleepiness
  - Hypotonia
  - Visual field defects
  - White matter lesions

IS treatment: Cost considerations

ACTH: $28,000 per vial; >$100,000 per treatment course for IS

Wray & Benke: J. Ped Neurology (2010)

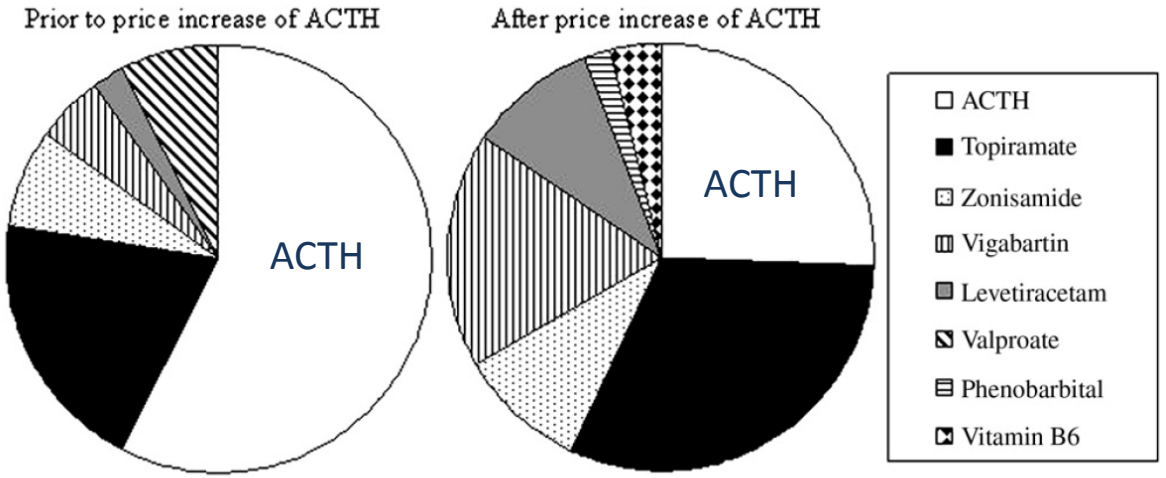

Figure 2. Use of adrenocorticotropic hormone and other therapies as initial therapy before (left) and after (right) the price increase of adrenocorticotropic hormone. ACTH = adrenocorticotropic hormone.

PHARMA & HEALTHCARE 4/07/2014 @ 9:41AM | 12,534 views

$5.6 Billion Questcor Deal Means High Drug Prices For Everybody

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Matthew Herper
Forbes Staff

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I cover science and medicine, and believe this is biology's century.
full bio →

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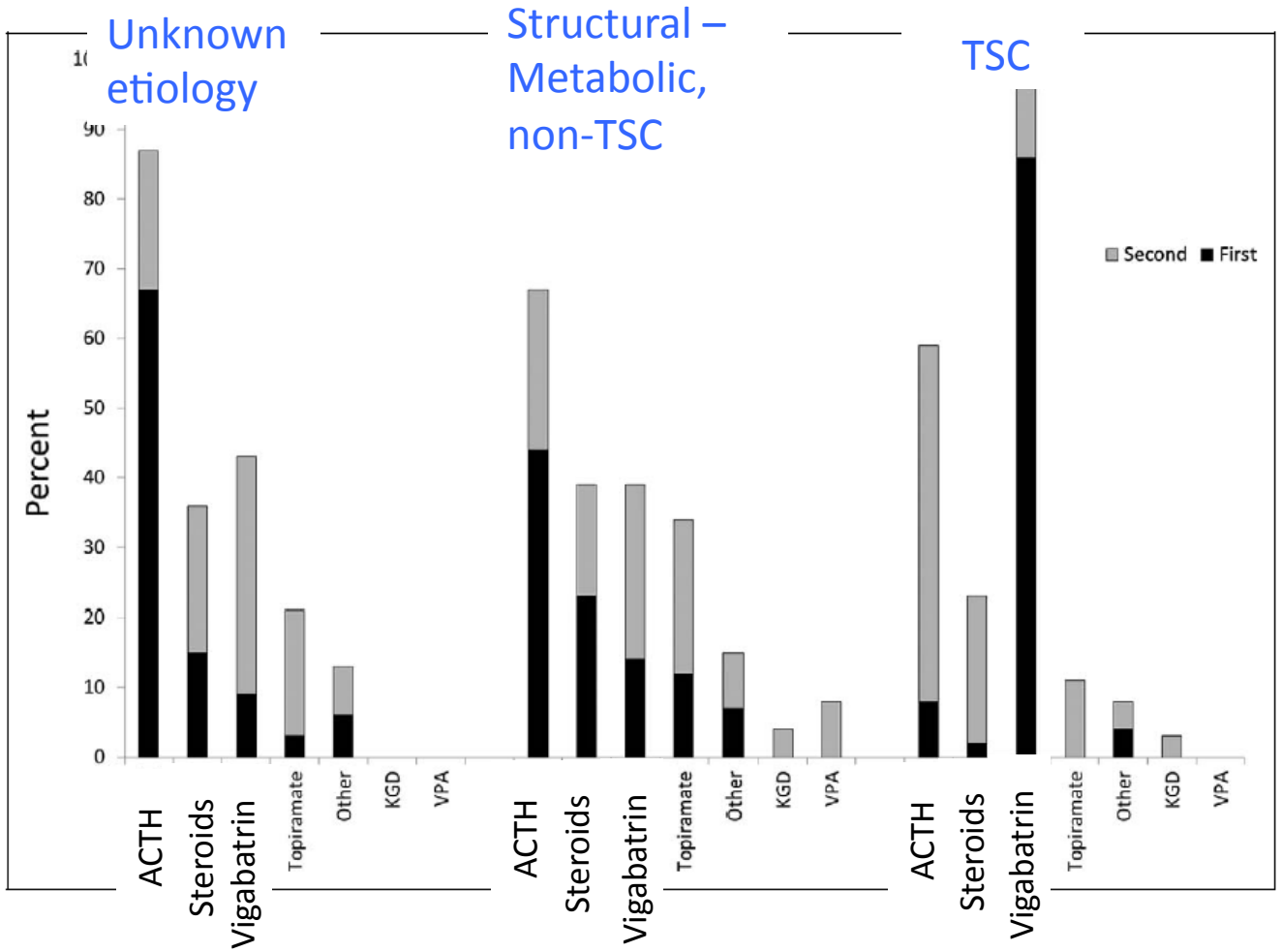
If you're starting a biotechnology company and thinking of developing anything other than a super-high-priced medicine for a niche market, this morning's news that Questcor Pharmaceuticals QCOR +4.38% is being bought by Dublin-based specialty pharma Mallinckrodt for $5.6 billion may make you reconsider. Forget new drugs for any common diseases, find an old one that you can justify charging a lot more for.

In December 2012 the New York Times' Andrew Pollack chronicled how Questcor had become an overnight success by raising the price of its product, Acthar Gel, used to treat kids with severe seizures, from $50 per vial to $28,000 per vial at that time. The drug was originally approved in the 1950s. Pollack wrote:

IS Treatment: choices per etiology



Mytinger & Joshi and the Pediatric Epilepsy Research Consortium, Section on IS (2012) J Child Neurol: 27(10): 1289-94

Early cessation of IS may have better outcomes

Improved outcomes:

- Finland (Riikonen 1982):
  - Early treatment lag: favorable prognosis
- Harvard (Lombroso 1983) (unknown etiology IS):
  - Early treatment:
    - improved cognition
    - Improved seizure outcomes
- UKISS study (Lux et al 2005, O'Callaghan et al 2011) (unknown etiology IS only):
  - No effect on seizure outcomes
  - Improved neurodevelopmental outcomes in *early response – unknown etiology* group (but NOT normal)

Improved outcomes:

- Israel
  - (Kivity et al 2004) (unknown etiology IS only, $ACTH_{1-24}$ depot)
    - Early treatment: 100% normal cognition
    - Late treatment: 40% normal cognition (*most had marked or severe MR at diagnosis at onset*)
  - Israel (Cohen-Sadan et al 2009) (unknown IS)
    - Early ACTH : 100% normal cognition; 0% seizures
    - Late ACTH: 67% normal cognition 33% seizures
    - Early Vigabatrin: 54% normal cognition 54% seizures

No difference in neurodevelopmental outcomes:

- Great Ormond, UK (Mohamed et al 2011)
  - 78% still with seizures a year later
  - 88% still with neurodevelopmental problems
  - Unknown etiology group better

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Infantile Spasms-'Ideal' Models

What are the features to model?

- Age specificity
- Multiple etiologies
- Specific ictal and interictal EEG patterns
- Poor outcome/mental retardation
- Response to "specific" treatments?
  - ACTH/steroids
  - Vigabatrin
  - Pyridoxine

Stafstrom, Moshé, Swann, Nehlig, Jacobs, Schwartzkroin, Models of Pediatric Epilepsies: Strategies and Opportunities, Epilepsia 47:1407-1415 (2006).