CASE

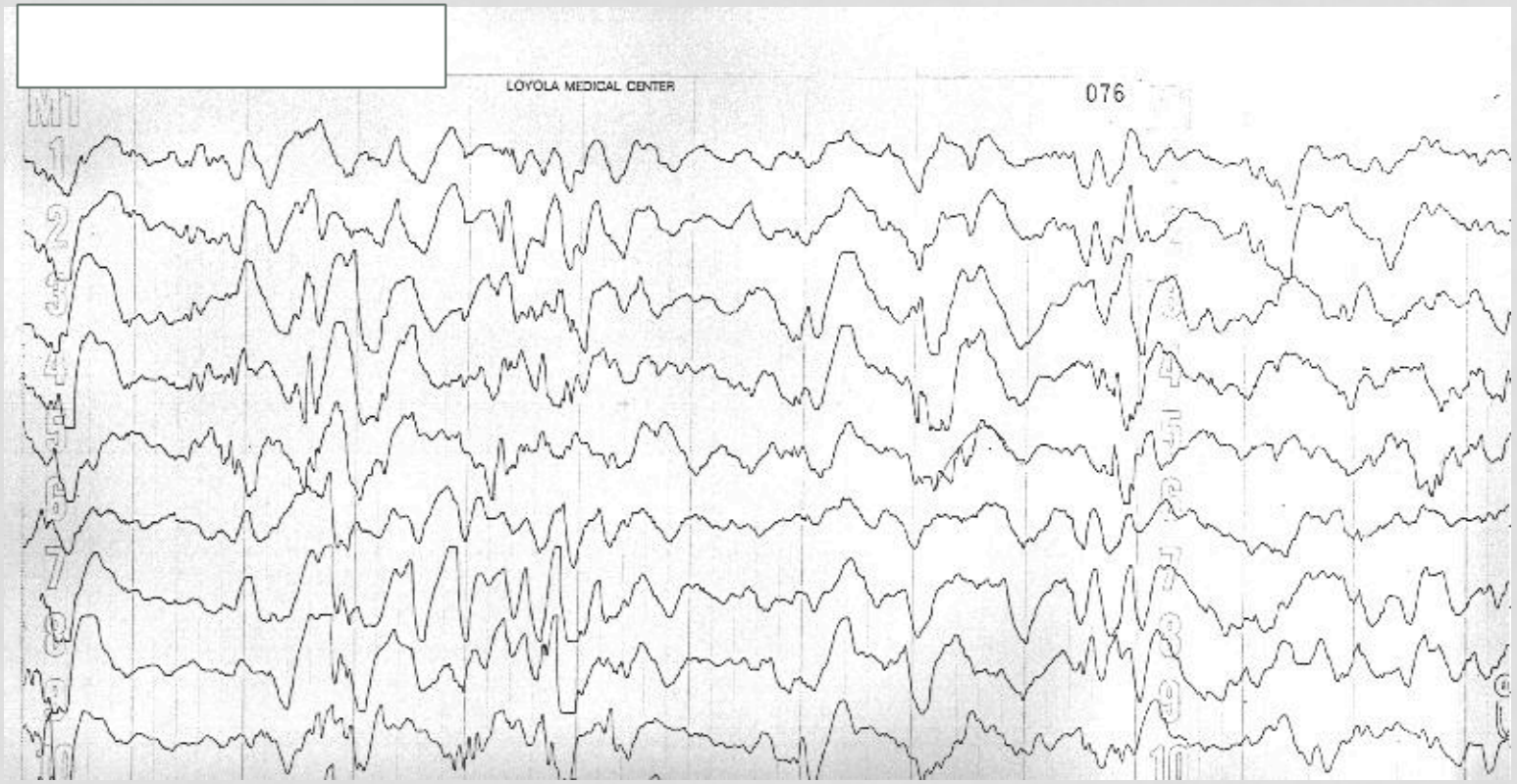
A 6 month old ex-full term previously healthy male presents to his primary care doctor for his well child check. He has been generally healthy, aside from a recent viral URI. He was noted to be developing appropriately at the 4 month visit. Parents have no major concerns, except they do happen to mention that their son started making some “funny jerking movements” a couple weeks ago. The parents show you a video they took on their cell phone.

DIFFERENTIAL DIAGNOSIS

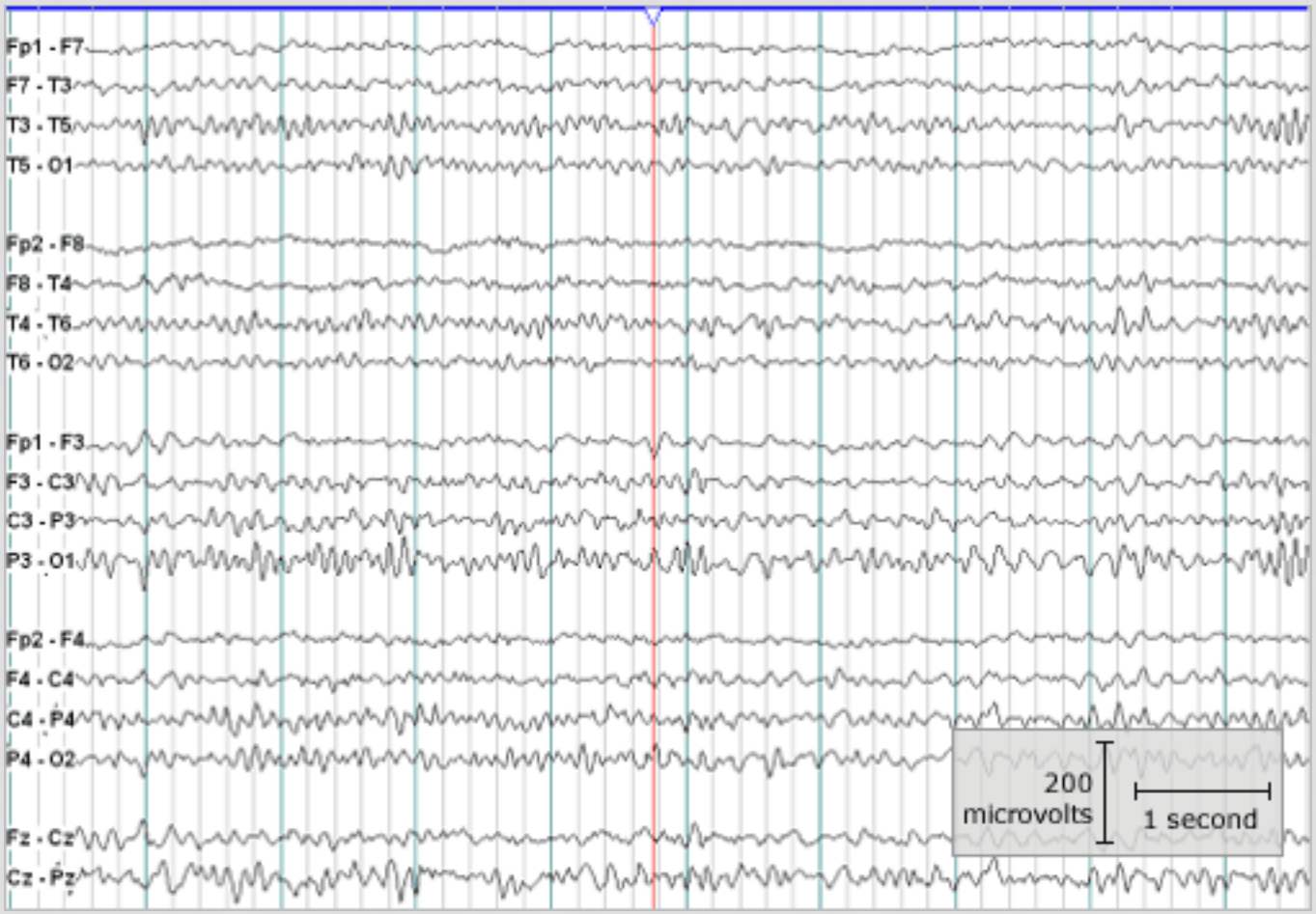
- Infantile spasms
- Exaggerated startle response
- Altered life threatening event (ALTE)
- Colic/Hyperirritability
- Benign myoclonus of early infancy
- Sleep myoclonus

VIDEO

YOUR PATIENT'S EEG



NORMAL EEG


Fp1 - F7
F7 - T3
T3 - T5
T5 - O1
Fp2 - F8
F8 - T4
T4 - T6
T6 - O2
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fz - Cz
Cz - Pz
200 microvolts
1 second

INFANTILE SPASMS AND DEVELOPMENT

RESIDENT PRESENTATION, 9/3/13

KATHERINE HILL, MD
SARAH HENDRICKSON, MD

CLINICAL FEATURES

- Onset
  - 90% before 1 year of age
  - Peak onset 3 to 7 months
  - Onset after 18 months is rare
- Age range
  - 1 day to 4.5 years
- Incidence
  - 2-5 per 10,000 live births worldwide
- West syndrome: The triad of
  - Spasms, arrest of psychomotor development, and hypsarrhythmia

Pellock JM, et al. Infantile spasms: a U.S. consensus report. *Epilepsia*. 2010;51(10): 2175.

CLINICAL FEATURES

- Spasms usually symmetric & involve the neck, trunk muscles, and/or extremities
- Often difficult even for practitioners to detect & diagnose
- 2 phases: Sudden, brief contraction (<2 seconds) followed by longer tonic phase (2-10 seconds)
- 80% occur in clusters (crescendo-decrescendo)

Pellock JM, et al. Infantile spasms: a U.S. consensus report. *Epilepsia*. 2010;51(10):2175.

TYPICAL CLINICAL COURSE

- Initial stage: mild and infrequent
  - Even occasional infantile spasms associated with abrupt arrest and/or regression in development
- Second stage (most severe): peak activity reached
  - Often hundreds of spasms each day
  - Most profound developmental regression
- Third stage: Gradual decrease in spasms, resolution, or transition to overt seizures (Usually occurs before age 5)

Lacy JR, Penry JK. Infantile spasms, Raven Press, New York 1976.

ETIOLOGY OF INFANTILE SEIZURES

- Symptomatic IS: known underlying cause
  - 70-80% have cause found after clinical evaluation and neuroimaging
  - The percentage of IS cases classified as symptomatic has increased over time due to improved diagnostic techniques, such as metabolic and genetic testing and neuroimaging
- Cryptogenic IS: no known underlying cause, usually previously healthy child
  - Likely genetic cause
  - Outcomes are usually more favorable among this subset of infants

Wong M, Trevathan E. Infantile spasms. *Pediatr Neurol*. 2001;24(2):89.

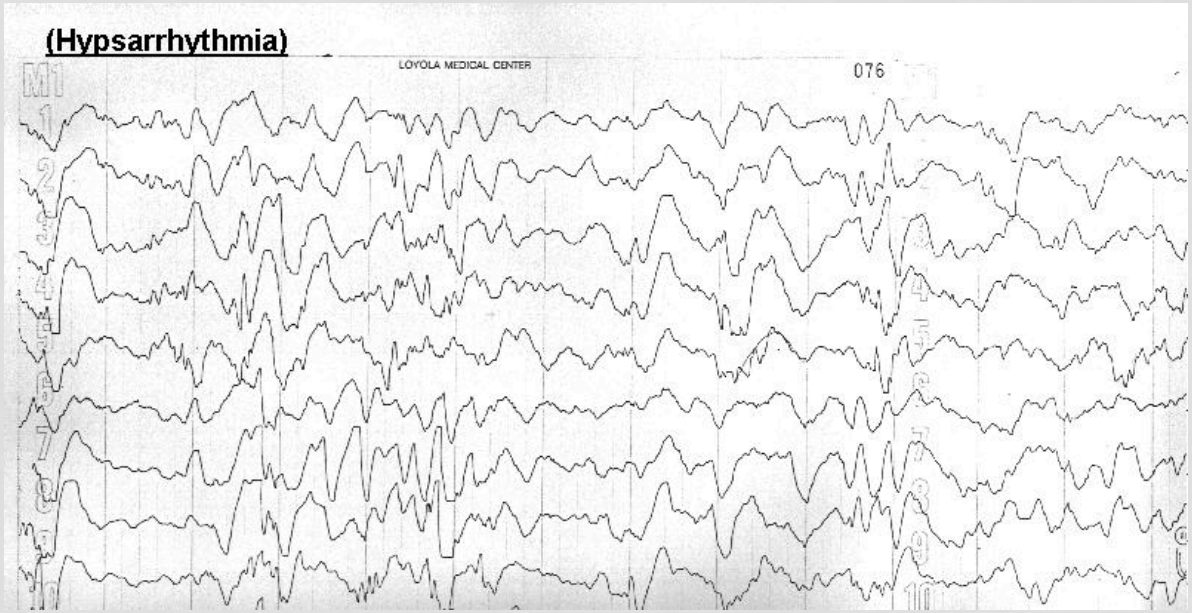
CAUSES OF SYMPTOMATIC IS

- **Prenatal/Genetic Causes:** Approximately 50%
  - Central nervous system malformation
  - Intrauterine insults
  - Neurocutaneous syndromes such as tuberous sclerosis complex (TSC)
  - Metabolic disorders
  - Genetic syndromes such as Down syndrome
- **Perinatal Causes:**
  - Hypoxic-ischemic Encephalopathy
- **Post-natal Causes:**
  - Infection
  - Trauma
  - Tumors (rare)

Wheless, et al. Infantile spasms (West syndrome): update and resources for pediatricians and providers to share with parents. BMC Pediatr. 2012; 12: 108

HYPSARRYTHMIA

- Characterized by very high voltage and slow waves/spikes in all cortical areas
- Most often present in Stages 2 and 3 of non-REM sleep
- May precede onset of spasms



CURRENT TREATMENTS

- Treatment is thought to be an "all-or-none" principle. Complete resolution of spasms and hypsarrythmia
- Practice guidelines from the American Academy of Neurology and the Child Neurology Society for the medical treatment of IS:
  - ACTH – Probably Effective
  - Vigabatrin – Possibly effective
- Pathophysiology:
  - stress/corticotropin-releasing hormone (CRH) hypothesis - increased release of stress-activated mediators in the brain, especially CRH in the limbic and brain stem lead to spasms
  - **ACTH suppresses CRH**

Wheless, et al. Infantile spasms (West syndrome): update and resources for pediatricians and providers to share with parents. BMC Pediatr. 2012; 12: 108

SPECIFIC TREATMENTS

Diagnosis	Specific therapy
Pyridoxine-dependent seizures	Pyridoxine
Phenylketonuria	Diet
Maple syrup urine disease	Diet
Biotinidase deficiency	Biotin
Menkes disease	Copper histidinate
Hyperammonemia disorders	Possibly diet, depending on which disorder
Nonketotic hyperglycinuria	Benzoate
Tumor	Surgery
Arterial-venous malformation	Surgery
Sturge-Weber syndrome	Surgery if medications fail
Tuberous sclerosis complex	Vigabatrin, ACTH (if vigabatrin fails), and possibly surgery if medications fail
Cortical dysplasias: focal cortical dysplasias, hemimegalencephaly	Possible cortical resection if medications fail
Malformations of cortical development	Epilepsy surgery

OUTCOMES OF INFANTILE SPASMS

- Retrospective review of 44 children with untreated IS
- Cumulative spontaneous remission rate of spasms
  - 2 percent at one month
  - 5 percent at three months
  - 25 percent at twelve months
- Most resolve by 3-4 years of age
  - Often progress to other seizure disorders
  - Often with permanent developmental delay

Hrachovy RA, Glaze DG, Frost JD Jr. A retrospective study of spontaneous remission and long-term outcome in patients with infantile spasms. Epilepsia. 1991;32(2):212.

PROGNOSTIC FACTORS OF IS

Abstract

Objectives: The aim of this study was to provide additional evidences on prognostic factors for infantile spasms and the possible role of a ketogenic diet. *Methods:* A retrospective analysis was performed for patients with infantile spasms who had been followed up for more than 6 months between January 2000 and July 2012 at Samsung Medical Center (Seoul, Republic of Korea). We analyzed the association between possible prognostic factors and seizure/developmental outcomes. *Results:* Sixty-nine patients were included in this study and their mean follow-up duration was 52.5 (9–147) months. In the patients who had been followed up for more than 2 years, 53.6% (n = 30/57) remained seizure-free at the last visit. Sixty patients (86.9%) showed developmental delay at last follow-up. Forty-two patients (60.9%) became spasm-free with one or two antiepileptic drugs, one patient with epilepsy surgery for a tumor, and seven patients with a ketogenic diet after the failure of two or more antiepileptic drugs. The etiology and age of seizure onset were the significant prognostic factors. *Conclusions:* In this study, about 60% of the patients became spasm-free with vigabatrin and topiramate. Ketogenic diet increased the rate by 10% in the remaining antiepileptic drug resistant patients. However, 86.9% of the patients showed developmental delay, mostly a severe degree. Early diagnosis and prompt application of treatment options such as antiepileptic drugs, a ketogenic diet or epilepsy surgery can improve outcomes in patients with infantile spasms.

Lee, J, Lee, J, Yu, H, Lee, M. Prognostic factors of infantile spasms: Role of treatment options including a ketogenic diet. *Brain and Development, 35(8): 821-826, 2013.*

PROGNOSTIC FACTORS OF IS

- **Review performed in 2010 of European literature show:**
- Cryptogenic spasms - cease and result in normal or almost normal development in about 80% of patients.
- Symptomatic spasms - the spasms will cease in 50% but development is normal in only roughly 20%.
- A rather benign course is associated with spasms due to: Down's syndrome, neurofibromatosis-1, periventricular leucomalacia due to prematurity, and neonatal hypoglycemia

Riikonen, R. Favourable Prognostic Factors with Infantile Spasms. Eur Journal of Paedtr Neurology. 2010; 14(1): 13-8

PROGNOSTIC FACTORS OF IS

"Factors associated with a favorable outcome include:

- No other seizures before onset of infantile spasms.
- Absence of atypical spasms, partial seizures and asymmetric EEG abnormalities.
- Age of onset after the age of 4 months.
- Early and sustained response to treatment.
- Short duration of hypsarrhythmia"

Riikonen, R. Favourable Prognostic Factors with Infantile Spasms. Eur Journal of Paedtr Neurology. 2010; 14(1): 13-8

LONG TERM OUTCOMES

- In Finland 214 children were followed up for 20–35 years or until death
- Prospective study in which children either received high dose ACTH (for 6 weeks) or low dose ACTH treatment
- The long-term intellectual outcome was better treated with lower doses than with larger doses
- 1/3 of Children died (Of which 1/3 were under the age of 3)
- 25% of children were found to have normal IQ scores, however 40% of these children had a specific learning deficit:
  - Psychiatric disorders, hyperkinetic behavior and infantile autism

Riikonen R. Long-term outcome of patients with West syndrome. Brain Dev 2001;23:683–7.

THE TEMPORAL LOBE?

- In 70% of the children found to have autism in the Finnish study, an abnormality was identified in the temporal lobe.
- Chugani et al. and De Long and Heinz also found that 70% of patients with infantile spasms and autism had bitemporal hypometabolism

Chugani H, Da Silva E, Chugani D. Infantile spasms: III. Prognostic implications of bitemporal hypometabolism on positron emission tomography. Ann Neurol 1996;39:643–9

DeLong G, Heinz E. The clinical syndrome of early-life bilateral hippocampal sclerosis. Ann Neurol 1997;42:11–7.

ASSOCIATION OF IS WITH AUTISM SPECTRUM DISORDERS SAEMUNDSEN ET AL, 2008

- Retrospective case-control study of 95 children (34 boys, 61 girls)
- Cases: children with autism
- Exposure: history of infantile spasm
- OR for ASD with exposure of IS: 5.53 (1.25-23)
- Conclusion: Infantile spasms predicted high risk for ASD, but association was mostly secondary to underlying cause for seizures

Saemunder, Ludvigsson, and Rafnsson. "Risk of autism spectrum disorders after infantile spasms: A population-based study nested in a cohort with seizures in the first year of life." *Epilepsia,* 49(11): 1865-1870, 2008.