Difficult to Treat Childhood Epilepsy:

Lessons from Clinical case Scenario

Charcrin Nabangchang, M.D.

Phramongkutklao College of Medicine

Case #1

A boy with intractable epilepsy

-Onset at 8 years of age, nocturnal GTC for 1 minute

-Numerous seizures shortly after: asymmetrical tonic seizures with versive head turning toward left for 1-2 minutes, sometimes right hand automatism, during both wakefulness and sleep

-Previous EEGx2 at another hospital= generalized spike-waves

-Previous Brain at another hospital MRIx2 normal

***Initial diagnosis**: Primary generalized epilepsy*

-Initially 2-3 times/ month but become almost daily recently

-PHx: no febrile convulsion, no significant past illness

-FHx: no epilepsy

-Development: mild psychomotor-speech delay

Case #1

-MRI 3 tesla at PMK: normal

-EEG: multifocal epileptiform abnormalities, maximal over the right parieto-temporal area and right hemispheric slowing, most prominent over the right parieto-temporal area.

-Prior medications: Topiramate, Levetiracetam, Carbamazepine

-Medications at PMK initial visit (June 17th, 2013): Valproate (VPA) 500 mg/d and Phenobarbital 180 mg/d (VPA level=37.26 mg%, Pb level=30 mg%)

Case #1

-Sequential dose increment of VPA to 1,750 mg/d (VPA level= 68.2 mg%), reintroduction of Levetiracetam (LEV) with dose up to 3,000 mg/d and tapering off Phenobarbital > still several seizures a week!

-Mom requested to stop valproate due to considerable weight gain (BW 107 Kg), more acnes, and itchy skin

-Add Clobazam 5 mg BID and Zonisamide with dose titrated up to 600 mg/d: still had seizures 1-2 times daily> Consider presurgical evaluation

Presurgical Evaluation (Oct 2014)

- ***Summary:***
- *1) Clinical semiology: right frontal symptomatogenic area*
- *2)Interictal EEG: right fronto-parieto-temporal area*
- *3)Ictal EEG: non lateralized*
- *Mri 3 tesla: no detectable abnormalities*

- ***Plan:*** *Ictal/ interictal SPECT, then invasive monitoring with 2 stage surgery*

Progress

- *November 21/2014: Lacosamide 100 mg/d titrated every 2 weeks to current doses of 300 mg/d and tapered off Zonisamide*
- *January 13th, 2015: marked improvement of seizures. Only 2 seizures since last visit on LEV 3,000 mg/d, Clobazam 5 mg/d and Lacosamide 300 mg/d*
- *March 10th, 2015 no seizure*
- *April 28th, 2015 no seizures*
- *July 7th, 2015 no seizures*

Case Presentation:

Girl NR (DOB June 24th, 2014)

A 1 year-old girl with super-refractory epilepsy since 4 days of age

-Born to 17 y/o mother, GA 42 weeks, NSVD, BW 2690 grams, APGAR 8,9 , unremarkable family history

-Day 4: lethargy, poor feeding, body/ limbs jerking

-Day 7: multiple episodes of desaturation and cyanosis, chewing, limbs twitching and eyes deviation/ rolling

Physical Examination:

-No facial dysmorphism, move limbs symmetrically, normal tone, normal head size

-Unremarkable general examination

Case Presentation:

Girl NR (DOB June 24th, 2014)

Investigations:

-Unremarkable sepsis work up (blood/CSF cultures)

-CSF: wbc=5, protein 80 mg%, CSF/ blood glucose 65/156 mg%

-Unremarkable CT brain with contrast (July14)/ Brain MRI (July 14)

-Initial EEG: Burst suppression with multifocal epileptiform discharges, ***DDx= EME***

-Urine organic acid, plasma amino acid, CSF/plasma glycine= normal

Case Presentation:

Girl NR (DOB June 24th, 2014)

Treatment:

-No improvement with IV pyridoxine 150 mg, phenobarbital 20 mg/kg bolus then 5.2 mg/kg/d, LEV 20 mg/kg/dose bolus then 40 mg/kg/d with dose titrated up to 100 mg/kg/d , Topiramate 10 mg/kg/d, Clonazepam 0.09 mg/kg/d

-Ketogenic diet: no response, developed hypoglycemia

-Partial responsed to phenobarbital and MDZ coma:

-Also developed adrenal insufficiency and BPD

-Family conference: no CPR, no intubation, palliative care

-Medications on discharges (Oct 31, 2014): Clonazepam 0.125 mg TID (0.07 mg/kg/d), PHT(50 mg) ¼ tab BID (4.6 mg/kg/d), LEV 125 mg BID (4.6 mg/kg/d), phenobarbital 15 mg BID (6 mg/kg/d), Topiramate (25 mg) 1 tab AM, 1.5 tab PM (15 mg/kg/d), Cortef (10 mg) ¼ tab TID

Case Presentation:

Girl NR (DOB June 24th, 2014)

Admission at 9 months of age (Feb 9, 2015): extremely frequent seizures daily

Treatment at PMK: not response to

-Vigabatrin (500 mg) 1x2pc (200 MKD), D/C April 2015

-phenobarbital (30 mg) ½ tab BID (6 MKD, level=25.2 mg%), D/C May 27, 2015

-Topiramate (25 mg) 3 tabs BID (30 MKD), continued

-Levetiracetam (500 mg) with dose titrated up to1/2 tab TID (150 MKD), continued

-Valproate IV up to 45 MKD, D/C March 2015

-Phenytoin (level 24 mg%), D/C March 2015

-Lacosamide (50 mg) up to 1 tab BID

-B6 100 mg/d

Case Presentation:

Girl NR (DOB June 24th, 2014)

April 2015: Family conference: decision to refer back to her hospital when she is extubated and is stable enough

-Perampanel (2 mg) 1/2tab OD on May 21, 2015, then increased to 1 tab OD> dramatic improvement of seizure control since then

-The child is more awake/ active with much more spontaneous movement

-Current meds: Topiramate (25 mg) ½ tab BID, Levetiracetam (500 mg) ½ tab TID (125 mg/kg/d), Perampanel 2 mg/ d, Lacosamide12.5 mg BID

Drug Resistant Epilepsy:

- *The prevalence of epilepsy was estimated at 7.2 per 1,000 population (Asawavichienjinda T, J Med Assoc Thai 2002)*
- *Approximately 500,000-600,000 Thai epileptic patients*
- *30% continue to have seizures despite treatment or at least 200,000 of Thai epileptic patients*

Natural History of Epilepsy with Onset in Childhood

(Average follow-up = 37 years)

- *Terminal remission: 66%*
- *Early remission 31% (16% continuing to terminal remission, 14% no remission after relapse> **worsening course**)*
- *Late remission: 50% (including 32% who achieved terminal remission without relapse> **remitting courses**)*
- *Remission following any relapse:19% (remitting-relapsing course)*
- *No remission: 19%*

Sillanpaa&Schmidt, Brain 2006; 129:617-24

Difficult to Treat Childhood Epilepsy

- *The tendency of refractory epilepsy to spontaneously remit or fluctuate has been recognized for many years (Neligan et al 2011)*
- *The introduction of a new AED resulted in seizure-freedom for one year or more in 16% of patients with refractory epilepsy and additional worthwhile improvement in 37% (Luciano& shorvon 2007 result of treatment changes in)*
- *In a small cohort study, 10% of pts who failed to respond to six AEDs became seizure free with the seventh agent (Callaghan 2007)*

New Molecular Targets for AEDs

SV2A

Novel binding site for levetiracetam, brivaracetam

$\alpha_2\delta$

Gabapentin , Pregabalin

NMDA Receptor Antagonist

Remacemide

Neuronal Gap Junction:

Tonabersat

AMPA Receptor Antagonist

Talampanel, Parampanel

Slow inactivation of sodium channel

Talampanel, Parampanel

HCN1& HCN2

Pacemaker in thalamic neurons, Lamotrigine

Kv7.2:

CNS voltage-gated, M current K+ channel, Retigabine

Difficult to Treat Childhood Epilepsy

- *Although the evidence suggest that some patients with refractory epilepsy who are likely to be referred for surgery may become AED treated responsive, a few studies identify specific patients or treatment related factors predicting responsibility*

Pediatric Epilepsy Surgery

- *Known poor prognosis of many pediatric epilepsy syndromes argue strongly against delay in surgical referral, especially in epileptic encephalopathy*
- *Delay in definitive treatment is associated with a known potentials for permanent brain damage*

ผู้ป่วยเด็กหญิงอายุ 4 ปี ภูมิลำเนา จ.พิษณุโลก

- Known case epilepsy with intractable seizure
- 1st onset seizure: อายุ 2 ปี 11 เดือน
- Seizure type: เริ่มจากมีแขนข้างขวากระตุกก่อน อีก 5 เดือนต่อมา ผู้ป่วยมีมุมปาก ตา และ ขาข้างขวากระตุกด้วย ระหว่างกระตุกผู้ป่วยสามารถทำตามคำสั่งได้
- Frequency: ช่วงแรกมีอาการ 3-4 ครั้งต่อวัน ตอนนี้เป็นเกือบตลอดวัน
- Interval: อาการเป็นทั้งขณะหลับและตื่น
- ก่อนมีอาการชัก พัฒนาการปกติ เดิน วิ่ง และพูดได้เป็นประโยคสั้นๆ หลังชักพัฒนาการถอยลง ตอนนี้ เดินไม่ได้ พูดได้เป็นคำๆ

ผู้ป่วยเด็กหญิงอายุ 4 ปี ภูมิลำเนา จ.พิษณุโลก

- รักษาที่โรงพยาบาลเชียงใหม่
- Medication:
  - Topamax (25) 125 mg/day
  - Levetiracetam (500) 1,000 mg/day
  - Carbamazepine (200) 600 mg/day
  - Clonazepam (0.5) 1.5 mg/day
- ยังมีอาการชักอยู่ จึงส่งตัวมารักษาต่อ

A 4-year-old boy, Rt handed

- เริ่มอาการชักอายุ 4 เดือน ชักเกร็งกระตุกทั้งตัวประมาณ 1 นาที ไม่ได้พามารพ.
- อายุ 6 เดือน มีอาการกระตุกทั้งตัวนานประมาณ 3 นาที ทานยากันชัก หลังทานยาไม่มีอาการชักอีก ทานยาจนครบ 2 ปี จึงพิจารณาหยุดยา
- อายุ 4 ปี (หลังหยุดยา 1 ปี) มีอาการชักขณะหลับ เริ่มมีอาการจากบริเวณมุมปากขวาจากนั้นตามด้วยใบหน้าข้างขวากระตุก และมือและขาข้างขวากระตุก จากนั้นมีเกร็งกระตุกทั้งตัว เริ่มยากันชักทานอาการไม่ดีขึ้น

A 4-year-old boy, Rt handed

- Previous AEDs: Sodium Valproate
- สรุปก่อนผ่าตัดได้ยากันชัก
  - Topiramate (50) 3-0-3 ½ (10.5 MKD)
  - Oxcarbamazepine (300) 2 ½-0-2 ½ (47 MKD)

3 y/o girl

- Refractory frequent seizures
  - Minor episodes with head dropping
  - Complex partial seizures with secondary generalisation, with initial head drop/minor turn followed by head version to L (sometimes to R).

3 y/o boy with symptomatic localization-related epilepsy

- History of infantile spasm at 6 months and was successfully treated with Vigabatrin and valproate. At age 15 months, developed asymmetrical tonic seizures involving right arm several times a day not controlled by several AED combinations as below:
  - Valproate (40 mg/kg/day and Vigabatrin (up to 150 mg/kg/day),
  - Valproate, Vigabatrin and Nitrazepam 2.5 mg tid. Valproate, Lamotrigine and Nitrazepam
  - Valproate, Topiramate and Nitrazepam

- Despite these AED combinations, he still experienced several seizures a day!

A 13 year-old right-handed girl with chronic epilepsy since the age of 6 years:

- *PI: Her seizures are characterized by stereotyped nocturnal episodes of sudden arousal from sleep with strange feeling of left arm followed shortly by dystonic posturing of left arm with or without versive head turning toward left side.lasting 30-60 seconds. These episodes occur approximately 3-4 times a month.*
- *She has been on almost all antiepileptic medications including Phenobarbital, valproate, carbamazepine, phenytoin. Her current AEDs are Topamax 150 mg bid, Keppra 750 mg bid.*

Epilepsy Surgery in Children

- Parents' attitude toward epilepsy surgery in young children
- Effects of ongoing seizures on developing brain
- Brain plasticity
- Risk of surgery in young children
- Several age-specific syndrome, genetic disease, heterogeneous etiology and outcome
- Spontaneous remission not infrequent

Thank You for Your Attention