Rett Syndrome

An Overview

October 4, 2011
Objectives

- **Medical expert:**
  - Understanding of neuropathology and genetics of Rett Syndrome
  - Understanding of the clinical features and co-morbidities
  - Understanding of the work up and differential

- **Collaborator:**
  - Importance of the interdisciplinary team in the management of Rett Syndrome

- **Scholar:**
  - Review of recent research and RCT on folate treatment
Pervasive Developmental Disorders

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)

Autistic Disorder
Childhood disintegrative disorder
Rett Syndrome
Asperger disorder
Pervasive Developmental disorder
Not Otherwise specified

Rett Syndrome

- Neuro-developmental disorder
- Female predominance
- Characterized by:
  - Loss of speech
  - Stereotypical hand movements
  - Gait abnormalities
  - Autism features

Epidemiology

- Prevalence 1: 22,800 between age of 2-18 years
- North American data base
  - Typical 1648
  - Atypical 259
- All racial/ethnic groups affected equally
- No pregnancy risk factors
- Life expectancy age 45
The Genetics

- The Gene: MECP2 gene
- The Chromosome: xq28
- The protein: methyl-CpG- binding protein 2
  - Distributed throughout all tissues
  - Highest concentration in brain

Neuro-pathophysiology

- http://www.youtube.com/watch?feature=player_embedded&v=eYrQoEhVCYA#!
Outcome

- Gene dysregulation (over-expression)
- Decreased length of dendrite growth into cortex
- Defective expression of proteins that initiate expansion
- Possible defect of cytoskeleton component of cortex
- Deficiency of substance P
  - Autonomic dysfunction
More on genetics

- Autosomal Dominant
- 99% de novo mutation
- X- inactivation random within all cells
  - Normal expression of protein in some cells
  - Genotype-phenotype variability
- Other genes: FOXG1, CDLK5
- MECP2 also related to:
  - Autism
  - X-linked MR
  - MECP2- related disorder

http://jmg.bmj.com/content/38/4/217.extract
What about the boys??

- MECP2 mutation in Rett Syndrome almost exclusively from paternal origin
- If boys do have MECP2 mutation is considered lethal
- Born with severe neonatal encephalopathy
The mutations:

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Phenotype</th>
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<tbody>
<tr>
<td>R106W</td>
<td></td>
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<tr>
<td>R133C</td>
<td>Milder</td>
</tr>
<tr>
<td>T158M</td>
<td>More Severe</td>
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<tr>
<td>R168X</td>
<td>More Severe</td>
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<tr>
<td>R255X</td>
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<tr>
<td>R270X</td>
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<td>R294X</td>
<td>Milder</td>
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<tr>
<td>R306c</td>
<td></td>
</tr>
<tr>
<td>C-terminal mutation</td>
<td>Milder</td>
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</tbody>
</table>
The Features

• Stereotypical Hand Movements
  • Unique to each child!
  • Constant during day
  • Finger kneading
  • Clapping
  • Writhing

• http://www.youtube.com/watch?v=53k1EsP5D8k
The Features

- **Microcephaly**
  - Brain growth stops at age 4
  - Deceleration of growth after birth
  - EARLIEST WARNING SIGN
  - Falls from 50%ile to <2%ile by age 4
  - Heart, kidney, liver, spleen arrest growth at 8-12 years

- **Gait disturbance**
  - Broad based
  - Clumsy, ataxic
  - Rock back and forth

- **Extrapyramidal**
  - Bruxism- 97%
  - Dystonia 59%
  - Excessive drooling 75%
  - Rigidity 44%
Stages

Stage 1
- Uneventful pregnancy
- Normal development up to 6 months
- Developmental arrest 6-18 month
- Can last months
- Less eye contact, less play
- Not as cuddly
- Decelerating head growth
- Unprovoked screaming episodes- TT

Stage 2
- Rapid deterioration and regression
- 1-4 years of age
- Can be acute or insidious
- Lose purposeful hand movements
- Develop hand stereotypes
- Develop breathing irregularities, sleep dysfunction
- Autistic behaviours
Stages

Stage 3
- Age 2-10
- Behaviours improve
- Can have less hand movements
- Improved communication – non verbal
- Seizures
- Gross motor changes

Stage 4
- Over age 10 usually
- Late motor deterioration
- Rigidity, bradykinesia, worsened mobility
- Stable communication
- Improved seizures
Co-morbidities

- Autonomic Dysfunction
  - Increased sympathetic tone: cold extremities
  - Apnea and hyperventilation during day
  - CARDIAC: electrical instability
    - Prolonged QTc (>0.45msec)
    - Increased rate of sudden death

- Sleep disturbances- 80%
  - Prolonged wakefulness, irregular sleep times
Co-morbidities

- Respiratory
  - Central apnea/hyperventilation
  - 20-120 sec
  - Associated with hypoxemia/cyanosis
  - Triggered by excitement/agitation
  - Not present in sleep

- Feeding impairment
  - Oropharyngeal dysfunction
  - Upper GI dysmotility
  - GERD

- Growth failure: height and weight <5%ile by age 4-7

- Scoliosis: 50-85%
Co-morbidities

- Epilepsy
  - Between age 5-10: 60% will experience seizures
  - No new cases after 30
  - All seizure types: complex partial, tonic clonic
  - “breath-holding” spells- ?absence
  - Twitching/ falling/ trembling often mistaken for seizures
- Abnormal EEG at age 2
  - Focal/multifocal epileptiform discharges
  - Theta activity in fronto-central regions
Diagnosis

**Typical**

- Meet all diagnostic criteria
  - A period of regression followed by recovery or stabilization
- The main criteria:
  - Partial or complete loss of acquired purposeful hand skills
  - Partial or complete loss of acquired spoken language
  - Gait abnormalities: impaired (dyspraxic) or absence of ability
  - Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms
- Exclusionary criteria for typical RTT are as follows
  - Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurologic problems
  - Grossly abnormal psychomotor development in first six months of life
Diagnosis

Atypical

• A period of regression followed by recovery or stabilization
  • Meet at least two of the four main criteria above
  • Meet at least 5 of the 11 supportive criteria below

• Supportive criteria for atypical RTT are the following
  • Breathing disturbances when awake
  • Bruxism when awake
  • Impaired sleep pattern
  • Abnormal muscle tone
  • Peripheral vasomotor disturbances
  • Scoliosis/kyphosis
  • Growth retardation
  • Small cold hands and feet
  • Inappropriate laughing/screaming spells
  • Diminished response to pain
  • Intense eye communication - “eye pointing”
Diagnosis

- Always do DNA MECP2
  - Consider FOXG1/CDKL5
- If no MECP2 mutation
  - Brain MRI
  - Serum aa
  - Urine organic acids
  - cGH chromosome 15
  - Hearing tests
  - Vision testing

- Differential
  - ASD
  - Hearing impairment
  - PKU
  - Urea cycle disorder
  - Encephalitis
  - Leukodystrophies
  - Lennox-Gastaut
  - Angelman Syndrome
Management

- The team:
  - Neurology
  - Development
  - Orthopedics
  - GI
  - OT
  - PT
  - Swallowing team
  - Dietitian
  - Cardiologist
  - Pediatrician

- Nutrition:
  - High calorie supplements
  - Oral/G tube fed
  - OT: utensils, consistencies, positioning

- GI:
  - GERD treatment
  - Constipation: polyethylene glycol 3350 17g daily
  - Swallowing dysfunction
Management

- Neurology
  - Video EEG
  - Anti-epileptic medications
  - Education

- Breathing dysfunction
  - No improvement with oxygen
  - Some improvement with Naltrexone and Magnesium citrate
Management

- Cardiac
  - All need EEG
  - May require annual follow up
  - Avoid medications: tCA, erythromycin

- Sleep
  - Routines are crucial
  - Medication options: trazedone, melatonin, clonidine

- Parental Education
  - CPR
  - Fracture risk
  - Daytime routines
    - Avoid daytime sleep
    - No caffeine
    - Evening slow down
  - Reproductive Health
Management

- **Motor:**
  - Spasticity clinic
  - OT/ PT involvement
  - Goal to continue ambulation
  - ?hand elbow restraints – mixed study results
  - Music, horseback riding therapy

- **Scoliosis:**
  - 2009 guidelines: assess spine every 6 months
  - No improvement with bracing
  - Fusion if Cobb angle between 40-50 degrees
Study of the treatment of Rett Syndrome with Folate and Betaine

- **P:** 73 MECP2 mutation diagnosed with Typical Rett Syndrome
  - Split into groups age <5 and age >5
- **I:** Treated with Folate and Betaine for 12 months
  - Double blind, placebo controlled RCT
- **C:** clinical assessments at 3, 6 and 12 months
  - Assessed breathing, hand movements, growth, motor skills, EEG and parent questionnaires
- **O:** No significant improvements found
Questions????

Thank you!
References:


References


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Image: http://jmg.bmj.com/content/38/4/217.extract