Bengt Hagberg

Andreas Rett

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CLINICAL DIAGNOSIS
Rett Syndrome
A Neurodevelopmental Disorder of Young Females Characterized by

- Cognitive Impairment
- Communication Dysfunction
- Stereotypic Movements
- Pervasive Growth Problems
Young friend with Rett syndrome
Rett Syndrome
Temporal Profile

- Apparently normal early development
- Arrest of developmental progress
- Regression including poor social contact and finger skills
- Stabilization: Better social contact and eye gaze; gradual slowing of motor functions
Developmental Skills

- Developmental skills generally acquired
- Developmental skill acquired late in most
- Gross motor and receptive language better than fine motor and expressive language
- More complex motor and communication skills delayed or absent
- As more skills acquired, clinical severity lower
- Better outcomes with R133C, R294X, R306C, and 3’ truncations

Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2

Ruthie E. Amir, Ignatia B. van den Veyver, Mimi Wan, Charles Q. Tran, Uta Francke & Huda Y. Zoghbi  Nature Genet 1999;23:185
Rett Syndrome
Consensus Criteria - 2010

- *Typical or classic RTT*
- Regression followed by recovery or stabilization
- All main criteria and all exclusion criteria
- Supportive criteria not required; often present

**Main criteria:**
- Partial or complete loss of purposeful hand skills
- Partial or complete loss of spoken language
- Gait abnormalities: Dyspraxic or absent gait
- Stereotypic hand movements

**Exclusion criteria:** traumatic brain injury, neurometabolic disease, or severe infection; very abnormal development in first 6 months of life
Rett Syndrome
Consensus Criteria - 2010

- Atypical or variant RTT
- Regression followed by recovery or stabilization
- 2 of 4 main criteria and 5 of 11 supportive criteria

Supportive Criteria: Awake breathing disturbances; bruxism when awake; impaired sleep; abnormal muscle tone; peripheral vasomotor disturbances; scoliosis/kyphosis; growth retardation; small cold hands and feet; inappropriate laughing/screaming; diminished pain response; intense eye gaze

What we know about MECP2 and Rett syndrome!

- Diagnosis based on consensus clinical criteria
- Classic RTT: >95% have MECP2 mutations
- 8 point mutations represent ~ 60%
- Deletions and insertions ~ 15-18%
- Incidence: ~1:10,000 female births
- Mainly sporadic: majority of paternal origin
- Familial Rett syndrome is <<1% of total
- Variant forms account for about 15% of total
  - MECP2 mutations in approximately 75%
**MECP2 Mutations**

**Female Phenotypes**

- Rett syndrome
- Preserved speech variant
- Delayed onset variant
- Congenital or early onset seizure variant
- Autistic-like variant
- Angelman syndrome
- Mild learning disability
- Normal carriers
MECP2 Mutations
Male Phenotypes

- RTT Syndrome
- RTT with Klinefelter syndrome or somatic mosaicism
- Not RTT
  - Severe encephalopathy
- X-Linked MR and progressive spasticity
- MECP2 duplications
MEDICAL ISSUES
Growth

- Small stature is typical
- Deceleration of growth
  - Head circumference as early as 1-2 months; median value at 2nd percentile by age 2 years
  - Weight as early as 8 months
  - Length as early as 12-14 months
- Hands and feet small; feet relatively more so
Weight in Rett syndrome

Age in Years

Weight in Cm

- Rett 98th
- Rett 90th
- Rett 75th
- Rett 50th
- Rett 25th
- Rett 10th
- Rett 2nd
- Normative 98th
- Normative 90th
- Normative 75th
- Normative 50th
- Normative 25th
- Normative 10th
- Normative 2nd
Epilepsy

- Occurrence variable; from 20 to 80% in different reports; ~ 53% in NHS
- Seizure types: focal, generalized, or atypical absence
- Video-EEG monitoring often required to differentiate from non-epileptic behaviors
- ~ 25-30% require medication
- ~6% have used vagal nerve stimulator or ketogenic diet
Sleep

- Often disrupted; frequent awakenings
- Sleep stages abnormal; REM reduced
- Consider infection (otitis media), hunger, constipation, GE reflux
- Sleep study if noisy breathing while asleep to rule out airway obstruction
- Good sleep hygiene essential for all; consider medication when family quality of life adversely affected
Breathing Irregularities

- Hyperventilation, breathholding, or both are common; may notice forced air expulsion
- Occur while awake
- Modified by hunger, agitation, stress
- Typically reach maximum in school years
- Significant air swallowing may occur
- Effective treatment may be elusive
Gastrointestinal Issues

- Chewing and swallowing often poor
- May choke on thin liquids
  - Consider swallow study
- GE reflux typical; it may hurt ... a lot
  - Often require anti-reflux medication
- Untreated may result in esophagitis
- Constipation also common; may require laxative; we recommend Miralax® or MOM
- Gall bladder dysfunction also possible
Nutrition

- Assuring adequate nutrition critical
- Above average daily calorie-protein needs
- Enriched supplements may be required
- Daily vitamin D is essential for bones
- In some instances, gastrostomy feeding necessary
- Use BMI (body mass index) to assess adequacy of nutrition
Osteopenia

- Occurs in almost all girls or women
- Worse with poor calorie-protein intake
- Fractures up to 4 to 5 times more common; may be unrecognized
  - Sudden limb immobility a big red flag
- Regardless of age, vitamin D (800 IU total/day) and oral calcium essential
- Supplementation should be considered
Scoliosis

- Present in ~8% of preschoolers; ~80% by age 16 years; and 87% by age 25 years
  - Progression should stop at maturity
- Usually apparent by age 8 years
- Curvature often greater if non-ambulatory
- Consider bracing above 25° curve
  - No systematic evidence that it works
- Consider surgery if curvature exceeds 40°
- ~13% will require surgery; most parents feel surgery improved quality of life
Ambulation

- 73% learn to walk, some with assistance
- About 20% lose this ability with regression
- Overall, ~ 50-55% remain ambulatory
  - Orthotic devices may be needed
- Great effort should be exerted to maintain ambulation even if assisted
- Standing frames, walkers, or parallel bars should be used at home and school for those who do not walk independently
Sexual Maturation

- Puberty onset premature; 25% prior to age 8; B2 to menarche = 3.9 yr (Normal = 3.0)
- Median ages: B2 = 9.3 yr (Normal = 10.0); PH2 = 10.0 yr (Normal = 10.5)
- Age at menarche = 13.0 yr (Normal = 12.5)
- Synchrony reversed: synchrony in 52%, but 15% thelarche first; 32% adrenarche first
- Increased BMI predicted early B2 and PH2; ‘milder’ mutations predicted earlier menarche

Cardiac Conduction System

- Cardiac conduction may be immature
- Prolonged QT interval observed in 18-20%
- At diagnosis, an electrocardiogram (EKG) should be obtained; likely to be normal
- A cardiologist should evaluate if abnormal; medical treatment should be effective
- If abnormal, other family members should be checked
Autonomic Nervous System

- Hands and feet tend to be cool to cold
- More likely in lower extremities; may have red or purple discoloration involving much of lower extremity
- Thought to be due to increased threshold of sympathetic nervous system
- Does not appear to cause discomfort
- No specific treatment available
Bruxism or Teeth Grinding

- Occurs in almost all girls or women
- Described by Bengt Hagberg as the sound of slowly uncorking a bottle of wine
- Varies in frequency and intensity
- May increase with anxiety or excitement
- Efforts to reduce generally unrewarding
- Tend to diminish or disappear with age
Other Motor Systems

- Hypotonia the rule during infancy
- Strength typically normal
- After puberty, motor activities may slow and muscle tone may increase
- In addition to hand stereotyped movements, other movements may be seen
  - Tremor, myoclonus, or choreiform
- Dystonia may be prominent with age
Phenotype-Genotype Correlation

- Clinical severity generally increases with age.
- Ambulation, hand use, and age at onset strongly linked to overall severity.

* Cuddapah et al., J Med Genet 2014.
Caveats

- Same genotype may yield *different* outcome
- X chromosome inactivation may differ
  - XCI (blood from 183) revealed 11% highly skewed, 26% moderately skewed, 51% random, and 12% uninformative
- Genetic background may differ
- Clonal distribution of normal and mutant X chromosomes in brain is different
- Environmental influences affect outcome
**Longevity**

- Overall longevity double Andy Rett’s original group

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<thead>
<tr>
<th>Age in years</th>
<th>% survival</th>
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<tbody>
<tr>
<td>0-10</td>
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<tr>
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Kirby et al., J Pediatr 2010;156:135-138
Recent Report on Survival

- Confirmed survival beyond age 50
- Cardiorespiratory issues lead to difficulties
- Ambulation, adequate weight, and effective seizure control promote survival
- Extreme frailty reported in the 1990’s rarely seen
- Emphasizes results of good diet and effective therapies

Quality of Life

- CHQ: Poor motor function yields fewer behavioral problems; better motor function results in more behavioral issues
  - Could modest improvement in motor function adversely affect behavior?
- SF-36: Parent quality of life: Over time, physical QOL declines whereas mental QOL improves; similar to other disorders
  - Lane et al. Neurol 2011;77:1812-1818.
RESEARCH TODAY
Fostered by Office of Rare Diseases Research, first in Office of Director, now National Center for Advancing Clinical Sciences (NCATS)

- NHS 1: Angelman, Prader-Willi, and Rett syndromes – 2003-09
- NHS 2: Continued same disorders – 2009-14
- NHS 3: New findings modified study targets to Rett syndrome, MECP2 duplication disorder, and Rett-related disorders (CDKL5, FOXG1, and MECP2-positive, non-Rett) – 2014-2019
The Current Team

Baylor College of Medicine
Children’s Hospital Boston
Children’s Hospital Oakland
Children’s Hospital Philadelphia
Greenwood Genetic Center
Rush Medical School
University of Alabama Birmingham
University of California San Diego
University of Colorado
University of Rochester
Vanderbilt University
NIH/NI CHD and NI NDS

Patient Advocates
Retts syndrome.org
Rett syndrome research trust
CDKL5
FOXG1
MECP2 Duplication Disorder

Team Leaders
Alan Percy – PI
Jeff Neul – Admin. Leader
Walter Kaufmann – Co-I
Jane Lane – Prog. Manager
Steve Kaminsky – Co-I
Natural History Study 3

- RTT, MECP2 Duplication, CDKL5, FOXG1, MECP2 positive-Non-RTT
- Enrollment in new NHS proceeding
- 5211: Longitudinal study of core features
- 5212: Advanced neurophysiologic correlates
- 5213: Biomarker outcome measures
- Pilot studies
  - 5214: Behavioral outcome measure
  - Metabolomics approach
Knock-out Mutant

- Is MeCP2 knock-out reversible?
- Using estrogen receptor controlled MeCP2 promoter:
  - MeCP2 knock-out phenotype reversed in both immature male and mature male and female mice
  - Rapid re-expression in immature males resulted in death in 50%
PHARMACOLOGIC APPROACHES
Prior Clinical Trials

- Lamotrigine for seizures
- Bromocriptine for motor performance
- Naltrexone for periodic breathing
- Folate-betaine to increase methyl-binding

- Little benefit aside from improved seizure management with lamotrigine
Gene Therapy

- Gene correction
  - Problem: Correcting only abnormal allele

- Stem cell transplant
  - No effect in symptomatic male mice; some improvement in asymptomatic females
  - Noted positive response in microglia
  - Suggests role for pharmacologic approach

- X chromosome activation of normal allele
  - Critical: activate normal allele in all cells
Symptomatic Therapy

- Serotonin reuptake inhibitors
  - ameliorate anxiety
- NMDA receptor blocker: Memantine
  - reverse glutamate hyperexcitability
- IGF-1: full length and tri-peptide
  - downstream effect in BDNF cascade
- BDNF-mimetics: TrkB agonists
  - restore BDNF levels
- Read-through compounds: Stop mutations
  - produce full length MeCP2
My First Friend with Rett Syndrome