Rett Syndrome: Developmental and Medical Guidelines

Eileen A. Dolan, M.D.
Institute for Child Development
Joseph M. Sanzari Children’s Hospital
Hackensack University Medical Center
Objectives

- Review the diagnostic criteria and recommended genetic testing for Rett Syndrome.
- Review the evidence-based care recommendations for the management of children diagnosed with Rett Syndrome.
- Discuss recent research studies and directions for future research.
Rett Syndrome (RTT)

X-linked neurodevelopmental disorder almost exclusively occurring in girls

Prevalence of one in 10,000 to 23,000 female births

Less than 1 percent of recorded cases are inherited

Most cases are sporadic/mutation occurs randomly, mostly during spermatogenesis
• Characterized by a period of typical development, followed by stagnation in development and regression, particularly in the areas of fine motor skills and communication
• Distinctive pattern of hand movements
• Acquired microcephaly
• Described in 1966 by Andreas Rett
• First described in English by Hagberg in 1983
• 1999 – mutations in MECP2 gene reported
• Most often caused by mutations in the MECP2 gene, which is found on the X chromosome
• MECP2 gene contains instructions for the synthesis of a protein called methyl cytosine binding protein 2 (MeCP2)
• MeCP2 acts as a biochemical switch that tells other genes when to turn off and stop producing their own unique proteins
• MECP2 gene does not function properly in those with Rett syndrome → insufficient amounts or structurally abnormal forms of the protein are formed

• The absence or malfunction of the protein is thought to cause other genes to be abnormally expressed
• The majority of girls with Rett syndrome have the MECP2 genetic mutation
• Remaining cases may be caused by partial gene deletions, by mutations in other parts of the gene, or by genes that have not yet been identified
• Mutations in CDKL5 are believed to cause an atypical form of Rett Syndrome called the early-onset seizure variant.
• Greater than 95% of cases of classic RTT are caused by a mutation in the MECP2 gene.
• Therefore, genetic testing is recommended if RTT is suspected.
• However, a MECP2 mutation is not specific to RTT, and this mutation is not necessary to make a diagnosis of RTT.
Diagnostic Criteria

- Apparently normal prenatal and perinatal history
- Apparently normal early development
- Postnatal deceleration of head size for most children
- Loss of achieved purposeful hand skill (½ - 2 ½ years)
- Regression in social interaction/interest, motor skills, communication, cognition, and gait dysfunction
- Development of stereotypic hand movements
- Gait disturbance (dyspraxic or failing locomotion)
Diagnostic Criteria

• Absence of:
  – Organomegaly
  – Optic atrophy
  – Retinal changes
  – Intrauterine growth retardation
Children with RTT typically progress through four clinical stages:

1. **Stage I** Early-onset stagnation
2. **Stage II** Rapid developmental regression
3. **Stage III** Pseudostationary period
4. **Stage IV** Late motor deterioration*

*A few patients with early serious neuromotor impairment never learn to stand and walk, and thus do not enter stage III, but progress directly from stage II to stage IV*
Stage I

- Onset: 6 months to 1.5 years
- Developmental progress delayed
- Developmental pattern still not significantly abnormal
- Duration: weeks to months
Stage II

- Onset: 1 year to 3 or 4 years
- Loss of acquired skills/communication
- Mental deficiency appears
- Duration: weeks to months, possibly one year
Stage III

- Onset: after passing stage II
- Some restitution of communication
- Apparently preserved ambulant ability
- Inapparent, slow neuromotor regression
- Duration: years or decades
Stage IV

- Onset: when stage III ambulation ceases
- Complete wheelchair dependence
- Severe disability; wasting and distal distortions
- Duration: decades
• Multiple problems occur in individuals with RTT, involving the cardiovascular, respiratory, gastrointestinal, musculoskeletal and neurologic systems, among others
• Particular developmental and behavioral patterns are also observed
Management Recommendations
by System
Cardiovascular

Reduced Heart Rate Variability

• Prolonged QTc (9-55%) – increases risk of developing life threatening arrhythmias

• Poor peripheral circulation

• Findings may be present at the time of diagnosis, however, they may also develop with later stages
Recommendations

1) Obtain ECG at diagnosis
2) If ECG is normal, repeat periodically (every few years)
3) If ECG is abnormal, refer to cardiologist
   - Cardiologist may monitor, or start medication (beta blocker) if indicated
3) If abnormal QTc, avoid medications which can lead to further QTc prolongation: antipsychotics, tricyclic antidepressants, prokinetic agents, antiarrhythmics, and some antibiotics (erythromycin, ketoconazole)
Dental

• Bruxism
• Secondary effects of medication

• Recommendation
  – Referral to dentist accustomed to working with children with delays
Development/ Behavior

• Limited verbal communication
• Limited fine motor skills
• Loss of ambulation
• Repetitive/stereotypic behaviors
• Anxiety
• Periods of laughter, crying, screaming
• Social withdrawal
Recommendations

1. Early Intervention programming
2. Evaluation by Speech Pathologist (communication assistance, feeding evaluation)
3. Braces have been used to limit hand movements, with limited evidence on effectiveness
4. Current trials are investigating the effect of various medications on behavior, social responsiveness, and communication
Gastrointestinal/ Nutrition

- Constipation (81-85%), Reflux (30-40%), Gall bladder disease(3%), Growth restriction, Feeding difficulties (oromotor dysfunction 63%, aspiration ), Low vitamin D, calcium, iron levels
Recommendations

1) Monitor growth parameters throughout lifespan
2) Treat constipation/reflux as in general pediatric population
3) Clinical evaluation of oromotor function at diagnosis, with development of feeding plan
4) Assessment of swallowing function by video-fluoroscopy at onset of clinic signs
5) Consider alternate methods of feeding if unable to safely achieve an adequate nutritional intake
6) Consider calcium supplementation
Growth

Weight in Rett syndrome
0 - 36 months

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Musculoskeletal

- Scoliosis
- Hip dysplasia
- Contractures
- Osteopenia
- Fractures
Recommendations

1) Monitor for scoliosis every 6 months, X-ray if evidence of a curve
2) Orthopedic care as indicated
3) Proper positioning and bracing can help minimize complications
Neurologic

- Seizures (86% by 20 years of age)
- Vacant spells
- Increased sensitivity to pain
Recommendations

Medication choice for seizure management should be determined by seizure type

- most commonly used medications are carbamazepine, lamotrigine, and levetiracetam

- Small studies and case reports have shown positive responses to multiple medications, including carbamazepine, lamotrigine, levetiracetam, and topiramate
Respiratory

- Breath holding spells
- Hyperventilation
- Air swallowing
- Pneumonia
Recommendations

1) No treatment indicated for breath holding spells
2) Swallow study if frequent respiratory infections (possible aspiration)
Sleep

• Irregular sleep cycle
Recommendations

1) Monitor for sleep problems and refer for sleep study as indicated by history

2) Melatonin may be beneficial for sleep onset (limited good quality evidence)
Life Expectancy

- Normal survival until age 10

- > 50% survival to age 50 (versus > 95% in all females and 27% in persons with profound motor and cognitive impairments)
• Rett Syndrome Natural History Study
• Rett Syndrome Clinical Trials
• Animal Models
• A Phase 2A Randomized, Placebo Controlled Trial of EPI-743 in Children with Rett Syndrome
• Safety Study of NNZ-2566 in Patients with Rett Syndrome
• Treatment of Rett Syndrome With Recombinant Human IGF-1 (Mecasermin [rDNA]Injection)
• Placebo-controlled Trial of Detromethorphan in Rett Syndrome
• Autonomic Dysfunction and Seizures in Rett Syndrome
• The Natural History of Osteopenia in Rett Syndrome
• Biliary Tract Disease in Rett Syndrome
Research

• Dr. Adrian Bird: introducing appropriate levels of MeCP2 to mice that are severely compromised by disease will reverse the symptoms
Resources

• www.rettsyndrome.org
• www.rett.com
• THE RETT SYNDROME HANDBOOK: Second Edition
References


• Local Expert Consensus (2011). "During guideline development timeframe.".


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