Rett 101 – notes for talk at ORSA meeting, September 2010

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Sometime in the mid-1950's Andreas Rett (an Austrian pediatrician) saw two unrelated patients with identical hand mannerisms sitting next to each other in his waiting room and first recognized the main clinical features of the disorder that was to bear his name. He published his first case series of 22 patients (in German) in 1966. The disorder came to international attention in 1983 with the first multi-center case series published in English (Bengt Hagberg and colleagues). The relevant gene, MECP2, was first recognized in the mid-1990's; mutations in the gene were identified as the pre-eminent cause of Rett syndrome (RTT) by Zogbi and co-workers at Baylor University in 1999.

The principal features of RTT, as originally put forward by Rett, include: female gender; normal status from birth to at least age 6 months; progressive slowing thereafter in the rate of head growth; partial or complete loss of functional hand use with the adoption of a characteristic hand-washing posture (age 12-30 months); partial or complete loss of acquired expressive language (if any); the development of involuntary hand movements or tremor (usually by age 3). Even if there is no retained speech in girls with RTT, eye contact and interest in surroundings are usually good. Some girls eventually learn to communicate and make choices using eye gaze.

The estimated prevalence of RTT in the population is 1:10,000 to 1:22,000, alternatively as 0.5-1.0 per 10,000 females. Recent survival data suggest that 79% of RTT girls remain living at age 25, 70% at age 35 (versus 98% for the general population). The most common cause of death is believed to be a cardiac rhythm abnormality, possibly in the context of an epileptic seizure during sleep.

It is important to recognize that, despite the history of a developmental regression in language and hand function between 1-3 years of age, RTT is <u>not</u> a degenerative disease of the nervous system. The brain in RTT girls is smaller than normal but structurally intact, whether on MR imaging or at post-mortem examination. The principal anatomical abnormality in RTT is a reduction in nerve cell (neuronal) size and in the development of cell processes (dendrites and synaptic spines – see epilepsy notes for explanation of terms). This developmental arrest and difficulty in establishing cell-to-cell contacts in learning situations is believed to stem from a loss of the ability of the mutated gene product (MeCP2) to regulate the normal switching off and on of many other genes that are crucial for normal brain development in toddlers.

As a result of malfunction in the MeCP2 protein, a complex array of medical problems may develop:

1) *epileptic seizures*

   50% of girls with typical RTT develop epileptic seizures in their lifetimes. It is uncommon for seizures to appear before age 2, with the peak age at first seizure being 4 years. Seizures vary in type from major (generalized tonic-clonic convulsions) to minor (loss of awareness, blank look, eye deviation to one side, unilateral limb posturing). Many RTT-associated movement disturbances can be confused with epileptic seizures and only recognized as non-epileptic when captured during an EEG recording.

2) *dystonia and parkinsonism*

Gradually increasing muscle rigidity and dystonia (twisted limb postures) develop in the majority of RTT girls in the second and third decades of life. The problem appears at first in the ankle and shoulder regions, then in the knees, hips, elbows and wrists; finally in the spine and even the face (leading to an expressionless appearance). This problem develops much less often in girls with atypical RTT. The onset of muscle rigidity can be slowed but not stopped by regular physiotherapy; it does not respond well to anti-spasticity and anti-parkinsonism medications.

3) *progressive scoliosis (curvature) of the thoracolumbar spine*

This feature of RTT usually develops toward the end of the first decade and is more likely to be a major problem in girls with muscle rigidity and dystonia. Its progression can be slowed with bracing devices and stopped with spine stabilization surgery.

4) *teeth-grinding, air-swallowing and abdominal distension*

5) *disordered breathing*

Both over-breathing (hyperventilation) and temporary arrests of breathing (apneic episodes) are common.

6) *gait apraxia*

Patients may retain the ability to stand but have difficulty walking because they do not seem to know how to put one foot in front of the other. This phenomenon may be accompanied by so-called "freezing episodes" in which the girl, while walking, suddenly stops and seems unable to move forward for 30-60 seconds.

7) *small hands and feet*

This phenomenon is part of a general reduction in growth (weight and height), especially in girls with classic RTT. As well, peripheral circulation tends to be poor in non-ambulatory patients, the feet and hands often being cold and blue.

8) *gastrointestinal tract dysfunctions*

These include difficulty swallowing with poor oral intake, malnutrition, gastro-esophageal reflux with burning pain in the esophagus and risk of aspiration pneumonia, gallstones and constipation. Long-term follow-up by gastroenterology services is often required.

9) *bone health problems*

In part due to lack of weight-bearing in girls unable to walk, in part possibly due to defective MeCP2 activity in bone, many girls with RTT develop osteoporosis (thin bones) and are at risk for fractures following relatively trivial injuries. Spontaneous vertebral fractures and chronic bone pain may also occur. These problems can be successfully addressed by bone health specialists.

10) *decreased responsiveness to pain*

Although GI tract pain problems are common, RTT girls tend to be relatively insensitive to musculoskeletal pain (fractures), bruises and accidental burns or cuts. In consequence there is often a delay in diagnosing fractures.

11) *episodes of night-time screaming*

RTT girls often have periods of unexplained screaming at night. Sometimes these turn out to be due to abdominal pain from air-swallowing, constipation, gallstones or urinary tract infection. At other times, there is no obvious cause, in which case the

problem may reflect a disordered sleep cycle with frequent wakening, airway obstruction (snoring) or night terrors.

As can be seen from the above list, girls with RTT may eventually require the help of neurologists, orthopedic surgeons, gastroenterologists and bone health specialists. As well, their habilitation programs require the assistance of physiotherapists, occupational therapists, speech and language specialists, dieticians, special educators and social workers. The need for these complex resources is what has led to the development of specialized clinics for the care of children and adults with RTT. These clinics deal not only with classic RTT, as originally defined by Rett, but also with patients having a variety of clinical pictures that do not necessarily look like RTT. These include:

1) Patients with many classic features of RTT but who do not have MECP2 mutations. Some of these girls have mutations in MECP2-related genes like CDKL5 and FOXG1; some have no identifiable genetic cause.
2) Patients with atypical RTT*
3) Girls with MECP2 mutations but few or no features of classic RTT. Many of these have retained speech, ambulation and hand function but have disorders of communication and socialization (pervasive developmental disorder not otherwise specified – PDDNOS). It is for this reason that any girl with unexplained autistic features should be analyzed for a possible MECP2 mutation.

* For the current clinical definitions of classic and atypical RTT, see the Tables that follow.

Table 1 - RettSearch criteria for classic RTT (2010- in press)

- Partial or complete loss of acquired purposeful hand skills
- Partial or complete loss of acquired babble or spoken language
- Gait abnormalities (dyspraxia or inability to walk)
- Stereotypic hand movements
- Period of regression followed by recovery or stabilization

Table 2 – RettSearch criteria for atypical RTT (2010)

- A period of regression followed by recovery or stabilization
- 2 out of 4 remaining main criteria (loss of hand skills, loss of acquired spoken language, gait abnormalities, hand stereotypies)
- 5 out of 11 supportive criteria (see Table 3)

Table 3 – RTT supportive criteria (RettSearch 2010)

- Breathing irregularities
- Bloating/air swallowing
- Harsh teeth-grinding
- Abnormal locomotion
- Scoliosis/kyphosis
- Lower limb muscle atrophy
- Cold, purplish feet, usually growth impaired
- Sleep disturbances including night screaming outbursts
- Laughing/screaming spells
- Diminished response to pain
- Eye communication