

# Pediatrician Alert: When Developmental Milestones are Missed

## RETT SYNDROME NEEDS YOUR ATTENTION

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Rett syndrome is a relatively rare neurodevelopmental disorder that achieved prominence in the early 1980s. Identified predominantly in females, Rett syndrome occurs equally in all ethnic groups with a prevalence of 1 in 10 to 20,000 females. Identification of mutations in the gene, *MECP2* (methyl-CpG-binding protein 2), in 1999 confirmed its genetic basis. More than 95% of females who fulfill consensus criteria for Rett syndrome have a *MECP2* mutation. Yet, Rett syndrome is generally sporadic with a recurrence risk well below 0.5%. Despite significant clinical and neurobiologic advances in recent years, physicians, related health care professionals, and educators remain relatively uninformed

about Rett syndrome. This commentary is designed to alert the medical community about the critical need for timely diagnosis and relevant intervention strategies for this unique disorder.

### HISTORY

In the early 1960s, two European physicians independently recognized Rett syndrome. The first, Andreas Rett, a developmental pediatrician in Vienna, Austria, identified a number of females who had a unique pattern of neurodevelopmental expression following a period of apparently normal development including deceleration in the rate of head growth, loss of purposeful hand skills and communication capabilities including

language and social interaction, and the appearance of stereotypic hand movements. At the same time, Bengt Hagberg, a child neurologist in Göteborg, Sweden, made similar observations. A chance meeting between these physicians generated the first widely-read publication in the *Annals of Neurology* [1]. Within a short time, Rett syndrome was diagnosed throughout the US, and the International Rett Syndrome Association (IRSA) was formed, becoming the clearinghouse in this country and to some extent, worldwide, for parents and other interested persons. Today, the IRSA database contains more than 3500 individuals with Rett syndrome. From the beginning, a genetic basis was suspected due to almost total occurrence in females, twin studies, and vertical transmission from an affected woman to her female offspring. Monozygotic twins, with a single exception, were concordant. After identification of *MECP2* mutations, the non-concordant identical twin pair was explained by unbalanced X chromosome inactivation. Studies on an X chromosome-autosome translocation [2] and familial recurrences [3, 4] restricted the target area to the X chromosome long arm (Xq28), leading to the identification of mutations in *MECP2* [5].



Clinical Picture Rett syndrome has its onset typically between 6 and 18 months of age. Pregnancy and delivery are usually normal; girls appear normal at birth and seem to develop normally in early infancy; and early motor development including sitting and walking appears appropriate. Many develop single words or phrases. However, they are also commonly hypotonic from birth and good babies, perhaps “too good.” During this early period, deceleration in the rate of head growth (as early as 3 months of age) and weight gain may be noted. Microcephaly is noted in about 50%. Deceleration in the rate of linear growth occurs but usually after the first birthday [6]. The first signs are increasing irritability, stagnation or plateauing in the acquisition of motor skills, and then loss of fine motor skills including playing with toys or manipulating objects. These are accompanied by diminished interest in other activities and in socializing with others, giving the appearance of autistic-like interactions. During or shortly after this regression, stereotypic hand movements emerge, generally, but not always occurring in the midline. These consist of hand-wringing,

hand-washing, hand-patting, hand-clasping or hand-mouthing or picking at the clothes. Each girl develops her own repertoire of stereotypies that evolve over time. Hand stereotypies occur only during wakefulness, are often incessant, and tend to be exacerbated by stress or excitement.

Approximately 80% learn to walk, but in a dyspraxic, non-purposeful fashion on a wide base. Gait occasionally features toe-walking, repetitive shifting of weight from one foot to the other, and by the first step being backwards.

Over time, other features including teeth grinding or bruxism, disturbed sleep, and abnormal breathing patterns may occur. Breathing patterns involve breath-holding or hyperventilation, or both. As with stereotypic hand movements, these happen only during wakefulness and increase with excitement or stressful situations. Scoliosis develops in most girls, requiring surgery in about 10%. Other features include GE reflux; GI dysmotility resulting in swallowing dysfunction and constipation; cold, often purplish extremities, more so in lower than upper; osteopenia with increased incidence of fractures; and EKG changes including prolonged QT syndrome.

Consensus diagnostic criteria have been refined recently [7]. These allow for standardized clinical diagnosis of Rett syndrome throughout the world (Table 1a). Variant forms of Rett syndrome are also recognized and criteria elaborated for

their diagnosis. These variants include an early onset seizure type, a congenital form lacking normal early development, a preserved speech variant with some purposeful language, and a delayed form or *forme fruste*.

The temporal profile of Rett syndrome is quite consistent (Table 1b). After the early regression, development stabilizes and interaction and socialization improve, particularly in choice-making and better eye contact. Conversely, during this period seizures may be prominent and irregular breathing may intensify. Later on, hand stereotypies may diminish in their frequency and in their overall expression. The absence of further cognitive loss provides strong support for employing therapies to maximize communication and socialization capabilities and to preserve motor function. Although much work remains, we now have a better understanding of the natural history of Rett syndrome, including survival as well as the many medical issues associated with it [8].

#### **LONGEVITY** \_\_\_\_\_

Rett syndrome is a neurodevelopmental disorder with likelihood of prolonged survival, particularly given the current intervention strategies. In an unpublished study, we noted normal survival through age 10, whereas survival through age 35 was 70% of the normal female population. With proper nutrition and medical care, prolonged survival is likely to be the rule. As a consequence, parents or other caretakers must plan for long-term care.

Sudden death has been described in Rett syndrome, generally of unknown cause, but possibly secondary to seizures, autonomic dysfunction, or a cardiac conduction abnormality.

### **MECP2 MUTATIONS**—————

More than 95% of females fulfilling criteria for Rett syndrome have a mutation in *MECP2*, displaying striking phenotypic variability. Females with such mutations may be completely normal or have clinical features ranging from mild learning disabilities to Angelman syndrome to autism to Rett syndrome. Females who appear normal or have learning disabilities generally share the same mutation as a sibling or child with Rett syndrome, but lack features of Rett syndrome due to favorable X inactivation skewing toward the normal X chromosome. Females with features of Angelman syndrome represent the close clinical overlap during early childhood between the two disorders, and females who have autism but not Rett syndrome reflect either favorable skewing in X inactivation or have a less severe mutation.

Rett syndrome has been identified in males under two circumstances: the first being males with Klinefelter syndrome who have an extra X chromosome making them, in that sense, similar to females [9]; the second being males with somatic mosaicism in which some cells express a normal X chromosome and others express an X chromosome with a *MECP2* mutation [10]. In this case, they resemble females in the sense of balanced X inacti-

vation. Other males have mutations in *MECP2* and do not have Rett syndrome, but rather, a much more severe disorder with motor and respiratory problems present from birth and premature death usually by 1½ years. About half with this progressive encephalopathy have the same mutation as an affected sibling(s) whereas the others represent sporadic occurrences [11]. Still other males demonstrating X-linked mental retardation without Rett syndrome have mutations in the *MECP2* gene. Most recently, males (and one female with the preserved speech variant) have duplication (extra copy) of *MECP2*. These males demonstrate severe cognitive impairment and progressive motor dysfunction (spasticity), but no other features of Rett syndrome [12].

### **DIAGNOSTIC TESTING** —————

Approximately 80% of females who have features of Rett syndrome fulfill the consensus criteria, and of those, more than 95% have a mutation in *MECP2*. Approximately 20% of females with Rett syndrome fall into one of the variant categories whether congenital, early onset seizure, preserved speech, or delayed onset (*forme fruste*). Of this group, approximately 50% have a mutation in *MECP2*. Children, who fulfill diagnostic criteria, whether typical or variant, should be tested for mutations in *MECP2*. This would include young females (6-24 months) who display only some features associated with Rett syndrome such as low muscle tone, deceleration in the rate of head growth, or unexplained develop-

mental delay. With the advent of effective treatment strategies, early diagnosis, prior to full expression of typical features, will be crucial. Testing should include sequencing of the four *MECP2* exons. If sequencing is normal, testing for large deletions should be performed. Health care providers should be aware that sequencing and large deletion testing involves different methodologies and order the tests for large deletions as appropriate.

*MECP2* testing should also be performed for the following individuals: 1) females who demonstrate the characteristics of Angelman syndrome but have normal methylation or mutation studies at the Angelman locus; 2) males with X-linked mental retardation and normal Fragile-X testing; and 3) infants with unexplained neonatal or infantile encephalopathy.

*MECP2* testing is available in a number of different clinical laboratories including those at the Baylor College of Medicine in Houston, Texas, and at the Greenwood Genetic Center in Greenwood, South Carolina.

### **CLINICAL RESEARCH** —————

Current clinical research is focused on refining the clinical aspects of Rett syndrome, including its natural history and effective intervention strategies. The Office of Rare Disease and the National Center for Research Resources within the National Institutes of Health are supporting a natural history study on Rett syndrome. This clinical research consortium has three

principal sites: Baylor College of Medicine, Greenwood Genetic Center in Greenwood, South Carolina, and the University of Alabama at Birmingham. The goal of this consortium is to evaluate and monitor 1000 individuals with Rett syndrome or mutations in *MECP2*. Through this project we expect expand our understanding of the natural history of Rett syndrome and to develop clinical and molecular (phenotype-genotype) correlations with the most common mutations in *MECP2*. The importance of understanding the natural history of Rett syndrome cannot be overstated. If we are to engage in treatment strategies that produce fundamental improvement, we need to know the course of this disorder so that we can judge the efficacy of these interventions as well as recognize untoward consequences that may occur. We are also updating the longevity information by probing the roster of clinical databases including IRSA. We will also be examining the quality of life both of the participants and their principal care providers. Throughout the course of these studies, new avenues for investigation should emerge.

#### **RETT SYNDROME RARE DISEASE CLINICAL RESEARCH SITES**

Data collected at the enrollment sites are transmitted electronically as confidential information to the Data Technology Coordinating Center (DTCC) at the University of South Florida in Tampa. The DTCC maintains an active public website that accepts disease specific contact registrants

([www.rarediseasesnetwork.epi.usf.edu/](http://www.rarediseasesnetwork.epi.usf.edu/)).

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#### **PARENT SUPPORT AND ADVOCACY**

The International Rett Syndrome Association provides support for families dealing with Rett syndrome and advocacy at the national level to promote awareness and generate interest in funding for research, particularly through the National Institutes of Health. IRSA is recognized throughout the world as the single most important source of comprehensive information about the clinical and research aspects of Rett syndrome ([www.rettsyndrome.org](http://www.rettsyndrome.org)).

The Rett Syndrome Research Foundation also provides research funding for promising basic science and transnational research and advocates as well for expanded funding for research at the national level ([www.rsrf.org](http://www.rsrf.org)).

The National Organization for Rare Disorders (NORD) represents the rare disease community by providing an alliance of voluntary health organizations to promote identification, treatment, and cure of these rare disorders through education, advocacy, research, and service ([www.rarediseases.org](http://www.rarediseases.org)).

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**TABLE 1A**

#### **Rett Syndrome Consensus Criteria**

- Normal at Birth
- Apparently Normal Early Development (may be delayed at birth)
- Postnatal Deceleration of Head Growth in Most
- Lack of Achieved Purposeful Hand Skills
- Psychomotor Regression: Emerging Social Withdrawal, Communication Dysfunction, Loss of Learned Words, and Cognitive Impairment
- Stereotypic Movements: Hand Washing/Wringing/Squeezing/Hand Clapping/Tapping/Rubbing; Hand Mouthing
- Gait Dysfunction: Impaired (dyspraxic) or Failing Locomotion

**TABLE 1B**

#### **Rett Syndrome Temporal Profile**

- Apparently Normal Early Development
- Arrest of Developmental Progress
- Frank Regression with Poor Social Contact and Finger Skills
- Stabilization: Better Social Contact and Eye Gaze, but Gradual Slowing of Motor Functions

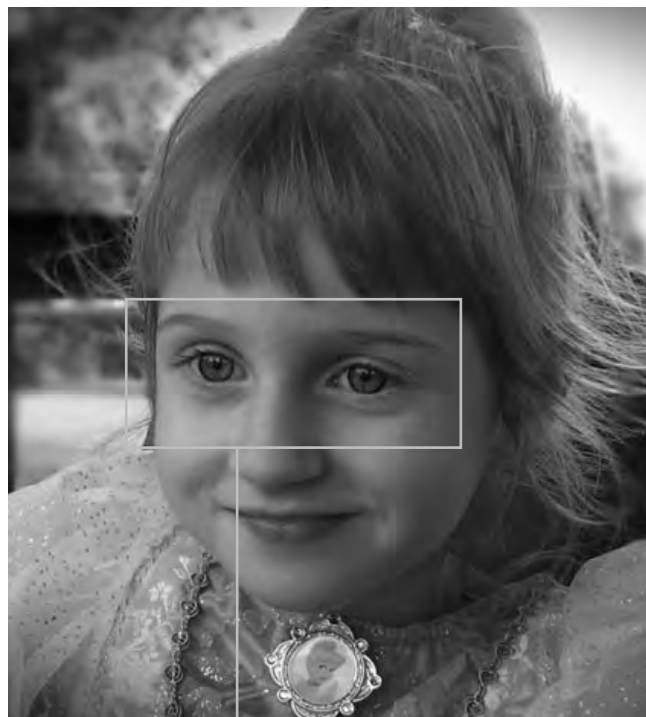


**REFERENCES**

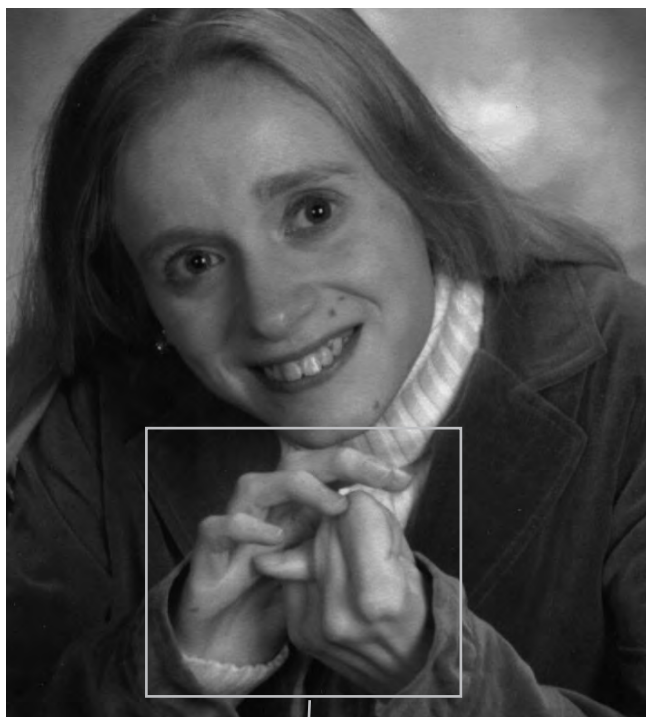
1. Hagberg B et al. A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. *Ann Neurol*, 1983; **14**: 471-479.
2. Zoghbi HY et al. A de novo X;3 translocation in Rett syndrome. *Am J Med Genet* 1990; **35**: 148-151.
3. Ellison KA et al. Examination of X chromosome markers in Rett syndrome: exclusion mapping with a novel variation on multilocus linkage analysis. *Am J Hum Genet*, 1992; **50**: 278-287.
4. Schanen C et al. A new Rett syndrome family consistent with X-linked inheritance expands the X chromosome exclusion map. *Am J Hum Genet*, 1997; **61**: 634-641.
5. Amir R et al. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nature Genetics*, 1999; **23**: 185-188.
6. Schultz RJ et al., The pattern of growth failure in Rett syndrome. *Am J Dis Child*, 1993; **147**: 633-637.
7. Hagberg B et al. An update on clinically applicable diagnostic criteria in Rett syndrome. Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Pediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001. *Eur J Paediatr Neurol*, 2002; **6**: 293-297.
8. Percy AK Lane JB, Rett syndrome: clinical and molecular update. *Curr Opin Pediatr*, 2004; **16**: 670-677.
9. Schwartzman JS et al., Rett syndrome in a boy with a 47,XXY karyotype confirmed by a rare mutation in the MECP2 gene. *Neuropediatrics*, 2001; **32**: 162-164.
10. Clayton-Smith J et al. Somatic mutation in MECP2 as a non-fatal neurodevelopmental disorder in males. *Lancet*, 2000; **356**: 830-832.
11. Kankirawatana P et al., Early progressive encephalopathy in boys and MECP2 mutations. *Neurology*, 2006; **67**: 164-166.
12. Meins M et al., Submicroscopic duplication in Xq28 causes increased expression of the MECP2 gene in a boy with severe mental retardation and features of Rett syndrome. *J Med Genet*, 2005; **42**: e12.



Hand wringing



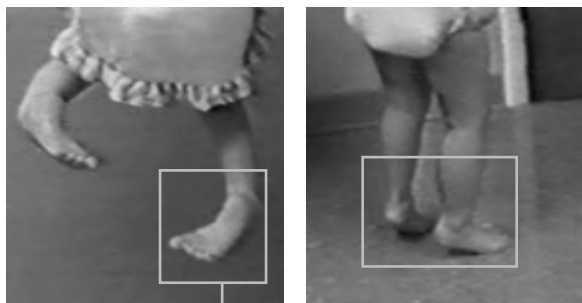
Intense Eye Gaze



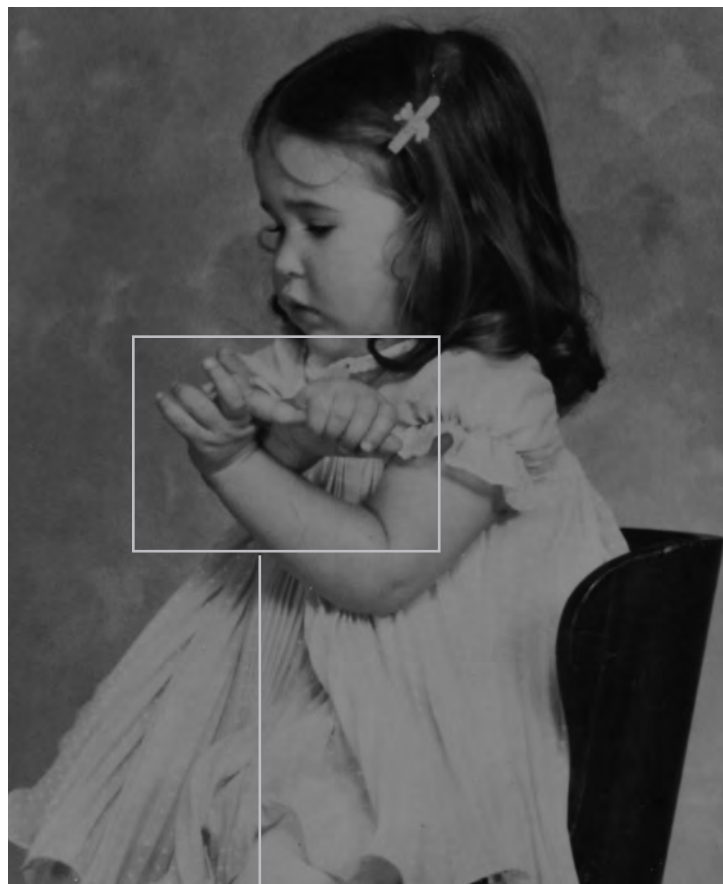
Hand wringing



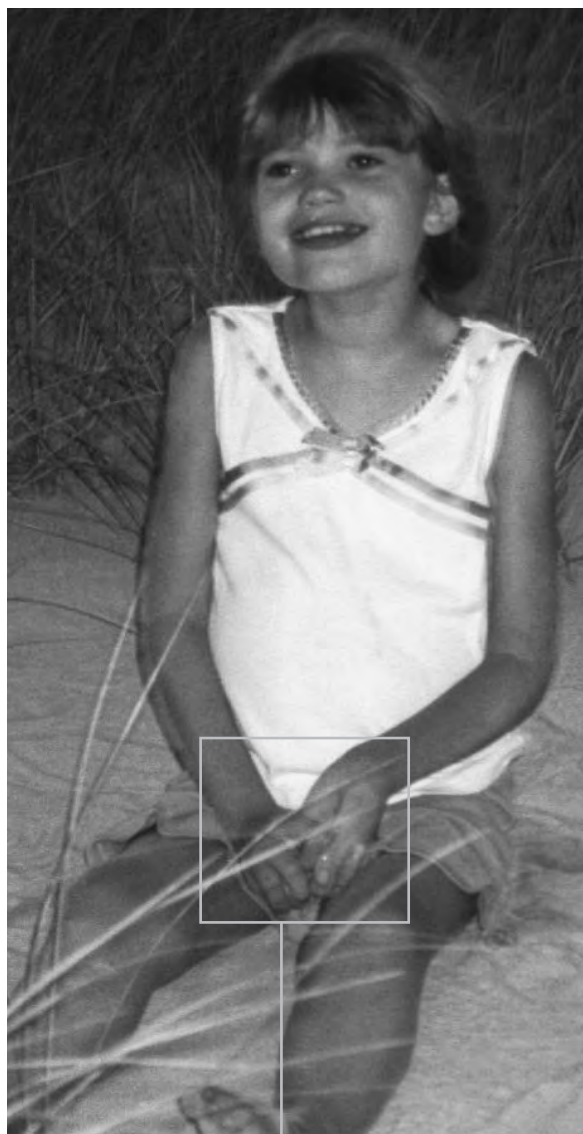
Hand mouthing



Open gait Toe walking



Hand wringing



Hand wringing



Dr. Alan Percy and patient