

Rett Syndrome: Model of Neurodevelopmental Disorders

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Published: 11/02/2005

Abstract and Introduction

Abstract

Rett syndrome is a neurodevelopmental disorder that primarily affects girls, most of whom have mutations in the transcription regulatory gene *MECP2*. However, mutations in *MECP2* also have been identified in normal carrier female individuals, female individuals with mild learning disabilities and features of Angelman syndrome, and male individuals with Klinefelter syndrome or Rett syndrome-like features, fatal neonatal encephalopathy, and familial X-linked mental retardation with or without motor abnormalities. Therefore, molecular testing should be considered for a wide spectrum of individuals. As such, Rett syndrome remains a clinical diagnosis. In this article, we also discuss three recent developments: (1) the recognition of significant gallbladder dysfunction, especially in those 20 years of age or younger; (2) a clinical trial of folate and betaine, which produced no objective improvement but did yield a subjective increase in attention and interaction; and (3) measurement of cerebrospinal fluid folate levels in a large cohort, which yielded normal values, indicating no need for supplementation.

Introduction

Although Rett syndrome has been recognized in the Western Hemisphere for the past 20 years, it was initially described by Andreas Rett in 1965.^[1] At the same time, Bengt Hagberg was evaluating female subjects with the clinical features of Rett syndrome in Sweden. Initial descriptions by Rett and others suggested the pattern of a neurodegenerative condition. However, as we have learned more about this unique disorder, we have come to recognize Rett syndrome as a model of neurodevelopmental disorders. In the following sections, we describe the basis for this view.

Although Rett and Hagberg were evaluating female patients with Rett syndrome virtually simultaneously, they had no direct contact and did not share their experiences for nearly 20 years. After the two met by chance in Canada, Hagberg collaborated with Jean Aicardi in France and Karin Dias and Ovidio Ramos in Portugal to report on 35 female subjects with Rett syndrome in the *Annals of Neurology* in 1983.^[2] This represented the first widely read English-language publication on Rett syndrome. Shortly thereafter, I (A.K.P.) had the opportunity to evaluate a young girl with Rett syndrome in Houston.^[3] Since that time, Rett syndrome centers at the Baylor College of Medicine in Houston^[4] and the University of Alabama at Birmingham^[5] have been established, and several hundred female subjects with Rett syndrome have been evaluated. In 1999, after a lengthy search for the gene responsible for Rett syndrome, Ruthie Amir,^[6] working in the Zoghbi laboratory at the Baylor College of Medicine, identified mutations in *MECP2* in several female subjects with Rett syndrome. Prior to this finding, we and others had come to recognize that Rett syndrome was most likely a genetic disorder that predominantly affected female individuals, occurring worldwide in all racial and ethnic groups, with a prevalence of between 1 in 10,000 and 1 in 20,000 female individuals.

Today, we understand that Rett syndrome is a neurodevelopmental disorder of young female individuals characterized by profound cognitive impairment, communication dysfunction, stereotypic movements, and pervasive growth failure. Clinical criteria for the diagnosis of Rett syndrome were promulgated in the 1980s^[7] and later refined.^[8] However, it became clear that application of these criteria and their translation from English resulted in some confusion and misunderstanding in other regions of the world. As a result, a consensus conference was held in 2001 in Germany prior to the European Pediatric Neurology Society Meeting. At that time, an international group of investigators met and crafted a set of consensus criteria for Rett syndrome^[9] to address the concerns noted above (Table 1).

Table 1.

Normal at birth
Apparently normal early development (can be delayed at birth)

Postnatal deceleration of head growth in most
Lack of achieved purposeful hand skills
Gait dysfunction: impaired (dyspraxic) or failing locomotion
Stereotypic movements: hand washing/wringing/squeezing; hand clapping/tapping/rubbing; hand mouthing
Psychomotor regression: emerging social withdrawal, communication dysfunction, loss of learned words, and cognitive impairment

Rett Syndrome 2001 Consensus Criteria

To summarize, individuals with Rett syndrome are regarded as normal at birth. Early development also appears to be normal, although it is recognized that some individuals with Rett syndrome can be delayed already from birth. Shortly after birth, deceleration in the rate of head growth occurs in most individuals with Rett syndrome and can be seen as early as 3 months of life. Although early hand skills are generally achieved, the ability to perform purposeful hand skills becomes severely impaired if not lost. Evidence of psychomotor regression with social withdrawal suggesting an autism-like picture, communication dysfunction-including loss of learned words and responsiveness to commands or gestures-and evident cognitive impairment also occur. Simultaneously or shortly thereafter, unusual stereotypic movements of the hands appear during waking hours. Less obvious stereotypic movements of the feet or oral musculature can be noted, especially if the hands are restrained. Hand stereotypies can consist of hand washing, hand wringing, and hand squeezing or hand clapping, hand tapping, and hand rubbing. Some female individuals will engage in hand mouthing or pulling at their hair or clothes. In general, these stereotypies occur with the hands together in the midline. This is not uniformly true because in some cases, one hand will be in the mouth and the other hand pulling at the hair or clothes or tapping another portion of the body. No specific stereotypy is characteristic because each female individual develops her own repertoire, which can evolve over time. Gait dysfunction is evident as well. Approximately 80% of female individuals with Rett syndrome do learn to walk, but their gait becomes very dyspraxic, with aimless or purposeless wandering. Approximately one fourth of those who learn to walk lose this ability.

In addition, individuals with Rett syndrome often exhibit a number of associated features specific to Rett syndrome that occur with variable frequency; that is, each female individual might not have all of these associated features. Such features include breathing irregularities in the form of hyperventilation or breath holding or both and significant air swallowing or bloating, with protuberance of the abdomen. It should be stressed that the breathing irregularities, along with the stereotypic movements, occur only during wakefulness. Bruxism, sounding like the slow uncorking of a wine bottle, as Hagberg has noted (personal communication, 1988), is common. Scoliosis, and to a lesser extent kyphosis, is also common. The response to pain seems to be diminished. Periods of laughing or screaming, for no apparent reason, can also be noted. Sleep is commonly disturbed, including the aforementioned laughing and screaming spells without apparent causation. Hands and feet tend to be cool and, in some cases, cold and discolored. As noted above, growth failure is typical. In addition to deceleration in the rate of head growth, the rates of increase in weight and length also decelerate, such that by age 2 years almost all girls with Rett syndrome are below the 5th percentile for the normal female population.

Rett syndrome has a characteristic temporal profile that differs from that seen in neurodegenerative disorders. Following the period of developmental stagnation and then regression, stabilization occurs, and, indeed, socialization is markedly improved, with intense eye gaze and eye pointing that in many cases results in a meaningful communication system between parents or other caretakers and individuals with Rett syndrome. Motor skills are generally preserved, although a gradual slowing or decline is noted in late adolescence or early adulthood.

About 1990, Hagberg and Skjeldal began to recognize girls or women who displayed the features of Rett syndrome but failed to meet the consensus criteria outlined in Table 1. As such, over the course of the subsequent 10 to 15 years, variant clinical patterns of Rett syndrome have been recognized.^[10] Consensus criteria were promulgated for these in 2001 as well.^[9] These include both main and supportive criteria. To be considered to have variant Rett syndrome, one must meet at least 3 of the 6 main criteria and at least 5 of the 11 supportive criteria. These are detailed in Table 2. The main criteria consist of absence of or reduction in hand skills, reduction in or loss of babble speech, reduction in or loss of communication skills, deceleration in the rate of head growth from the first years of life, the presence of stereotypies (particularly in the hands), and a pattern of clinical involvement mirroring the profile of individuals with Rett syndrome. Namely, the regression stage is followed by a

period of apparent recovery of socialization and communication skills, along with a slow decline in motor function. The supportive criteria as detailed in Table 2 are those already described among the associated features for classic Rett syndrome.

Table 1.

Normal at birth
Apparently normal early development (can be delayed at birth)
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Lack of achieved purposeful hand skills
Gait dysfunction: impaired (dyspraxic) or failing locomotion
Stereotypic movements: hand washing/wringing/squeezing; hand clapping/tapping/rubbing; hand mouthing
Psychomotor regression: emerging social withdrawal, communication dysfunction, loss of learned words, and cognitive impairment

Rett Syndrome 2001 Consensus Criteria

Table 2.

<p>Main criteria</p> <ul style="list-style-type: none"> • Absence of or reduction in hand skills • Reduction in or loss of babble speech • Reduction in or loss of communication skills • Deceleration of head growth from first years of life • Monotonous pattern of hand stereotypies • Rett syndrome disease profile: regression stage followed by recovery of interaction contrasting with slow neuromotor regression
<p>Supportive criteria</p> <ul style="list-style-type: none"> • Breathing irregularities • Bloating/air swallowing • Abnormal locomotion • Scoliosis/kyphosis • Lower limb amyotrophy • Intense contact/eye pointing

- Diminished response to pain
- Laughing/screaming spells
- Cold, purplish feet, usually growth impaired
- Sleep disturbances, including night-screaming outbursts
- Bruxism (harsh sound)

Variant Rett Syndrome 2001 Consensus Criteria

Table 2.

Main criteria

- Absence of or reduction in hand skills
- Reduction in or loss of babble speech
- Reduction in or loss of communication skills
- Deceleration of head growth from first years of life
- Monotonous pattern of hand stereotypies
- Rett syndrome disease profile: regression stage followed by recovery of interaction contrasting with slow neuromotor regression

Supportive criteria

- Breathing irregularities
- Bloating/air swallowing
- Abnormal locomotion
- Scoliosis/kyphosis
- Lower limb amyotrophy
- Intense contact/eye pointing
- Diminished response to pain
- Laughing/screaming spells
- Cold, purplish feet, usually growth impaired
- Sleep disturbances, including night-screaming outbursts

- Bruxism (harsh sound)

Variant Rett Syndrome 2001 Consensus Criteria

To summarize, the temporal profile of Rett syndrome is now well recognized (Table 3). After a period of apparently normal development, affected individuals have an arrest of developmental progress and then demonstrate frank regression with poor social contact and limited finger skills. Beginning around school age, stabilization occurs, with better social contact and eye gaze and the gradual slowing of motor functions. In addition, those individuals with variant Rett syndrome often retain many motor skills, have better social interactions, and retain language in the form of words, phrases, or short sentences.

Table 3.

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

Rett Syndrome Temporal Profile

Additional Facts on Rett Syndrome

We now understand that Rett Syndrome is indeed a genetic disorder that predominantly affects female individuals. It has a variable clinical expression. It is associated with growth failure and consistent neuropathology. Finally, > 80% of female individuals with Rett syndrome have mutations in *MECP2*.^[11] Indeed, for individuals meeting the consensus criteria for classic Rett syndrome described above as implemented at the Baylor College of Medicine and the University of Alabama at Birmingham, more than 95% will have such mutations (Huda Zoghbi, personal communication, 2004).

Data on longevity in Rett syndrome have not been published, although many individuals with Rett syndrome live well into middle age. In studies at the Baylor College of Medicine more than 10 years ago, we found that the survival of female patients with Rett syndrome follows that of the general female population up to age 10 years. By age 35 years, approximately 70% of women with Rett syndrome will be living compared with 98% in the female reference population.

Brain morphology in Rett syndrome is very characteristic.^[12] Brain weight is uniformly less than normal for age. Based on volumetric magnetic resonance imaging, reduction seems to be selective or more significant in frontal and temporal regions and in deep gray matter. Melanin is reduced in pigmented nuclei, such as the substantia nigra. Microscopically, neurons are smaller than normal, with a reduction in the number of dendritic arborizations. Equally significant is the absence of any recognizable disease pattern, that is, no evidence of nerve cell loss or degeneration, as would be expected for a neurodegenerative disorder. Of interest, other neurodevelopmental disorders have a similar pathology.^[11] In Down syndrome, dendritic branches and spines are reduced from early infancy. In autism, cell-packing density is increased and cell size is reduced. In Angelman and fragile X syndromes, dendritic arborizations and spines are reduced.

Molecular Testing

With the identification of mutations in *MECP2* as the molecular basis for Rett syndrome, systematic testing revealed that > 80% of female individuals meeting the consensus criteria for Rett syndrome had mutations in this gene. Although more than 200 different mutations have been identified, 8 common mutations account for approximately 70% of those meeting consensus criteria.^[11] Recently, additional mutational events in *MECP2* have been identified, namely, large-scale deletions that would not be detected by standard polymerase chain reaction-based methodologies^[13,14] and the discovery of mutations in exon 1.^[15] Implementation of all three testing modalities for *MECP2* increases the number of positive tests in those meeting consensus

criteria to > 95%.

The phenotypic spectrum of individuals with mutations in *MECP2* is very broad. In addition to classic and variant Rett syndrome, other phenotypes include normal carrier female individuals, female individuals with mild learning disabilities, female individuals meeting clinical criteria for Angelman syndrome, male individuals with fatal infantile encephalopathy, male individuals with typical Rett syndrome with Klinefelter syndrome (47,XXY), male individuals with Rett syndrome-like features with X-chromosome mosaicism, and male individuals with familial X-linked cognitive impairment with or without motor abnormalities.^[11] When the clinician is faced with this broad array of clinical presentations, the question is "Who should have *MECP2* testing?" At a minimum, the following scenarios should lead the clinician to request mutation analysis in *MECP2* (Table 4). Individuals meeting the criteria for classic and variant Rett syndrome should have such testing, along with male individuals who have an unexplained fatal encephalopathy in infancy or who have Rett syndrome-like features, female individuals with features of Angelman syndrome and normal methylation studies, and male individuals with familial X-linked mental retardation and normal fragile X testing.

Table 4.

Females with typical and variant Rett syndrome features
Infants, especially male, with unexplained progressive encephalopathy
Male individuals with Rett syndrome features
Children with Angelman syndrome features and normal methylation
Children with familial X-linked mental retardation and normal fragile X testing

Who Should Have *MECP2* Testing?

Recent Developments

In the past year, an unusual frequency of gallbladder disease was recognized in girls or women with Rett syndrome (Kathy Hunter, International Rett Syndrome Association, personal communication, 2004). We have known for many years that constipation and swallowing dysfunction, with or without gastroesophageal reflux, are very common in Rett syndrome. These symptoms can be associated with persistent crying or apparent abdominal pain. However, we now realize that gallbladder dysfunction can account for gastrointestinal complaints in Rett syndrome. Through the International Rett Syndrome Association, 34 girls or women with evidence of gallbladder dysfunction were identified. The ages of 29 of the 34 individuals are known, ranging from 3 to 43 years. The age distribution of these individuals is depicted in Figure 1. Remarkably, nearly 45% (13/29) were < 20 years of age. In addition, as shown in Table 5 , two thirds had gallstones and nearly 90% required a cholecystectomy. Two expired, one as a result of the gallbladder dysfunction and one postoperatively. These preliminary data indicate that female patients with recurrent pain that appears to be abdominal in origin and who lack evidence of gastroesophageal reflux or severe constipation should have a comprehensive assessment of gallbladder function.

Table 5.

Feature	Number	%
Gallstones	19	66
Sludge	3	10
Cholecystomy	25	86
Death	2	7

Gallbladder Disease Clinical Status

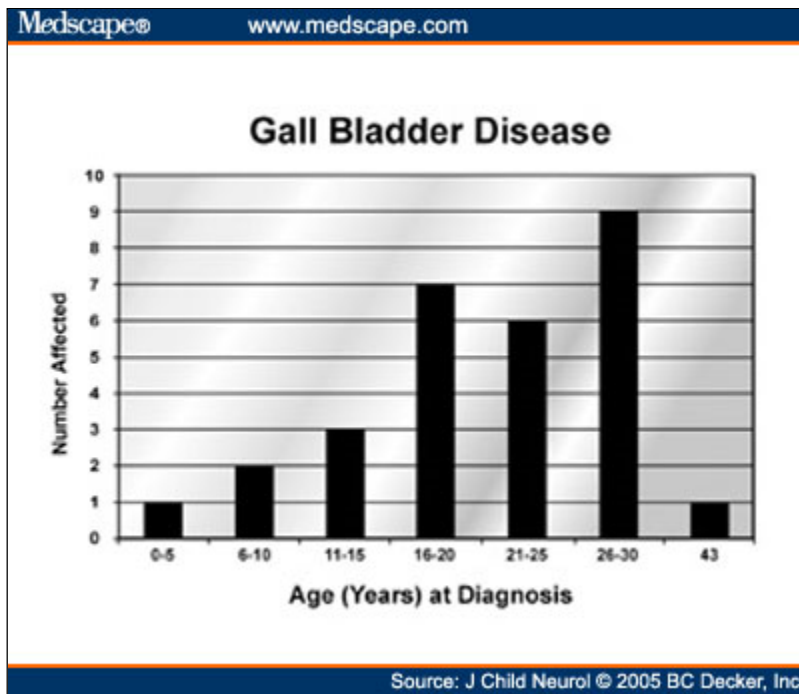


Figure 1. Evidence of gallbladder disease in female individuals with Rett syndrome.

After the identification of mutations in *MECP2*, we conducted a treatment trial at Baylor College of Medicine and the University of Alabama at Birmingham involving folate and betaine. Although data from this trial are still being analyzed, we can say that use of folate and betaine (trimethylglycine) in pharmacologic doses led to no objective improvement. No adverse affects were noted. However, the parents of participants who were receiving the active ingredients reported subjective improvement in mood and attention. Through the two centers, we also conducted an assessment of cerebrospinal fluid folate levels in a large cohort of individuals with Rett syndrome. We studied cerebrospinal fluid folate in 70 female subjects between the ages of 2 and 22 years meeting the criteria for Rett syndrome. Except for one individual who appears to have a systemic problem in folate transport, all cerebrospinal fluid folate levels were within the normal range. These findings do not support the previous report by Ramaekers and colleagues describing four female subjects with Rett syndrome.^[16] That study revealed significantly reduced levels of cerebrospinal fluid folate. Replacement therapy with folic acid produced a response similar to that noted by us in the folate-betaine treatment trial.

Summary

On the basis of clinical and neuropathologic features, Rett syndrome is a model neurodevelopmental disorder that can provide insight into other neurodevelopmental disorders. Clinical diagnosis requires strict application of the consensus criteria for classic and variant Rett syndrome. Mutations in *MECP2* are found in more than 95% of the individuals who meet the consensus criteria for classic Rett syndrome. At the present time, we are engaged in a longitudinal study of female subjects with Rett syndrome at Baylor College of Medicine, the University of Alabama at Birmingham, and Greenwood Genetic Center in Greenwood, SC. We hope that the information gained from this study will set the stage for implementation of clinical trials in the near future.

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Acknowledgments

We thank Kathy Hunter, International Rett Syndrome Association, for valuable input and the many children and families affected by Rett syndrome participating in these studies.

Funding Information

The authors are supported in part by National Institutes of Health grants HD40301 (Program Project), HD38985 (Mental Retardation Research Center), and RR019478 (Rare Disease Clinical Research Center) and University of Alabama at Birmingham General Clinical Research Center grant MO1 RR00032 from the National Center for Research Resources.

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