

# Rett syndrome: from recognition to diagnosis to intervention

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Rett syndrome is a relatively rare neurodevelopmental disorder (incidence: approximately one out of 10,000 female births) that reached worldwide prominence in the early 1980s. Owing to its overwhelming predominance in females, Rett syndrome was regarded as a genetic disorder. However, its occurrence is sporadic, with a recurrence risk well below 0.5%. Confirmation was provided by the demonstration in 1999 of mutations in the *MECP2* gene. At present, more than 95% of females who fulfill consensus criteria for Rett syndrome have a mutation in this gene. Over the past 25 years, understanding of the clinical features and natural history of this unique neurodevelopmental disorder has evolved dramatically. However, large segments of healthcare professionals and the general public still remain relatively uninformed. This review details the clinical picture of Rett syndrome and the diagnostic strategies required, explores the critical medical issues and recent advances in molecular neurobiology, provides an overview of intervention strategies that have been developed to date and sets the stage for future treatment trials as novel, and potentially effective, pharmacologic or molecular interventions become available.

**KEYWORDS:** genotype • medical issues • methyl-CpG-binding protein 2 (*MECP2*) • mutations • neurobiology • phenotype • Rett syndrome • treatment

Physicians and related healthcare professionals, basic scientists and educators are, generally, uninformed about Rett syndrome (RS). Indeed, RS is a relative newcomer to the field of neurodevelopmental disorders. Despite being one of the 'new kids on the block', significant advances have emerged in recent years regarding our understanding of the clinical features, molecular genetics and neurobiology of RS, particularly following the recognition that mutations in a gene, *MECP2*, are responsible. In the absence of a fundamental therapy, serious energies have been directed to developing rational intervention strategies. Excitement was generated within the past year by the potential for reversing the devastating consequences of RS [1,2]. Through molecular manipulation, a mouse model for RS was engineered to allow activation of *Mecp2* once the mice had developed the clinical phenotype associated with absence of this gene. At the same time, studies in another mouse model provided important new information on the molecular neurobiology of RS [3,4]. These studies allowed

the authors to suggest a neuroendocrine component involving elevated corticotrophin-releasing hormone (Crh) and elevated corticosterone levels (cortisol in humans) in the pathobiology of this disorder. Taken together, the findings support the notion that the clinical features of RS could be modified by appropriate interventions and suggest at least one potential avenue for doing so. This review provides background information on RS, including diagnosis, medical issues, genetics and molecular neurobiology, and explores potential therapeutic strategies.

## History

Rett syndrome is a relatively rare neurodevelopmental disorder found almost exclusively in females. RS was recognized independently in the early 1960s by two European physicians, Andreas Rett in Vienna and Bengt Hagberg in Göteborg, Sweden. However, widespread prominence was not achieved until 1983 following a chance meeting between them, which generated

the first widely read description [5]. Within a short time, RS was diagnosed throughout the USA, and the International Rett Syndrome Association (IRSA) was formed, becoming the information clearing house in this country and, to some extent, worldwide. RS has been identified across the world in all racial and ethnic groups with an incidence approximating one in 10,000 females [6]. In the 1980s, RS was already presumed to be X linked, based on almost total occurrence in females, twin studies and vertical transmission from an affected woman to her female offspring [5]. Detailed molecular studies taking advantage of an X chromosome-autosome translocation in one girl with RS [7], and several instances of familial recurrence [8,9] restricted the X-chromosome target area to Xq28, a gene-rich region where *MECP2* resides. In 1999, the identification of mutations in *MECP2* confirmed its genetic basis [10]. Nonetheless, RS is generally not transmitted from generation to generation but is sporadic: the recurrence risk is well below 0.5%. At present, more than 95% of females who fulfill consensus criteria for RS have a *MECP2* mutation [11]. In the North American databases, 91% of females who met consensus criteria for RS and who had *MECP2* testing had a mutation [12]. This number is lower because testing for large deletions was not conducted routinely in this cohort.

### Diagnosis

The diagnosis of RS is based on recently refined consensus diagnostic criteria [13]. These criteria provide the basis for standardized clinical diagnosis of RS throughout the world (Box 1). Approximately 85% of females with RS will fulfill these criteria. The remaining 15% have one of several variant forms for which diagnostic criteria [13] have also been elaborated (Box 2). 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*. 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 RS, such as low muscle tone, deceleration in the rate of head growth, or unexplained developmental delay or frank regression. With the advent of effective treatment strategies, early diagnosis prior to full expression of typical features will be crucial. Individuals meeting consensus criteria, of whom 95% or more will have a mutation [12], should have molecular genetic testing for mutations in *MECP2*. Such testing should include sequencing of the four exons associated with this gene, as well as testing for large-scale deletions in those individuals who have negative results by standard sequencing analyses. For those mutations identified by sequencing, the vast majority will occur in exons 3 and 4. Of the individuals meeting variant criteria, 55–60% will have a mutation [12]. It is critical that healthcare providers be aware that sequencing and large deletion testing involve different methodologies. Analyses for large deletions should be requested whenever sequencing fails to identify a mutation.

*MECP2* testing should also be requested for females who demonstrate the characteristics of Angelman syndrome but have normal methylation or mutation studies at the Angelman locus. Males with features of RS or with X-linked mental retardation and normal Fragile-X testing, and infants with unexplained neonatal or infantile encephalopathy, should also be tested [14]. Recently, males with cognitive delay, little or no speech, and an unusual gait, with or without recurrent upper respiratory infections, have been described in association with duplications of *MECP2* [15–20]. These individuals should have deletion/duplication or comparative genomic hybridization (CGH) array testing [19].

*MECP2* testing is available in a number of different clinical laboratories throughout the world. In the USA, these include the Baylor College of Medicine in Houston (TX) and the Greenwood Genetic Center in Greenwood (SC).

### Genetics

More than 95% of females fulfilling criteria for RS have a *MECP2* mutation [11]. More than 200 distinct mutations have been identified, but eight common mutations (four nonsense and four missense mutations) account for most individuals with RS. In the recently published North American database [12] and in the International Rett Syndrome Association-funded Australian RettBase, the four most common mutations are T158M, R168X, R255X and R270X. Missense mutations represent 39.0%, nonsense mutations 35.2%, large deletions 6.4% and C-terminal truncations 8.8% of the total mutations in the North American cohort. As stated previously, the number of large deletions is likely to be underrepresented in this cohort because of incomplete testing in some females, especially those diagnosed prior to 2000.

Phenotypic variability may be striking [12]. Females with such mutations may be completely normal or have clinical features ranging from mild learning disabilities, to Angelman syndrome, to autism and to RS. Females who appear normal or have learning disabilities generally share the same mutation as a sibling or child with RS, but lack features of RS owing to favorable skewing of X-chromosome inactivation. 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 RS reflect either favorable skewing in X-chromosome inactivation or less severe mutations.

Rett syndrome has been identified in males who have an extra X chromosome (Klinefelter syndrome) [21] and in males with somatic mosaicism, some cells expressing normal X chromosomes and others expressing *MECP2* mutation-bearing X chromosomes [22]. These males resemble females with balanced X-chromosome inactivation. Most males with *MECP2* mutations display a much more severe progressive encephalopathy with motor and respiratory problems present from birth or early infancy and premature death often by 1–2 years. Approximately 50% have the same mutation as an

**Box 1. Consensus criteria: typical Rett syndrome.**

- Normal prenatal and perinatal periods
- Normal at birth and apparently normal early development (may be delayed at birth)
- Postnatal deceleration of head growth in most cases
- Lack of achieved, purposeful hand skills
- Psychomotor regression: emerging social withdrawal, communication dysfunction, loss of learned words, and cognitive impairment
- Stereotypic movements during wakefulness: hand washing/wringing/squeezing/clapping/tapping/rubbing, hand mouthing; finger rubbing
- Gait dysfunction: impaired (dyspraxic) or failing locomotion

affected sibling(s), whereas others represent sporadic occurrences [14,15]. Still, other males demonstrate only X-linked mental retardation. A majority of these males will have a duplication of the Xq28 locus including *MECP2*. Based on the numbers presently reported, this *MECP2* duplication disorder is likely to be the most common finding in males associated with *MECP2* mutations or extra copy number [15–20].

**Phenotype–genotype correlations**

Clinical severity does depend on mutation type and position. A number of reports have appeared in recent years dealing with the relationships between the clinical picture and the specific *MECP2* mutation. Over time, these analyses have been derived from increasingly larger datasets and, hence, provided greater reliability. In general, mutations more distally in the gene, such as R294X, R306C and C-terminal truncations, produce milder involvement [23]. However, strikingly milder features have also been associated with the R133C mutation that is much more proximal in the gene. Two papers in *Neurology* (one currently in press), support these findings and provide the most extensive published information to date [11,24]. The largest longitudinal dataset is currently held with the NIH-sponsored Rare Disease Clinical Research Network data repository. Preliminary analyses of data from more than 400 participants substantiate the general conclusions noted previously [25]. Any conclusions derived solely from mutation type and position will most likely be affected by other factors, the most prominent being imbalances in X-chromosome inactivation or differences in the specific neuronal populations impacted by an abnormal *MECP2*.

**Clinical picture**

Rett syndrome typically becomes evident between 6 and 18 months of age. Before then, most parents report normal pregnancy, birth and early motor and social development, but the infants are, perhaps, ‘too good’. Early development may not be normal, but this is often difficult for parents to discern. Single words or phrases often appear. However, hypotonia or reduced

muscle tone is commonly noted during this early period, and growth patterns are often problematic, including deceleration in the rate of head growth (as early as 3 months of age) and poor weight gain. It should be emphasized that deceleration in the rate of head growth does not necessarily mean microcephaly. Many of these children have head circumferences in the normal range, while in approximately 50% head circumferences decline into the microcephalic range. Indeed, a small number may demonstrate no decline in head circumference growth rate at all, despite having the other features of RS. Deceleration in the rate of linear growth typically follows the first birthday [26]. The first abnormal clinical signs may include increasing irritability with inconsolable crying and stagnation or plateauing in motor development, ultimately leading to frank regression and virtual loss of fine motor skills. It is during this period that autistic-like behavior appears, as contact with others diminishes or is lost. Other communication elements may also be lost, with some appearing as if they do not hear despite normal hearing assessments. Persistent stereotypic hand movements, noted only while awake, emerge during or shortly after this regression period. These may consist of hand-wringing, -patting, -clapping, -squeezing, or mouthing, picking at the clothes or skin, or twirling their hair. Generally, but not always, the hands are held in the midline. Each girl will have her own repertoire of stereotypies that continue to evolve over time. The hand stereotypies often dominate waking moments and tend to be exacerbated by stress or excitement.

Approximately 80% develop independent ambulation (PERSONAL OBSERVATIONS FROM THE UAB DATABASE). However, the gait is dyspraxic and nonpurposeful, generally on a wide base. Toe-walking, repetitive shifting of weight from one foot to the other, and retropulsion (first step is backwards) are common.

Other features may occur, but are not seen uniformly. These include seizures, teeth grinding (bruxism), disturbed sleep, and abnormal breathing patterns consisting of breath-holding or hyperventilation, or both. Abnormal breathing patterns, just like stereotypic hand movements, occur only during wakefulness and increase with excitement or stress. Scoliosis develops in most young females, with approximately 10% requiring surgery [27,28]. Additional features may include gastroesophageal reflux and other evidence of gastrointestinal dysmotility including chewing and swallowing dysfunction, poor stomach emptying and constipation, cold, often purplish extremities (e.g., in the feet), osteopenia with increased incidence of fractures [29] and EKG changes, including prolonged QT syndrome [30].

Rett syndrome has a very consistent temporal profile (Box 3). First comes the period of regression. Then, development stabilizes with disappearance of the autistic-like features and emergence of markedly improved interaction and socialization. Eye contact resumes to a variable degree and the ability to make choices can be developed. However, during this period, seizures and irregular breathing may be much more prominent. These tend to diminish during adolescence or somewhat later, along with reduced frequency and intensity of hand stereotypies. The absence of further cognitive loss provides strong support for

**Box 2. Consensus criteria: typical Rett syndrome.**

Main criteria (must fulfill at least three out of the six main criteria):

- Absence or reduction of hand skills
- Reduction or loss of babble speech
- Reduction or loss of communication skills
- Deceleration of head growth from the 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 (must fulfill at least five out of the 11 supportive criteria):

- Breathing irregularities
- Bloating/air swallowing
- Bruxism (harsh sound)
- 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

employing therapies to maximize communication and socialization capabilities and to preserve motor function. This is also in line with the notion that RS is not a progressive disorder and could respond to fundamental therapies aimed at a cure. Although much work remains, we now have a better understanding of the natural history of RS, including survival and the many medical issues associated with it [31].

**Medical issues**

A wide variety of medical issues will be considered in the following paragraphs. Not all girls or women will manifest every one, but the care provider should be aware of them should problems arise that are otherwise unexplainable [31,32].

**Growth**

Pervasive failure of growth is typical. As stated previously, the first evidence is often a deceleration in the rate of head growth already beginning at 3 months of age [26]. Deceleration in the rate of weight gain also appears in the first year of life, and deceleration in the rate of linear growth becomes noticeable after the first birthday. The median value for head circumference approaches the 2nd percentile value for the normal female population by 2 years of age.

Hand and foot growth also diminish, more so for feet than hands [33]. Nonetheless, both tend to be smaller than in the general population. The decline in the rate of foot growth follows the pattern of decline in linear growth rate.

**Epilepsy**

Reported rates for occurrence of epilepsy are quite variable, ranging from a low of 20–25% to a high of more than 80%. Our experience, based on video-EEG monitoring, suggests that as few as 25% of clinical behaviors are epileptic seizures that require medical management [34]. Many of the events that parents, teachers and other caregivers report as seizures are not associated with abnormal cortical discharges when captured by video EEG. However, subtle clinical events identified by video EEG as representing seizures may not be appreciated by parents as such. Seizures may be generalized, focal, or atypical absence in character and, in some small numbers, may represent infantile spasms. Should any question arise regarding the possible occurrence of seizures, video-EEG monitoring is recommended or, at the very least, prolonged ambulatory monitoring with automatic spike-detection capabilities.

The management of seizures in general involves available medications designed specifically to control epilepsy. A number of these medications may be effective (e.g., carbamazepine or oxcarbazepine, valproic acid or sodium valproate and newer medications including lamotrigine, zonisamide and levetiracetam). The importance of being certain that the diagnosis of seizures is correct should be emphasized in order to minimize the number of girls that are placed on these medications.

**Sleep**

Sleep is often disrupted with frequent night-time awakenings, in many instances without evidence of distress but, rather simply, playing in bed, occasionally punctuated by laughter for no apparent reason. On other occasions, sleep is interrupted by evidence of upset or fussiness in which case it is important to be certain that general care issues are addressed, such as the need for diaper change or hunger, or other medical issues, such as constipation, gastroesophageal reflux, or even an intercurrent infection (e.g., an upper respiratory infection, otitis media or urinary tract infection). The importance of ruling out hunger and other gastrointestinal issues cannot be stressed too strongly. Evidence of excessive daytime sleepiness, that is, frequent napping, should alert the clinician to monitor night-time sleep for disruptions that might be caused by airway obstruction during sleep. When studied in detail, it is quite clear that stage rapid eye movement sleep is substantially reduced in RS. In addition, other sleep stages are also abnormal [35].

Good sleep hygiene is essential. Going to bed and awakening from sleep should occur at consistent times. In the morning, the use of a bright light will encourage arousal; in the evening, a dim light will promote going to sleep. If going to and staying asleep are problematic, such that the family life is disrupted or the quality of life is adversely impacted, medications should be considered. Clearly, if the parents are not obtaining adequate rest, their ability to care for their daughter will be adversely affected. Several medications may be effective for achieving sleep. These have included an antihistamine, such as hydroxyzine, as well as other classes, such as the benzodiazepines or

**Box 3. Temporal profile in Rett syndrome.**

- Early development appears to progress normally
- Developmental progress stagnates
- Frank regression ensues with poor social contact and loss of communication and finger skills
- Stabilization during early school-age children with improved social contact, eye gaze and communication skills; motor functions slow down gradually

melatonin. The antihistamines may have initial effectiveness, but for only a short time owing to the development of tolerance. Melatonin may be helpful in inducing sleep, although it may not decrease or prevent arousals during the night. Trazodone and the newer non-benzodiazepine agents, such as zolpidem, may be helpful and safe in promoting a full night of sleep. Chloral hydrate is also an effective medication that can be used safely in quantities up to 50 mg/kg/dose. However, it is most commonly formulated as a liquid that will often be refused because of its taste unless administered by gastrostomy. It may be found as a gel cap and some private pharmacies are able to formulate it in a capsule or as a suppository, very acceptable options.

**Breathing irregularities**

Periodic breathing in the form of breath holding and hyperventilation, or both, is quite common [35]. These activities occur only during wakefulness and are modified by factors such as hunger, agitation and other stressful situations. Irregular breathing usually begins well after the other features of RS are clearly apparent but is typically present by early childhood with a peak of occurrence in the school-age period through to adolescence. Breath holding in particular may be quite prolonged and associated with color changes around the mouth or in the nailbed. These events are not known to cause additional medical problems. Breath holding can be quite subtle and often first apparent by the sudden expulsion of air (air puffing). Breath holding may also be accompanied by copious air swallowing, producing significant abdominal distension. This distension will dissipate on its own during periods of quiet breathing or sleep, but for some girls can be extremely distressful.

Various approaches have been attempted to mitigate the irregular breathing with variable success. Naltrexone or magnesium citrate has been found to be effective in some individuals. Naltrexone has been utilized in doses ranging from 1–3 mg/kg/day. In our own study, we were limited to 1 mg/kg/day. In this study, it appeared that naltrexone was exerting its effect simply by producing sedation [36]. The utilization of any particular agent has not been promoted in the absence of systematic studies showing efficacy.

**Gastrointestinal issues**

Gastrointestinal issues in RS may represent the single most vexing medical issue, covering the gamut from top to bottom [37].

Chewing and swallowing are often performed poorly with evidence on imaging studies of poor coordination in the movement of food from oropharynx to the hypopharynx and dysmotility in transiting the esophagus. Choking is a common complaint, particularly on thin liquids, often requiring the use of thickening agents to obviate possible aspiration. If laryngeal penetration is observed on swallowing or upper-gastrointestinal imaging studies, caution should be given to continuing oral feeding (see following text). Conversely, dry foods may require moistening with liquids such as sauces or gravies.

Gastroesophageal reflux is also common and can be confirmed by swallowing, upper gastrointestinal, or pH probe studies. In some instances, gastroesophageal reflux rises to the larynx. As such, it is important to investigate both primary and secondary aspirations. Antireflux medications should be utilized as needed to inhibit acid production and promote gastric emptying. In the absence of treatment, one runs the risk of developing a chronic or persistent esophagitis, Barrett's esophagus and secondary esophageal changes including cancer, ulceration or stricture. Gastroesophageal reflux may be enhanced by delayed gastric emptying, for which the clinician should be alert and may wish to evaluate with radionuclide study.

Constipation is also a significant problem, further reflecting the poor motility of the intestinal tract. In some instances, stool retention will produce marked enlargement of the colon. In order to prevent the adverse consequences of constipation, a variety of strategies can be employed including GlycoLax (also marketed as MiraLAX<sup>®</sup> or Milk of Magnesia<sup>®</sup>) increased fiber in the diet and adequate fluid intake. This should ensure that a bowel movement occurs every day or two. Some parents have complained that the generic form produces excessive gas.

Finally, gallbladder disease, gallstones or reduced function, appears to be another consideration in RS, related to reduced motility and delayed emptying of the gallbladder. Gallbladder disease has been recognized in the pediatric age range, as well as in adulthood. Of those with gallbladder disease known to IRSA, nearly 40% are under the age of 20 years. In some instances, abdominal ultrasound fails to identify gallbladder disease, suggesting that a hepatobiliary iminodiacetic acid (HIDA) scan should be considered when other explanations for abdominal discomfort are lacking.

In summary, any period of inconsolable crying, apparent distress, night-time awakenings, or undue irritability should provoke a thorough evaluation of gastrointestinal function to consider the problems noted above.

**Nutrition**

Assuring adequate nutrition in RS is critical. It does appear that girls with RS have a well-above average daily protein and calorie intake requirement [38]. As such, particular attention must be given to meeting nutritional requirements and, if necessary, to providing high-calorie nutritional supplements or frequent snacks, including lower cost supplements, such as Carnation Instant Breakfast<sup>™</sup>, and milkshakes with additional

nutritional ingredients. Appropriate vitamin supplementation should be provided. However, one should be aware that nutritional supplements are so enriched in vitamins that excessive vitamin intake must be avoided. As girls with RS tend to be small in stature, it is appropriate to monitor BMI as an indicator of nutritional well-being (BMI is calculated by multiplying the weight in kg by 10,000 and dividing by the square of the patient's height in cm).

When adequate calories cannot be taken by mouth or primary aspiration prevents oral feeding, gastrostomy or gastrojejunostomy feedings are required. Depending on the presence of gastroesophageal reflux, a fundoplication may be required at the same time. Any girl who has failed to gain weight for 6 months to 1 year, or is losing weight, should be considered for this alternative feeding method.

### **Osteopenia**

Osteopenia occurs quite commonly in RS, being more significant in those girls or women who have inadequate calorie and protein intake [29]. Even in those who have adequate calorie-protein intake, osteopenia is present, but to a lesser degree. Owing to the frequency and extent of osteopenia, fractures are much more common [29]. As such, the possibility of a fracture should be considered if use of an extremity ceases suddenly despite the absence of complaints. Fractures often go undetected because of the girls' inability to express and localize pain. Regardless of age, consideration should be given to oral calcium supplementation, beginning in childhood based on recommended daily amounts (preadolescents: 800 mg; adolescents: 1300 mg; adults: 1000 mg and postmenopausal women: 1500 mg). Systematic studies on the occurrence of, and possible therapies for, osteopenia are ongoing at the Baylor College of Medicine (TX, USA) under the direction of Kathleen Motil.

### **Scoliosis**

Scoliosis occurs with increasing frequency in RS, beginning as early as age 5 years and occurring in at least 80% of patients by the age of maturity [28]. Scoliosis tends to be more significant in those girls who are not ambulatory. Scoliosis often progresses dramatically and at curvatures above 40°, corrective surgery should be considered. At lesser degrees of curvature, body jackets have been employed. No systematic studies have been performed to judge their efficacy. However, they remain an option in retarding the progression of scoliosis. Regardless of ambulation status, proper upright positioning is critical, including lateral supports for those in wheelchairs. Once girls with RS have matured and are through puberty, further progression of scoliosis is generally considered to be unlikely.

### **Ambulation**

Up to 80% of girls with RS acquire the ability to walk (PERSONAL OBSERVATIONS FROM THE UAB DATABASE). During the course of their developmental regression, approximately a quarter of this group will lose this ability. Overall, approximately 60% remain

ambulatory [25]. Toe-walking is common, as well as abnormal foot postures in which instances ankle/foot orthoses or other orthotic devices should be implemented. Significant effort should be allocated to maintaining ambulation as long as possible. In those girls who do not walk, standing frames should be employed both at home and at school along with parallel bars to promote supported ambulation.

### **Sexual maturation & gynecologic issues**

As adolescence approaches, puberty should be anticipated. Ordinarily, girls with RS will enter puberty at similar ages to their peers (PERSONAL OBSERVATIONS FROM THE UAB DATABASE). As these young women are quite vulnerable, appropriate consideration should be given to protecting them from unwarranted contact.

Menstrual cycles generally occur with predictable regularity after they have become established (PERSONAL OBSERVATIONS FROM THE UAB DATABASE). Parents or other responsible caregivers may choose to deal with these in the usual fashion or may choose one of a variety of strategies to eliminate or minimize menstrual flow. These include Depo-Provera, birth-control pills, or endometrial ablation. Depo-Provera is not recommended, primarily because it adversely affects bone mineralization, but also because of its long period of action should other side effects arise. The use of birth-control pills is common and completely acceptable. Formulations of levonorgestrel/ethinyl estradiol provide menstrual management for 1 year (marketed as Lybrel®) or for 90 days (marketed as Seasonale® or Seasonique®), such that menstrual flow can be effectively eliminated or minimized.

When unexplained irritability or inconsolable crying occurs, consideration should be given to a possible gynecologic issue. An abdominal ultrasound, as well as consultation with a gynecologist, should be considered strongly.

### **Cardiac & autonomic systems**

A prolonged QT interval and ST-segment changes may be observed with increasing frequency through the age range [30,32]. As such, at the time of diagnosis, an EKG is recommended to assess QTc or other significant abnormality. If normal, repeating the cardiogram in 2–3 years is appropriate. If abnormal, referral to a cardiologist for consideration of an appropriate intervention strategy is indicated. Prolonged QTc is quite treatable problem with medication and should not be overlooked. Should a QT-segment abnormality be identified, it would be appropriate to have other members of the patient's family screened in the event this finding is unrelated to the RS.

The hands and feet tend to be cool to cold in RS. This is more typically noted in the lower extremities and may consist not only of cold but discolored feet, ranging from red and mottled to purple, and extending well up on the lower extremity. This finding is believed to be related to excess sympathetic nervous system tone. No specific intervention is available, but it is important to keep the hands and feet appropriately warm.

### Bruxism

Bruxism (teeth grinding) occurs in virtually all girls at some point in time, varying in frequency and intensity, and exacerbated by anxiety, excitement or stressful situations. The sound created is really quite characteristic, having been described by Bengt Hagberg as that of slowly uncorking a bottle of wine.

Efforts to reduce the teeth grinding are generally unrewarding. Over time, they diminish, in many actually disappearing after school age.

### Other motor system functions

Hypotonia is the rule early in RS. Over time, muscle tone may be increased, representing rigidity rather than spasticity (upper motor neuron signs are generally absent). During this period, motor activities, including hand stereotypies and ambulation persist when present, but their speed slows down.

Other disorders of movement occur, including tremor, myoclonus and choreiform activities [39]. Tremor is particularly apparent upon awakening from sleep or a nap or when placed in an unstable position, such as upright on their feet or on the edge of a chair or lap. Myoclonus may be focal or multifocal and can also be exacerbated by excitement or anxiety. Focal or multifocal dystonia, especially at the ankles and feet and at the wrists and hands, is common, particularly with advancing age. Without proper alignment, contractures can develop at the involved joints, particularly when sitting in a wheelchair for long periods of time without effective mobilization. In those girls who tend to keep their hands together in the midline at the chest level, contractures at the elbows and, to some extent, limitation of motion at the shoulders will develop. Ankle-foot orthoses or elbow splinting may reduce the risk for development of contractures. Botulinum toxin may be effective in alleviating limitations of joint movement.

### Longevity

Unlike the original suggestion that RS is a progressive neurodegenerative disorder, it is now understood to be a neurodevelopmental disorder, with prolonged survival likely. Current intervention strategies are much more aggressive than 20–30 years ago. This alone would be expected to lead to greater longevity. We are aware of many women aged in their 40s and 50s and expect that with proper nutrition and medical care, prolonged survival is indeed likely to be the rule. Few systematic studies of survival have been conducted. A prior unpublished study conducted while the author was at Baylor noted that survival through age 10 years was normal, whereas survival through to age 35 years was approximately 70% of the normal female population. More recently, preliminary information from a cohort of more than 1900 USA and Canadian females indicates at least 80% survival to the age of 20 years and 50% survival for those over 50 years of age (PERCY AK, GLAZE DG, KOZINETZ C, DEL JUNCO D, UNPUBLISHED OBSERVATIONS). These data are similar to those recently reported from Australia [6].

The consequence of prolonged survival is that in many cases parents or other caregivers will themselves be elderly and due consideration must be given to long-term care of these women when their parents are no longer able to provide it.

Sudden death has been described in RS. In most cases the actual cause is unclear, but may well involve autonomic dysfunction or a cardiac conduction system abnormality, such as prolonged QT.

### Clinical research

Current clinical research is focused on refining the clinical aspects of RS, including its natural history and quality of life, both for the participants and their principal care providers, and on developing effective intervention strategies. The current US Clinical Research Consortium has three sites: Baylor College of Medicine, Greenwood Genetic Center in Greenwood (SC) and the University of Alabama at Birmingham, and a data coordinating site at the University of South Florida that maintains a public website [101].

### Molecular neurobiology

Dramatic advances in our understanding of the neurobiologic aspects have occurred over the past few years. These have emanated in large part from molecular neurobiologic studies of *MECP2* in mouse models for RS. Studies in a knockin mouse model demonstrated abnormal social behaviors and poor spatial and contextual fear memory [3]. Similar findings were reported from a knockout mouse model [40]. Knockout mice were shown to have reduced levels of brain-derived neurotrophic factor (BDNF) and mice lacking BDNF had features similar to *Mecp2* knockout mice [41,42]. When BDNF was over-expressed in these mice, onset of Rett-like behaviors was delayed, but brain weight did not increase.

Regulation of breathing is a key abnormality in RS. Reduced levels of norepinephrine and serotonin were observed in the brainstem (medulla) respiratory control pathways in knockout mice and supplementation of norepinephrine stabilized the respiratory control network [43]. Subsequent studies demonstrated that desipramine, an inhibitor of norepinephrine reuptake, improved breathing abnormalities substantially, prolonged survival by several weeks and increased the number of tyrosine hydroxylase-containing neurons in the brainstem [44].

Studies on the longitudinal expression pattern of *Mecp2* in cortical neurons from female knockout mice suggest a change in X-chromosome inactivation status with increasing age, that is, cells that express the wild-type protein increased from 50 to 70%. One might speculate that this change can be related to the pattern of stabilization and improved interaction in older girls [45].

Very recent results suggest a neuroendocrine component to RS. Studies in a knockin mouse model revealed increased corticosterone release and *Crh* expression, not only in the hypothal-

## Key issues

- Consensus diagnostic criteria (both typical or variant) including a deceleration in rate of head growth in most patients, stagnation of developmental progress followed by the loss of fine motor skills and communication (including socialization) and onset of stereotypic hand movements and gait apraxia, together with a consistent temporal profile, provide the basis for standardized clinical diagnosis.
- *MECP2* testing (sequencing of all four exons and deletion/duplication analysis) should be conducted in any child, male or female, meeting consensus criteria, demonstrating an unexplained neonatal or infantile encephalopathy, or having features of Angelman syndrome or X-linked mental retardation in which other molecular diagnostic tests are normal.
- The medical aspects of Rett syndrome (RS) require careful attention, particularly, nutrition, gastrointestinal function, epilepsy and scoliosis.
- Longevity is better understood, with survival beyond 50 years of age now quite likely. This requires careful family counseling and planning for the future.
- Phenotype–genotype correlations are now quite robust, allowing for anticipatory guidance to families.
- Studies in mouse models provide proof of principle that fundamental therapies could reverse the features of RS, in whole or in part.
- Other studies in mouse models suggest a neuroendocrine aspect of RS involving, among others, corticotropin-releasing hormone and providing a potential target for direct or indirect pharmacologic interventions, including agents that would regulate corticotropin-releasing hormone or ameliorate anxiety and fear.
- Perhaps the primary key to early diagnosis and intervention is informing both medical professionals and the general public about RS. Despite the suggestion of reversibility, we intuitively believe that intervention should be early and not late. Implicit in this then, are the development of effective treatment strategies and the availability of a simple, inexpensive, and reliable screening tool.

lamus, but also in the amygdala and stria terminalis [4]. Furthermore, the authors showed that *Mecp2* binds to the *Crh* promoter and may regulate its expression. Mutant *Mecp2* does not bind to this promoter. The amygdala has important downstream connections to autonomic system nuclei subserving gastrointestinal, respiratory and cardiovascular functions. As anxiety and fear are common clinical features in RS, these results provide a potential therapeutic avenue.

Studies in human tissues revealed abnormal developmental progression of serotonin-transporter binding in the brainstem from individuals with RS with increasing age, compared with controls, providing further evidence of dysregulation of gastrointestinal and cardiac responses [46]. Along the same lines, *Mecp2* also regulates *IGFBP3* [47] and *AVP* in brain tissue [48].

## Therapeutic intervention

Individuals with RS require a variety of therapies throughout their lives [49]. These include physical and occupational therapies to promote sitting, standing, ambulation and fine motor functions. Wherever necessary, standing frames and devices to assist with walking should be employed. In some cases, adaptive equipment such as tricycles may be considered and some girls may use small trampolines or treadmills. Hippotherapy and swimming are extremely popular and well tolerated by most individuals with RS. In terms of fine motor skills, goals in therapy must be realistic and, when improvements or advancements do occur, it often requires daily repetition to preserve them.

As they mature, individuals with RS give intense eye contact, which may be employed to develop communication skills, such as choice making, using simple picture boards or sophisticated computer-based technologies. Some girls are able to use their hands to activate switches; others can use ocular devices to acti-

vate switches. These opportunities to make choices in all aspects of their lives ranging from eating, to socializing, to types of entertainment should be maximized. Music seems to be particularly appealing, each girl or woman developing her own preference panel probably based on what music is played within the home.

## Emerging therapeutic strategies

The complexities of gene therapy coupled with the specific requirement to correct only cells with abnormalities in *MECP2* render gene-based therapies for RS problematic at this time. One promising strategy is to identify pharmacologic agents capable of correcting so-called ‘stop’ (nonsense) mutations by reading through the premature stop codon to produce a full-length protein. Efforts are currently underway to develop such agents. This strategy is particularly attractive in that approximately a third of *MECP2* mutations in RS are the nonsense type. Alternatively, therapies directed at known *MeCP2* gene targets, as noted previously for the gene encoding *Crh*, suggest another avenue for therapy. Agents that would directly down-regulate *Crh* might offer the possibility to intervene fundamentally in *Crh*-related systems and, in particular, to modify anxiety and fear that are quite prominent in individuals with RS. Efforts to identify or develop these agents should be considered. Alternatively, an indirect approach would be to employ available pharmacologic agents, such as the serotonin-reuptake inhibitor class of drugs, to address the core problems of anxiety and fear or the norepinephrine reuptake inhibitors to address periodic breathing patterns.

The previously noted abnormal development of serotonin-transporter binding in post-mortem samples of brainstem nuclei from girls or women with RS [46] and the mouse model studies

showing beneficial effects of desipramine, provide additional support for establishing clinical trials of serotonin and/or norepinephrine reuptake inhibitors in order to address the significant dysregulation of gastrointestinal and respiratory function.

### Expert commentary & five-year view

The pace of advancement in understanding the clinical and basic science aspects of RS since the identification of mutations in the *MECP2* gene in 1999 has been extraordinary. To date, studies have expanded the severity range of clinical involvement associated with such mutations to encompass not only RS, but also learning disabilities and autism on the one hand, and severe encephalopathy on the other, and have advanced clinical interventions dramatically such that the long-term outlook is very different today. Together with recent studies aimed at

identifying the fundamental role of *MECP2* in developmental neurobiology and the proof-of-principle studies in the mouse model regarding reversibility, clinical and basic science investigators seem poised for even more dramatic advances in the coming 5 years. During this period, the molecular targets of *MECP2* will be more fully explained, enhancing possibilities for developing specific therapies.

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