



# INSPIRING RETT SYNDROME AWARENESS (IRSA)

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## INTRODUCTION -----

Rett syndrome is a relatively rare neurodevelopmental disorder that burst onto the scene prominently in the early 1980s [1, 2]. From this point on, it was quickly recognized as occurring in all ethnic groups at approximately the same frequency, namely, with a prevalence of 1 in 10 to 20,000 females. From the beginning, Rett syndrome was regarded as a genetic disorder as it occurred predominantly in females, but it was very clear that its occurrence in a given family was sporadic with a recurrence risk of well below 0.5%. As such, confirmation was provided by the association of Rett syndrome with mutations in the gene *MECP2* (methyl-CpG-binding protein 2) as demonstrated in 1999 [3]. Since that time, more than 95% of females who fulfill the criteria for Rett syndrome have been found to have a mutation in this gene [4]. During the past 25 years we have greatly advanced our understanding of the clinical features and natural history of this unique neurodevelopmental disorder. Nevertheless, large segments of the medical and allied health care professional communities, as well as our educational community, remain relatively uninformed. In the following sections, we will review the clinical picture of Rett syndrome including the variability in clinical expression, detail the diagnostic strategies required, explore the associated medical issues, and provide an overview of various intervention strategies that have been developed to date. Finally, we will conclude with a description of ongoing studies and efforts to increase

our knowledge of the natural history of Rett syndrome, to develop phenotype/genotype correlations, and to set the stage for potential treatment trials as novel and potentially effective pharmacologic or molecular interventions become available.

## HISTORY -----

Beginning already in the late 1950s and early 1960s, two European physicians in particular began to recognize the clinical picture of 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 during infancy [1]. These girls demonstrated deceleration in the rate of head growth, loss of purposeful hand skills and communication capabilities including language and social interaction, and the appearance of unusual stereotypic hand movements consisting predominantly of hand wringing or hand washing activities or in some cases hand patting, tapping, or mouthing behaviors. Professor Rett traveled throughout Europe at various meetings attempting to develop interest among other clinicians and to elicit their experience with similar clinical features. Unfortunately, he wrote mainly in German and published in the local Vienna medical newsletter. His only English language publication appeared in the *Handbook of Clinical Neurology* and associated this disorder with the hyperammonemias. At approximately the same time Professor Bengt Hagberg in Göteborg, Sweden was

recognizing girls with similar behavior patterns. While he documented these carefully, he did not pursue their investigations farther in terms of scientific publications, rather incorporating them into the large group of children with unexplained mental and motor impairments. A chance meeting between these two physicians in Canada in the late 1970s generated the first widely read English language report, that occurring in 1983 in the *Annals of Neurology* [2]. It was at this time that the disorder received any significant attention in the United States. Within a short time, Rett syndrome was being diagnosed throughout the country and the National Institutes of Health became sufficiently interested to support the initial research programs involving this disorder. It was also during this period that the International Rett Syndrome Association (IRSA) was formed and became the single most important clearinghouse in this country and to some extent worldwide for parents and other interested persons. IRSA continues to provide the necessary family support and public advocacy so important to elucidating and solving the daily as well as the fundamental problems posed by Rett syndrome. Further, IRSA has held an annual meeting devoted to addressing these issues within the Rett family for more than 20 years. Presently, more than 3500 girls and women are enrolled in the IRSA clinical data base. During the period from 1983 until the association of Rett syndrome with mutation *MECP2*, considerable effort was expended to understand the clinical features as well as

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the etiologic basis for Rett syndrome. From the beginning, most child neurologists reasoned that Rett syndrome was indeed a genetic disorder based on the almost total occurrence in females, the presence of a small number of families with recurrence in which siblings or aunt/niece combinations demonstrated the features of Rett syndrome, the pattern of expression in twins, and one instance of vertical transmission from an affected woman with Rett syndrome to her female offspring, has also been reported. In monozygotic or identical twins, in all cases with a single exception, if one twin developed Rett syndrome the second twin would also develop Rett syndrome. With the identification of a gene associated with Rett syndrome [3], the lone identical twin pair representing the exception was explained by unbalanced X chromosome inactivation in the more normal twin. It was through a series of studies in the familial recurrences and one girl who had a chromosomal translocation involving the X chromosome that the area of interest on the X chromosome was restricted to the very end of the long arm of the X chromosome, namely at Xq28 [5, 6]. Thus, it was with great excitement that in 1999, mutations in *MECP2* were identified in a small number of girls with Rett syndrome confirming the genetic basis of this disorder [3].

#### CLINICAL PICTURE -----

Rett syndrome has its onset typically in the period between 6 and 18 months of age. In most instances, the pregnancy and delivery are normal. The girls appear quite normal during birth and seem to develop normally in early infancy. They often appear to have appropriate motor development including sitting and walking, although a normal reciprocal crawl is rarely described. Many girls also develop initial language in the form of single words or phrases. However, they are also noted commonly to be hypotonic from birth and to be particularly good babies, perhaps “too good.” During

this early period, deceleration in the rate of head growth may be noted as early as 3 months of age and shortly thereafter and usually within the first year of life, deceleration in the rate of weight gain is also noted. Deceleration in the rate of linear growth also occurs but usually after the first birthday. It should be emphasized that deceleration in the rate of head growth does not necessarily mean microcephaly and many females have head circumferences that remain in the normal range. The first signs of clinical involvement are often increasing irritability, stabilization or plateauing in the acquisition of motor skills, and then obvious loss of fine motor skills including playing with toys or manipulating other objects. It is also during this time that the girls may have less interest in their surroundings and in socializing with others, and in some cases, they give the appearance of autistic-like interactions. Other communication elements are lost as the girls may appear as if they do not hear despite normal hearing assessments. In the period after the loss of motor skills and change in communication and socialization, stereotypic hand movements emerge. These consist of hand-wringing or washing, hand-patting or tapping, hand-clasping or flicking, hand-mouthing or picking at the clothes. Hand stereotypies often, but not always occur in the midline. In many instances, the hands are not together. Each girl appears to develop her own repertoire of stereotypic movements, and over time they may well go through an evolutionary pattern even within the individual girl. These stereotypic hand movements are only noted during wakefulness, but during waking hours, they are often incessant. They do tend to be exacerbated by stress or excitement and if one restrains the hands, one may see or unmask similar movements with the feet or even stereotypic movements involving the oral facial musculature. Approximately, 80% of girls who develop Rett syndrome learn to walk, but ultimately their walking becomes dyspraxic in the sense that the pur-

poseful character is first diminished and then lost. Ultimately, gait is performed on a wide base in a wandering, non-purposeful fashion. The gait is also occasionally accompanied by toe-walking and by the first step being backwards or by repetitive shifting of weight from one foot to the other. Over time, a number of other features have been associated with Rett syndrome, but these are not seen uniformly. Such behaviors include teeth grinding or bruxism, disturbed sleep, and abnormal breathing patterns. These breathing patterns may consist of breath-holding or hyperventilation, or both, and like the stereotypic hand movements they are only present during wakefulness. Also, like the hand stereotypies, breathing irregularities may also be heightened by excitement or stressful situations. A significant number of girls will develop scoliosis, in some cases requiring surgery, and unusual autonomic features may be noted. These include GE reflux or gut dysmotility resulting in constipation, cold, often discolored to the point of, purplish extremities, more so in the lower extremities than the uppers, and EKG changes.

Over the past 25 years, specific diagnostic criteria have been elaborated (Table 1). These most recent consensus criteria established in 2001 have allowed us to make the clinical diagnosis of Rett syndrome throughout the world in a standardized fashion [7]. At the same consensus criteria meeting, the variant patterns of clinical appearance have been noted and criteria have been elaborated for their diagnosis as well (Table 2). The diagnosis of variant or atypical Rett syndrome is based on fulfilling three of six main criteria and five of eleven of the associated criteria such as bruxism, periodic breathing, and scoliosis noted above. Variant forms include early onset seizure type, a congenital form in which no normal early development may be noted, a preserved speech variant in which some purposeful language is retained, and finally the late onset or *forme fruste*.

Girls with Rett syndrome do undergo a

fairly consistent pattern of evolution of their clinical features (Table 3). After this early period of regression, development seems to stabilize and indeed interaction and socialization improve, particularly in the form of choice-making and better eye contact. Conversely, during this period seizures may appear in some and the amount of periodic breathing may intensify reaching a maximum during the school year period and well into adolescence. Later on, motor activities such as the hand stereotypies may slow in their frequency and be reduced in their overall expression. The absence of further cognitive loss provides strong support for continuous application of therapies to maximize communication and socialization capabilities and to preserve motor function. Although much work remains to be done, we have learned a great deal about the natural history of Rett syndrome, including survival as well as the many medical issues that may emerge during this time. These will be discussed individually in subsequent sections.

#### MECP2 MUTATIONS-----

More than 95% of females who fulfill the criteria for Rett syndrome have been found to have a mutation in this gene [4]. Females with mutations in *MECP2* may be completely normal, may have mild learning disabilities, may express features of Angelman syndrome, or may have features of autism in addition to having Rett syndrome. In those females who appear normal or have learning disabilities, they generally share the same mutation as a sibling or child who does demonstrate all the features of Rett syndrome. In this situation, the female who is normal or has a learning disability is a transmitting parent and lacks the features of Rett syndrome due to favorable skewing of X inactivation toward her normal X chromosome. Females with features of Angelman syndrome simply represent the close clinical overlap in many instances between the two disorders. Finally, females who have autism but not Rett syndrome reflect either a skew-

ing in X inactivation toward the more normal X chromosome or have a mutation which is milder in its consequences.

Rett syndrome has been identified in males under two circumstances [8]. The first being males who also have Klinefelter syndrome and therefore have an extra copy of their X chromosome making them from that point of view similar to females. The second situation is in males who have somatic mosaicism in which some of their cells express a normal X chromosome and others express an X chromosome with the Rett syndrome mutation. In this case, they are similar to females in the sense of balanced X chromosome inactivation. Other males have mutations in *MECP2* but do not express Rett syndrome [9]. Rather, they have a much more severe disorder with motor and respiratory problems present from birth and premature death already by 1\_ years in most instances. In about half of those with this progressive encephalopathy, the males have the same mutation as an affected sibling(s). In the remainder, these males represent a sporadic occurrence without prior involvement of a female sibling(s) [10]. Other males have been identified with a pattern of familial X-linked mental retardation with or without associated spasticity [11-13]. These males do not fulfill criteria for Rett syndrome but may have mutations in the *MECP2* gene. Yet other males (and one female with the preserved speech variant form) have been identified with duplication of *MECP2* [14, 15]. These males demonstrate severe cognitive impairment and progressive motor dysfunction (spasticity), but none of the other features of Rett syndrome. In these families, the mothers are asymptomatic due to complete skewing of their X chromosome inactivation.

#### DIAGNOSTIC TESTING -----

As noted above, the diagnosis of Rett syndrome is based on a set of consensus criteria which were provided in 2001. Approximately 80 percent of females who have features of Rett syndrome will fulfill

these diagnostic criteria and of those more than 95 percent will have a mutation in *MECP2*. Approximately 20 percent of females with Rett syndrome fall into one of the variant categories (see above) whether they be congenital, early onset seizure, preserve speech, or delayed onset (*forme fruste*) variants. Of this group, approximately 50 percent will have a mutation in *MECP2*. Children, who fulfill diagnostic criteria, whether typical or variant for Rett syndrome, should have the diagnostic test for mutations in *MECP2* [4]. 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 developmental delay. With the advent of effective treatment strategies, early diagnosis, prior to the full-fledged expression of typical features, will be crucial. Such testing should include sequencing of the four exons associated with this gene as well as the test for large scale deletions in those individuals who have negative results by standard sequencing. For those mutations identified by sequencing, the vast majority will occur in exons 3 and 4. Exon 1 sequencing should be conducted when exons 3 and 4 are normal. If the results of exon 1 testing are also normal, large scale deletion testing should be conducted. The methodologies for sequencing and large scale deletions are not the same. As such, the health care provider should be cognizant of this and order the tests for large scale deletion as appropriate. Females who demonstrate the characteristics of Angelman syndrome but have normal methylation studies at the Angelman locus should have *MECP2* testing. Similarly males with X-linked mental retardation and normal Fragile-X testing should also be considered for *MECP2* testing. Finally, infants with an unexplained severe neonatal or infantile encephalopathy should also be tested for *MECP2* mutation.

*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.

#### MEDICAL ISSUES -----

A wide variety of medical issues will be considered in the following paragraphs. Not all girls will have every one of these issues, but the care provider should be aware of them should problems arise which are otherwise unexplainable [8].

**Growth:** Pervasive failure of growth is typical of Rett syndrome. As stated above, the first evidence is often a deceleration in the rate of head growth beginning already at 3 months of age. Deceleration in the rate of weight increase also appears in the first year of life, and deceleration in the rate of linear growth becomes noticeable after the first birthday. Some of the girls with Rett syndrome will become microcephalic, but a significant number will have a head circumference that remains within the normal range. However, the median value for head circumference in girls with Rett syndrome approaches the 2nd percentile value for the normal female population by age 2.

Hand and foot growth is also diminished in Rett syndrome, foot growth much more so than that of the hands. Nonetheless, both tend to be smaller than that in the general population. Available data do show that the decline in the rate of foot growth follows that for the decline in the rate of linear growth. Approaches to management of weight gain will be discussed under nutrition.

**Epilepsy:** The occurrence of epilepsy in Rett syndrome is quite variable between reports ranging from a low of 20-25 % to a high of more than 80 %. Based on our experience utilizing video-EEG monitoring, we believe that as few as 25 % of clinical behaviors are determined to be epileptic seizures that may require medical management [16]. Many of the events that parents, teachers, and other caretakers report as seizures are not associated with abnormal cortical dis-

charges during video-EEG recording. Correspondingly, subtle clinical events that are not appreciated by parents as representing seizures have been identified by these video-EEG recordings. Seizures may be generalized, focal, or atypical absence in character and in some small number may demonstrate the features pattern of infantile spasms. Should any question arise regarding the possible occurrence of seizures, our recommendation is for video-EEG monitoring 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, valproic acid or sodium valproex and newer medications including lamotrigine, oxcarbazepine, and levetiracetam). We emphasize that it is important to be certain that it is seizures that are being treated in order to minimize the number of girls that are placed on medication.

**Sleep:** Sleep in Rett syndrome is often disrupted with frequent night-time awakenings, in many instances without the girl being upset, but rather simply playing in bed and occasionally punctuated by laughter for no apparent reason. Upon other occasions, sleep is interrupted by evidence of being upset or fussy in which case it is important to be certain that general care issues are addressed such as the need for diaper change, hunger, or other medical issues such as constipation, gastroesophageal reflux, or even an intercurrent infection such as an upper respiratory infection or otitis media. The importance of ruling out hunger and other GI issues cannot be stressed too strongly. It is also important to notice whether or not the girls take too many naps or have excessive daytime sleepiness, in which case it would be important to monitor sleep at night for disruptions including those which are not recognized such as might be caused by airway obstruction dur-

ing sleep. Good sleep hygiene is essential. Going to bed and awakening from sleep should occur at consistent times. In the morning, use of a bright light will encourage arousal; in the evening, a dim light will promote going to sleep.

When studied in detail, it is quite clear that stage REM sleep is substantially reduced in Rett syndrome. In addition, the other sleep stages are also abnormal [17].

If going to and staying asleep remains a problem 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. In our experience, we have several medications to be effective for achieving sleep. These include antihistamine such as hydroxyzine as well as other classes such as the benzodiazepines or melatonin. The antihistamines may have initial effectiveness, but for only a short time due to the development of tolerance. Studies with small sample sizes suggest melatonin may be helpful in inducing sleep though it may not decrease or prevent arousals during the night. Others have found medications such as trazodone and the newer non-benzodiazepine agonists such as zolpidem to be helpful and safe in promoting a full night of sleep. Still other have found chloral hydrate to be a particularly effective medication that can be used safely in amounts up to 50 mg per kg per dose. However, it is formulated as a liquid that has a very strong or burning character in the mouth. As such, girls will often refuse it unless they are fed by gastrostomy device. Some private pharmacies are able to formulate it as a suppository, a very acceptable option.

**Breathing Irregularities:** Periodic breathing in the form of breath-holding and hyperventilation, or both, is common among girls with Rett syndrome [17]. These activities occur only during wakefulness and are modified by factors such as hunger, agitation, and other stressful situations. Irregular

breathing is usually noted well after the other features of Rett syndrome are clearly apparent but is typically noted already by early childhood with a peak of occurrence in the school age period up through 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 or air-puffing. The irregular breathing pattern may also be accompanied by copious air-swallowing producing significant abdominal distension. This distension will dissipate on its own and certainly during periods of quiet breathing or sleep.

Various approaches have been attempted to mitigate the irregular breathing with variable success. These include the use of naltrexone, 1 to 3 mg per kg per day or magnesium citrate which have been found to be effective in some individuals. Naltrexone may be exerting its effect simply by producing sedation. In our own experience, we have not promoted the use of any particular agent in the absence of a systematic study showing efficacy.

**Gastrointestinal Issues:** Gastrointestinal issues in Rett syndrome cover the gamut from top to bottom [18]. 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.

Gastroesophageal reflux is also a common occurrence that can be confirmed by swallowing studies. In some instances, GE reflux rises to that of the larynx. As such, it is important to assess the girls both for primary and secondary aspirations based on their feeding capabilities and the possible presence of reflux. Available anti-reflux medications should be utilized as the reflux

is particularly uncomfortable. In the absence of treatment, one runs the risk of developing a chronic or persistent esophagitis.

Constipation is a significant problem in those with Rett syndrome, also relating to 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 MiraLax or Milk of Magnesia, fiber in the diet, and adequate fluid intake. This should ensure that a bowel movement occurs every day or two.

Finally, gallbladder disease appears to be another consideration in Rett syndrome 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 percent are under the age of 20.

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

**Nutrition:** Assuring adequate nutrition in Rett syndrome is critical. It does appear that girls with Rett syndrome have a well-above average requirement regarding daily protein and calorie intake [19]. As such, particular attention must be given to nutritional requirements and if necessary to providing supplemental nourishment in the form of high-calorie nutritional supplements or frequent snacks including lower cost supplements such as instant breakfast and milk shakes with additional nutritional ingredients. Appropriate vitamin supplementation should be provided. However, one should be aware that to the extent supplemental formulas are used, these are enriched in vitamins and one must be careful not to provide excessive vitamin intake. As girls with Rett syndrome tend to be small in stature, it is appropriate to reference their weight and height by using the body mass index nomo-

gram which provides the normal percentiles. Body mass index may be calculated by multiplying the weight in kilograms by 10,000 and dividing by the square of the length in centimeters.

In some instances, girls with Rett syndrome are not able to take in adequate calories by mouth, or because of primary aspiration are unable to ingest food at all by mouth. In these girls it is important to implement alternative feeding strategies such as gastrostomy or gastrojejunostomy feedings. Depending on the presence of gastroesophageal reflux, a fundoplication may need to be performed at the same time. Any girl who has failed to gain weight over a period of several months to a year should be considered for this alternative feeding method.

**Osteopenia:** Osteopenia occurs in virtually all girls and women with Rett syndrome, being more significant in those girls or women who have inadequate calorie and protein intake [20]. Even in those who have adequate calorie-protein intake, osteopenia is present but just to a lesser degree. Due to the frequency and extent of osteopenia, fractures are much more common in the girls or women with Rett syndrome. As such, if use of an extremity suddenly is abandoned despite the absence of complaints, consideration should be given to assessing the possibility of a fracture in that extremity. We do know that these 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 already in childhood.

Systematic studies on the occurrence of and possible therapies for osteopenia are currently being conducted at the Baylor College of Medicine under the direction of Kathleen Motil, M.D.

**Scoliosis:** Scoliosis occurs with increasing frequency in girls with Rett syndrome. Scoliosis may be recognized as early as age 5 and by the age of maturity is present in up to 80% [21]. Scoliosis often progresses signifi-

cantly and at curvatures above 40 degrees, corrective surgery should be considered. At lesser degrees of curvature, consideration has been given to the use of body jackets. It is not clear whether or not these are effective. To date, no systematic studies have been performed to judge their efficacy. However, they remain an option in retarding the progression of scoliosis. Scoliosis tends to be more significant in those girls who are not ambulatory. Regardless of ambulation status, during the time they are seated, proper upright positioning is critical, including for those in wheelchairs the appropriate use of lateral supports. Once the girl with Rett syndrome has matured and is through puberty, further progression of scoliosis is generally considered to be unlikely.

**Ambulation:** Eighty percent of girls with Rett syndrome acquire the ability to walk. During the course of their developmental regression, approximately one-fourth of this group will lose the ability to walk. Overall, about 60% of those with Rett syndrome remain ambulatory. Significant effort should be allocated to maintaining ambulation as long as possible and to resist utilization of strollers or wheelchair devices except for activities that require covering long distances or for safety considerations. In those girls who do not walk, effort should persist in developing upright posture through the use of standing frames both at home and at school and use of parallel bars to promote supported ambulation.

In some instances, toe-walking is common as well as abnormal foot postures. For these, ankle/foot orthoses or other orthotic devices should be implemented.

**Sexual Maturation and Gynecologic Issues:** As those with Rett syndrome progress through adolescent years, puberty should be anticipated. Ordinarily, girls with Rett syndrome will enter puberty at similar ages to their peers. 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. Parents or other responsible caretakers 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. We have had the most experience with the use of birth control pills and have found them to be completely acceptable. It is possible to provide birth control pills across the month such that menstrual flow can be eliminated.

Once again, under circumstances when unexplained irritability or inconsolable crying occurs, appropriate consideration should be given to the possible presence of problems in the gynecologic system. An abdominal ultra-sound as well as consultation with a gynecologist should be strongly considered.

**Cardiac and Autonomic Systems:** We have learned that the cardiac conducting system appears to be quite immature based on pathological examination and at the clinical level have discovered that prolonged QT interval and ST segment changes may be observed with increasing frequency as time goes by [8, 22]. As such, at the time of diagnosis we recommend that an EKG be obtained to assess QTc or other significant abnormality. If this is normal, we then recommend repeating the cardiogram in 2 to 3 years. If it is abnormal, we recommend referral to a cardiologist for consideration of an appropriate intervention strategy. In addition, should an abnormality in QT interval be identified in a girl with Rett syndrome, it would be appropriate to have other members of her family screened as well as this finding is certainly not specific to Rett syndrome and may occur in the general population. It is a quite treatable problem with medication and one which should not be overlooked.

The hands and feet tend to be cool to cold in individuals with Rett syndrome. This is

more typically noted in the lower extremities and may consist not only of cold feet but discoloration from red and mottled to purple, extending well up on the lower extremity. This is believed to be related to excess sympathetic nervous system tone. No specific intervention is available but it is important to keep their hands and feet appropriately warm. It is of interest that in some instances when scoliosis surgery involves an anterior approach and the sympathetic chain is interrupted on that side by virtue of the operation, the foot on the operated side becomes warm and may actually begin to grow more than the foot on the non-operated side.

**Bruxism:** Bruxism occurs in virtually all girls or women with Rett syndrome at some point in time. Teeth-grinding or bruxism varies in frequency and intensity and may be exacerbated by those factors which increase hand stereotypies such as anxiety, excitement, or stressful situations. The sound created is really quite characteristic and has been described by Bengt Hagberg as that of the sound of slowly uncorking a bottle of wine.

Efforts to reduce the teeth grinding are generally unrewarding. One can be reassured that over time they do seem to diminish and in many cases actually disappear after school age.

**Other Motor System Function:** As noted above, hypotonia is the rule at the onset of this disorder, and in most cases is present already from the time of early infancy. In general, over time the muscle tone increases and whether this increase should be called rigidity or spasticity is a matter for debate. In keeping with the slowing down of motor activities including hand stereotypies and ambulation, when present, one does have the feeling that this is more a rigidity phenomenon and not spasticity, particularly in view of the general absence of upper motor neuron signs.

A variety of other movements occur including tremor, myoclonus, and choreiform activities [23]. Tremor is particularly

apparent upon awakening from sleep or a nap and 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 is a common feature particularly with advancing age and especially at the ankles and feet and at the wrists and hands. These abnormal postures can be overcome by passive movement. This distinguishes them from spasticity or fixed deformity. In that regard, contractures can develop at joints, particularly when sitting in a wheelchair for long periods of time without effective mobilization of joints. Further, in those girls who tend to keep their hands together in the midline at the chest level, one may note contractures at the elbows and to some extent limitation of motion at the shoulders.

**Longevity:** Unlike the original suggestion that Rett syndrome is a progressive degenerative disorder, we now understand that it is a neurodevelopmental disorder with likelihood of prolonged survival. Current intervention strategies are much more aggressive than two to three decades ago. This alone would be expected to lead to greater longevity. Few systematic studies of survival have been conducted. In a prior study from Baylor, we noted that survival through age 10 was the same as the general female population, whereas survival through age 35 was about 70% of the normal female population. We are aware of a number of women with Rett syndrome living in their 40s and 50s and expect that with proper nutrition and medical care, prolonged survival is indeed likely to be the rule. The consequence of prolonged survival is that in many cases parents or other caretakers 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 Rett syndrome. In most cases the actual cause is unclear, but may well involve autonomic

dysfunction or a cardiac conduction system abnormality like prolonged QT.

#### THERAPEUTIC INTERVENTION -----

Individuals with Rett syndrome require a variety of therapies throughout their lives [24]. 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 in a small number of instances, girls may use small trampolines or treadmills. Hippotherapy and swimming are extremely popular and well-tolerated by most individuals with Rett syndrome. 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 Rett syndrome give intense eye contact which may be employed to develop a communication system in the form of 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 activate switches. They should be given every opportunity to make choices in all aspects of their lives ranging from eating to socialization to types of entertainment. 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.

#### CLINICAL RESEARCH -----

The importance of continued study of the clinical aspects of Rett syndrome, including its nature history, intervention strategies and other aspects, cannot be overestimated. Such efforts must continue if we are to make any progress at all in improving the lives of individuals with Rett syndrome. At the present time, 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; one at the Baylor College of Medicine, the second one at the Greenwood Genetic Center in Greenwood, South Carolina, and the third at the University of Alabama at Birmingham. The goal of this consortium is to enroll up to 1000 girls and women with Rett syndrome and to follow them for an extended period of time. Through this project we expect expand our understanding of the natural history of Rett syndrome and to the extent possible to develop clinical, namely phenotype, and molecular, namely genotype, correlations, particularly with the most common mutations in *MECP2*. To repeat, the importance of understanding the natural history of Rett syndrome cannot be overstated. If we are engaged in treatment strategies that produce fundamental improvement, we need to know what the natural course of this disorder is so that we can judge the efficacy of these therapeutic agents as well as recognize untoward side effects that may occur. In addition, during this natural history study, we will be updating the survival data information by probing the roster of IRSA that now contains about 3500 individuals. We will also be looking at the nutritional status and the quality of life both of the participants in the natural history study and also that of their principal care providers whether their parents or others. Throughout the course of this natural history study, we may identify new avenues for investigation, for example, the appropriateness of calcium supplementation for osteopenia or new approaches to better nutritional support.



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In addition to these consortium enrollment sites, remote enrollment sites have been established at regional locations to facilitate accessibility for families throughout the country to this natural history study. These remote clinics operate in Oakland, CA, Chicago, IL, New Brunswick, NJ, and Boca Raton, FL.

Data collected at the respective enrollment sites are transmitted as confidential information electronically 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/)).

An international consortium of investigators does exist. This group will be met in San Francisco following the 2006 annual meeting of IRSA to discuss strategies for potential clinical trials.

At the international level, the Rett syndrome study group in Australia led by Helen Leonard with support from the IRSA among others has created a cross-sectional clinical database with several hundred registrants at present. Also, with support from IRSA, a gene database is maintained by Dr. John Christodoulou in Sydney, Australia.

**PARENT'S SUPPORT AND ADVOCACY:**

The International Rett Syndrome Association provides both support for families dealing with Rett syndrome and advocacy at the national level to promote awareness and generate interest in federal funding for research, particularly through the National Institutes of Health. IRSA has been in existence now for more than 20 years and is recognized throughout the world as the single most important source of comprehensive information about the clinical and research aspects of Rett syndrome.

The Rett Syndrome Research Foundation also provides research funding for promising basic science and translational research and advocates as well for expanded funding for research at the national level.

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)).

**TABLE 1**

**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 2**

**Variant Rett Syndrome Consensus Criteria**

**Meet at Least 3 of 6 Main Criteria and**

**Meet at Least 5 of 11 Supportive Criteria Main Criteria**

**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 First Years of Life
- Monotonous Pattern of Hand Stereotypies
- RS Disease Profile: Regression Stage Followed by Recovery of Interaction Contrasting with Slow Neuromotor Regression

**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

TABLE 3

**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

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## PRODUCTS OF IRSA RESEARCH SUPPORT

### INTRODUCTION -----

Since its inception in 1984, IRSA has provided support for international conferences and for individual research projects. Listed below is a summary of this financial support. These conference and research activities represent the fruits of the labor of love by the many individuals and groups that have generated the necessary funding in behalf of IRSA's three-part mission (Research, Education, and Advocacy) to support these important programs. Perusal of these products will provide a rich picture of the progression in our knowledge and understanding of Rett syndrome and the many clinical and research advances that have occurred over the years. In each case, IRSA funding was a critical component. Everyone in the IRSA family should take pride in this legacy.

### CONFERENCE SPONSORSHIPS -----

**1986: Kennedy Institute, Johns Hopkins University American Journal of Medical Genetics 1986;Supplement 1:1-404.**

**1988: San Diego (prior to Child Neurology Society Annual meeting) Journal of Child Neurology 1988;3(supplement):S2-S93.**

**1988: 5th International Conference, Vienna, Austria Brain & Development 1990;12:1-191.**

**1993: 2nd International workshop, Orlando Journal of Child Neurology 1993;8:97-105.**

**1994: International Symposium, Portland (OR) Neuropediatrics 1995;26:57-128.**

**1996: World Congress, Gothenburg, Sweden European Child and Adolescent Psychiatry 1997;6(supplement 1):1-108.**

**2000: World Congress, Karuizawa, Japan Brain & Development 2001;Supplement 1:S1-S256.**

**2005: Child Neurology Society Symposium, Ottawa Journal of Child Neurology 2005;20:707-783.**

**2006: Rett Syndrome Clinical Trials Conference, San Francisco**

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