Rett Syndrome: Meeting the Challenge of This Gender-Specific Neurodevelopmental Disorder

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Abstract and Introduction

Abstract

Rett syndrome (RS) is an incurable neurological disorder that occurs in females. Although the biological basis is unknown, there is substantial evidence suggesting a genetic basis. RS is characterized by an initial period of apparently normal psychomotor development followed by loss of communication skills and purposeful hand movement. Then, hand stereotypies, gait dyspraxia, and deceleration of head growth become apparent. Other problems include growth failure and epilepsy. There is no biological marker for RS; the diagnosis is based on well-delineated clinical criteria. The prevalence of RS is 1:23,000 live female births. Survival to 30-40 years or beyond is the rule rather than the exception. Treatment is both palliative and supportive. A vigorous approach to all aspects of care, including educational, medical, and psychosocial issues, is recommended.

Introduction

Rett Syndrome (RS) is a neurological disorder that occurs almost exclusively in females. Andreas Rett provided the first description of this disorder 30 years ago, but this condition has been internationally recognized only since 1983. During the last 10 years, intensive research has extended our knowledge about the clinical characteristics of RS; however, the origin and cause of RS remain unknown. Although many health professionals are not familiar with RS, it is a frequent cause of neurological dysfunction in females. This article reviews the challenges of diagnosis and management of RS.

Diagnostic Categories

The presentation of RS in the middle childhood years is so distinctive that misdiagnosis is unlikely. The lack of a biological marker makes the initial diagnosis at age extremes--early infancy and adulthood--more problematic. An early, "hard" clinical finding is a decline in fronto-occipital circumference (FOC) curves beginning as early as 2-3 months; this finding suggests deceleration of brain growth. While neurologic dysfunction is suggested by this feature and other signs--such as delays in gross motor skills and a placid, calm appearance--the diagnosis of RS cannot be made with certainty until girls are in or pass through the regression phase (stage II) between 1-3 years and show other features of the RS disease profile.

Most RS patients are diagnosed in childhood. In the adult woman, medical records and someone with memory of historical information are often unavailable. However, the typical RS profile, including the prominence of motor problems with progression from a hyperkinetic to a bradykinetic state, and lower motor neuron features are useful in establishing the diagnosis in a mentally retarded woman with limited communication abilities.[2, 4]

A provisional subgrouping into 3 diagnostic categories has been suggested[5]:

1. **Classic Rett syndrome**. This diagnosis is made according to specific diagnostic criteria provided in Table I.
2. **Provisional (potential) Rett syndrome**. This subgroup comprises girls, typically 1-3 years old, with some clinical evidence of RS, but not enough to meet necessary criteria for the diagnosis.

3. **Atypical Rett syndrome**. This subgroup addresses the observation that there is a discrepancy between the clinical concept of RS, restrictive in its classic type, and the underlying biological condition, which is likely to include a wider range of patients. Females with RS present with a much more heterogeneous pattern of phenotypes than originally realized. These atypical or variant cases include girls at least 10 years of age with mental retardation of unknown origin who meet specific inclusion criteria presented in Table II and exclusion criteria previously presented for classic RS.[6,7]

Epidemiology

An epidemiological study of a large, well-defined population of girls in Texas, age 2-18 years, suggested the prevalence of classic RS to be 1 case per 23,000, without significant differences across race or ethnic group.[8] It has been suggested that if RS were viewed as a syndrome of several variants, RS would be second only to Down Syndrome as the most important disease underlying mental retardation in females.[8]

Preliminary results indicate that the survival curve for RS follows the general female population until age 10 years. Thereafter, survival declines, most precipitously after 20 years of age, to 70% at 35 years of age, compared with 98.4% in the general US female population. The majority of deaths appear to be either sudden and unexplained or secondary to pneumonia. At this time, we have no means to predict those RS women at risk of sudden death. Mortality risk factors include seizures, loss of mobility, and difficulties with drinking/swallowing. Compared with other groups of severely retarded individuals who retain self-feeding skills and some degree of ambulation, however, those with RS have a more favorable life expectancy; for example, the 70% survival of RS patients at age 35 contrasts sharply with an estimated 27% survival for other profoundly mentally retarded individuals.[4]

Genetics

The biological basis for RS is unknown, but there is convincing evidence that RS is a genetic disorder: First, RS appears to occur exclusively in girls. Second, it recurs in families. The risk of having a second girl with RS is increased, but still very low, probably less than 0.4%.[1] Third, there is almost universal concordance in monozygotic twins and discordance in dizygotic twins.[1,9-11]

Involvement of the X-chromosome has been suggested, but there are no conclusive data that entirely support this hypothesis. One study has shown a high consanguinity rate within RS families in Sweden and notes that many of the RS cases there can be traced back to cases occurring in a small number of homesteads in the 18th century. The genetic link between the cases followed both the maternal and paternal lines. It has been suggested that this observation supports a 2 mutational model with involvement of the X-chromosomes and an autosomal locus.[2,11] Any genetic model must take into consideration the frequent, apparently sporadic, nonfamilial occurrence of RS. This raises the possibility that the gene locus is very susceptible to mutation. The occurrence of Rett variants also raises the issue of whether more than 1 gene locus may give rise to the Rett phenotype.

Treatment Modalities

While there is no known cure for RS, we believe the course of RS can be ameliorated by therapies aimed at retarding the progression of motor disability and improving communication skills. Diagnosis is the first important step in the care of RS individuals. Such knowledge can be a relief for parents and bring into focus the spectrum of clinical problems that will be experienced.

We advocate a vigorous approach to caring for RS individuals. The degree of difficulties experienced following the regression period are influenced by the consistency with which physical therapy, an active lifestyle, and good nutrition are offered. Components in the therapy program are aimed at maintaining ambulation and balance (physical therapy); promoting use of hands (occupational therapy), including the use of hand splints (which may result in reduction of hand stereotypies); promoting communication with utilization of eye-gaze response and picture boards; and utilizing music therapy as an adjunct to other therapies and as an incentive

to perform them. Hippotherapy (horseback riding) and hydrotherapy promote balance and help develop protective responses that can help avert falls. Further, these activities can be enjoyable for RS girls and women.

Somatic growth retardation has been well documented in RS. Many RS girls meet the criteria for moderate to severe malnutrition. Potential factors contributing to this problem include inadequate energy intake secondary to swallowing difficulties, energy expenditure imbalances, and inappropriate utilization of nutrients. Evaluation for swallowing difficulties and gastroesophageal reflux is indicated in most girls with RS. A program of supplemental feeding via oral or nasal/gastric tube or gastrostomy button has been associated with significant gains in weight and height over a short period of time. Parents frequently note that with improved growth their daughters show greater alertness and interaction.

Motor dysfunction is a characteristic feature of RS. All females with RS have stereotyped hand movements and gait disturbances. The majority have bruxism, dystonia, and Parkinsonian features including excessive drooling, rigidity, bradykinesia, and paucity of facial expression called hypomimia. Scoliosis develops in 50%-70% of RS girls. It frequently develops between 8-11 years of age and may progress rapidly. However, as many as 17% of girls with scoliosis show no progression. The likelihood of progression and worsening of scoliosis appears to be greater if there are also problems of early hypotonia, dystonia, or loss of ambulation. Early identification of RS girls whose previous developmental problems have identified them as "at risk" and early repeated follow-up of scoliosis are suggested. Bracing appears to be at best a temporary or nonhelpful treatment. Therefore, early referral and aggressive surgical management for scoliosis are recommended.[1]

Another common problem in RS is that of seizures, which are reported in 60%-90% of RS individuals. Additionally, EEGs recorded in RS girls and women are frequently characterized by epileptiform abnormalities. Seizures and EEG epileptiform abnormalities appear to be age related, with greatest frequency during clinical stage III. Studies utilizing prolonged video-EEG polygraphic monitoring indicate that the occurrence of seizures is overestimated. Most episodes identified by parents represent nonepileptic behavioral events, while actual seizures may be under-recognized by parents and occur during sleep. Video-EEG monitoring may be necessary to determine appropriate antiepileptic therapy for RS patients.[4]

The Adult RS Woman

Survival into adulthood is the rule rather than the exception for RS. However, a woman with RS continues to function at a cognitive level of 6 to 12 months though she may continue to walk. She remains dependent on caretakers to help her complete activities of daily living. She will continue to require assistance with bathing, eating, and dressing. Although some women with RS are "time-trained" to void on a schedule, they require physical assistance with toileting. While seizures and nutritional problems often lessen with age, motor disabilities frequently may worsen. Once a female with RS reaches 22, mandatory state education programs that provide therapy usually end. In the absence of an ongoing therapy program, the RS woman may lose ambulatory skills, as well as other motor skills, such as use of hands and communication skills. Because this may lead to a rapid decline in her general health, quality-of-life provisions should be made for ongoing physical, occupational, and speech therapy.

With good care and nutrition, most RS women will be healthy. However, RS women are at risk for developing any of the medical problems common to women in general, some of which are exacerbated by the symptoms of RS. Discerning specific problems may be difficult and challenging given the fact most RS women are unable to describe or pinpoint pain or discomfort.

Therefore, every RS woman needs a health care provider who knows how to manage women's health issues in general and RS in particular. The approach to health care must be to prevent unnecessary illness and comprehensively treat health problems with the goal of maximizing quality of life.

Girls with RS go through puberty, menstruate, and may become pregnant. One RS woman has been reported to have given birth to a girl who has subsequently developed RS.[1] Issues and options concerning birth control and hygiene should be discussed with parents or guardians of women with RS. For example, while a contraceptive implant may seem practical, there is some evidence that contraceptives may worsen the bone

demineralization often apparent in RS girls before puberty. [12] The pathogenesis of bone demineralization, its natural history, and whether it will respond to calcium supplementation in RS are unclear.

Parents and guardians of RS girls and women are faced with number of caretaking responsibilities, ranging from long-term care needs and possible placement in a residential facility to guardianship and trust funds. If the decision is made for the RS woman to live at home, then family support resources such as home health aides, nursing care, and financial aid should be established. Respite care is essential. Parents must take a break--time for themselves, each other, and other family members. Taking time to "have fun" helps families to replenish energy needed to accept and deal with the daily challenges and stress of caring for a daughter or sibling with RS.

Community resources for family support are, unfortunately, often limited in scope and accessibility. State and federal programs, however, offer financial aid for purchase of equipment (bathroom aids, wheelchairs), architectural changes (such as ramps and doorway modifications), and transportation or other services that enable parents to care for their daughter at home. These programs can be located through the Mental Health Mental Retardation Agency. The International Rett Syndrome Association, (301/856-3334 or 1-800-818-RETT) has a wealth of information and knowledge to share with families and health care providers.

If the decision for residential placement is made, parents need to anticipate long waiting lists. In order to make an appropriate choice, they must allow ample time to visit and evaluate potential care facilities. Parents should be advised to ask staff at residential placement facilities about physical, occupational, and communication therapy. Other issues that should be dealt with include staff and resident relations, contact with family members, commitment to personal appearance and hygiene, provision of individualized, quality care, and the overall ambiance of the environment. Staff members must be educated about RS and the individual needs and communication techniques of the child or adult with RS. In some areas, staff in community-based group homes offer individualized care and one-on-one attention.

One of the major concerns of parents is "what will happen to my daughter after I'm gone?" This is a frightening and therefore often-avoided question. The laws assume that anyone who has reached age 18 is an adult, fully capable and responsible for her own actions. The laws do not acknowledge the special needs of the woman with RS unless the parent specifically arranges for protection and guardianship. Therefore, parents--even young ones--should make provisions for a guardian who can make important decisions regarding the welfare of the woman with RS, in case something happens to them. Estate planning is also essential to ensure that the RS woman will always have a comfortable environment, adequate funds, and competent people to care for her. Parents are advised to seek professional advice regarding these issues.

Once a person with RS reaches adulthood, all health care providers should interact with her as a woman, not as a child in a "bigger" body. RS teenagers/women can show strong likes and dislikes, and appear to perceive what is being said in general around and about them. The child and woman with RS should be informed about and participate in their health care to the extent possible, and must be treated with dignity and compassion.

Summary

RS was first described by Andreas Rett 30 years ago. Over the past decade, the unique clinical profile of RS has been well characterized. We recognize that RS is one of the most important causes of neurological impairment in females, and that it is a developmental disorder rather than a progressive, degenerative disorder. Survival into adulthood is expected.

The lack of a diagnostic marker and "cure" for RS presents health care providers with formidable challenges. Diagnosis is an all-important first step and must be followed by a comprehensive program aimed at maximizing quality of life. This program includes therapies to promote communication and motor function, and intervention in the anticipation of nutritional deficits.

We must be advocates for these girls and women who cannot speak. We must provide support for their families, whose burden begins when they realize that their beautiful little girl is not developing normally and

continues as they face the demands of providing round-the-clock care for a physically growing, developmentally impaired daughter. Lastly, we are challenged to continue our own education concerning RS and to share with our associates and community all we have learned about living with this devastating illness.

Tables

Criteria and Staging

Table 1. Diagnostic Criteria

- **Necessary Criteria**
  - Apparently normal pre- and perinatal period
  - Apparently normal development through at least first 5-6 months of age
  - Normal head circumference at birth
  - Deceleration of head growth (ages 3 months to 3 years)
  - Loss of acquired skills (ages 3 months to 3 years):
    - Learned purposeful hand skills
    - Acquired babble/learned words
    - Communicative abilities
  - Appearance of obvious mental deficiency
  - Appearance successively of intense hand stereotypies:
    - Hand wringing/squeezing
    - Hand washing/patting/rubbing
    - Hand mouthing/tongue pulling
  - Gait abnormalities among ambulant girls:
    - Gait apraxia/dyspraxia
    - Jerky truncal ataxia/body dyspraxia
  - Diagnosis tentative until 2-5 years of age
- **Supportive Criteria**
  - Breathing dysfunction:
    - Periodic apnea during wakefulness
    - Intermittent hyperventilation
    - Breath-holding spells
    - Forced expulsion of air or saliva
  - Bloating/marked air swallowing
  - EEG abnormalities:
    - Slow waking background and intermittent rhythmical slowing (3-5Hz)
    - Epileptiform discharges, with or without clinical seizures

    - Epilepsy--various seizure forms
    - Spastic signs, later muscle wasting and/or dystonic traits
    - Peripheral vasomotor disturbances
    - Scoliosis of neurogenic type
    - Hypotrophic small and cold feet
    - Growth retardation
- **Exclusion Criteria**
    - Organomegaly or other signs of storage disease
    - Retinopathy or optic atrophy
    - Microcephaly at birth
    - Existence of identifiable metabolic or other heredodegenerative disorder
    - Acquired neurological disorder resulting from severe infections or head trauma
    - Evidence of intrauterine growth retardation
    - Evidence of perinatally acquired brain damage

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Table 2. Rett Syndrome: The Variant Delineation Model According to Hagberg and Skjeldal

Inclusion criteria

A girl of at least 10 years of age with mental retardation of unexplained origin and with at least 3 of the 6 following primary criteria:

A1 Loss of (partial or subtotal) acquired fine finger skill in late infancy/early childhood

A2 Loss of acquired single words/phrases/nuanced babble

A3 RS hand stereotypies, hands together or apart

A4 Early deviant communicative ability

A5 Deceleration of head growth of 2SD (even when still within normal limits)

A6 The RS disease profile: a regression period (stage II) followed by a certain recovery of contact and communication (stage III) in contrast to slow neuromotor regression through school-age and adolescence

AND, in addition, at least 5 of the following 11 RS supportive manifestations:

B1 Breathing irregularities (hyperventilation and/or breath holding)

B2 Bloating/marked air swallowing

B3 Characteristic RS teeth grinding

B4 Gait dyspraxia

B5 Neurogenic scoliosis or high kyphosis (ambulant girls)

B6 Development of abnormal lower limb neurology

B7 Small blue/cold impaired feet, autonomic/trophic dysfunction

B8 Characteristic RS EEG development

B9 Unprompted sudden laughing/screaming spells

B10 Impaired/delayed nociception

B11 Intensive eye communication--"eye pointing"

Exclusion criteria as presented in Table I.

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References

1. Hagberg B (ed): Rett Syndrome--Clinical and Biological Aspects. Clinics in Developmental Medicine, No 129. London, Mac Keith Press, 1993.
2. Kerr AM: Early clinical signs in the Rett disorder. Neuropediatr 26:78-80, 1995.
3. Armstrong DD: The neuropathology of Rett syndrome--Overview 1994. Neuropediatr 26:100-104, 1995.
4. Glaze DG: Commentary: The challenge of Rett syndrome. Neuropediatr 26:78-80, 1995.
5. Hanefeld F, Hagberg B, Percy A: Molecular and neurobiology aspects of Rett syndrome. Neuropediatr 26:60-61, 1995.
6. Hagberg B: Clinical delineation of Rett syndrome variants. Neuropediatr 26:62, 1995.
7. Hagberg B, Skjeldal OH: Rett variants: A suggested model for inclusion criteria. Pediatr Neurol 11:5-11, 1994.
8. Kozinetz CA, Skender ML, MacNaughton N, et al: Epidemiology of Rett syndrome: A population-based registry. Pediatr 91:445-450, 1993.
9. Percy AK: The Rett Syndrome: The recent advances in genetic studies in the USA. Brain Dev 14(suppl): S104-S105, 1992.
10. Zoghbi HY: Genetic aspects of Rett syndrome. J Child Neurol 3(suppl): S76-S78,1988.
11. Åkesson HO, Hagberg G, Wahlström J, et al: Rett syndrome: Search for gene sources. Am J Med Genet 42:104-110, 1992.
12. Armamento-Villareal R, Villareal DT, Avioli LU, et al: Estrogen status and heredity are major determinants of premenopausal bone mass. J Clin Investigation 90:2464-2471, 1992.

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