ISSUES IN NEUROLOGY

Rett Syndrome and Autism

EDITED BY

Richard H. Haas, Isabelle Rapin, Hugo W. Moser

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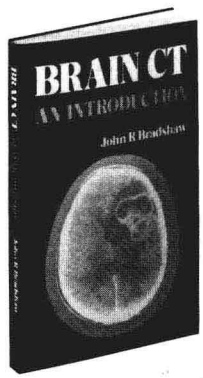

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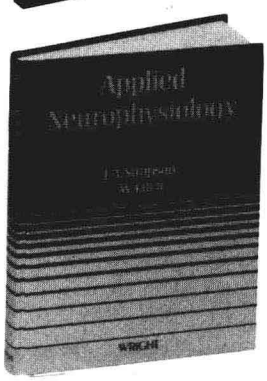

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Introduction

Hugo W. Moser, MD; Richard H. Haas, MD

More than 1,200 patients in all parts of the world have been found to have a consistent set of clinical manifestations which conform to the complex and unique phenotype of classic Rett syndrome. It is this fact which has led to the general acceptance that Rett syndrome represents a distinct entity, even in the absence of a specific diagnostic marker. Studies in various parts of the world indicate that it affects between 1:10,000 to 1:15,000 females, and it thus represents a significant clinical problem.

This special issue of the *Journal of Child Neurology* is a modified account of a symposium on Rett syndrome and autism that was organized by one of us (R.H.H.) on October 21, 1987, just prior to the annual meeting of the Child Neurology Society. This special issue and the symposium aim to fulfill the following goals:

1. *To increase the medical community's awareness and knowledge about Rett syndrome.* The first five articles discuss the history,[1] clinical features and differential diagnosis,[2] epidemiology and public health significance,[3] cognitive profile,[4] and peripheral nerve findings[5] in Rett syndrome.
2. *To update information about the management of patients with Rett syndrome.* The roles of physical therapy, nutrition, and orthopedic surgery in the management of girls with Rett syndrome are explored in articles by Lieb-Lundell,[6] Rice and Haas,[7] and Hennessy and Haas.[8]
3. *To specify the relationship between Rett syndrome and autism.* It is our impression that the most frequent diagnostic error in respect to Rett syndrome is the assignment of this label to children who fall within the spectrum of the diagnostic category of autism as described in detail in the papers by Allen[9] and Schreibman.[10] Percy et al[11] and an earlier publication by Olsson and Rett[12] contrast the behavioral abnormalities in Rett syndrome with those in autism. Even though, in our view, Rett syndrome and autism represent distinct entities, research about autism and its therapy provides important lessons for Rett syndrome. These are highlighted in Dr Rimland's analysis of the therapy of autism.[13]
4. *Specify strategy for research about Rett syndrome and present preliminary findings.* Papers from Baylor[14,15] and Kennedy-Hopkins[16] describe the research planned at these two centers. The role of the International Rett Syndrome Association is described by its President, Mrs Kathy Hunter.[17] The symposium closes with two papers that deal with a sensitive topic, the urgent need for postmortem studies. While not unique to the study of Rett syndrome, this topic is of particular importance for this disorder, because of the lack of a diagnostic marker and the fact that the only known pathology involves tissues that are inaccessible to definitive study during life (that is, the brain and other parts of the nervous system). Dr Isabelle Rapin's paper[18] recounts her personal approach to this issue, an approach that has been proven to be constructive and successful and of great value for the study of a variety of other neurodegenerative disorders. Percy et al[19] present a protocol for the initial processing of postmortem samples.

The recent delineation of a complex, devastating and rather common disease entity has provided the clinical research community with an exciting but difficult challenge. The National Institutes of Health has made Rett syndrome one of its research priorities and at this time provides funding for program project grants at Baylor College of Medicine and at the Kennedy Institute–Johns Hopkins. Epidemiological studies are being conducted by the Centers for Disease Control. The International Rett Syndrome Association is providing a unique role in the dissemination of information, and in the support and coordination of research. Through this organization and the personal commitment of Dr Andreas Rett and investigators in France, Germany, Japan, Portugal, Scandinavia, Switzerland and the United Kingdom,

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The History and Challenge of Rett Syndrome

Richard H. Haas, MD

Abstract

Rett syndrome was first described in 1966 by Dr Andreas Rett, who reported in German his findings in 22 patients. Recognition of the syndrome grew slowly until 1983, when a series of 35 patients from several countries was reported in English. By 1987, the number of known cases had grown to over 1,250 worldwide, the International Rett Syndrome Association had been founded, and international conferences on the syndrome were being held regularly. Although a developmental staging system has been devised, many questions remain concerning the course of the disease. Rett syndrome poses a challenge to the physicians, therapists, psychologists, educators, and families involved with affected patients, as well as to researchers investigating the syndrome. (*J Child Neurol* 1988;3(Suppl):S3–S5).

The recognition of Rett syndrome as a distinct phenotype is appropriately attributed to the clinical expertise of Dr Andreas Rett. Working in his Vienna clinic Dr Rett observed two thin patients sitting on their mothers' laps next to each other, both girls, both rocking back and forth, and both constantly wringing their hands in what we now know is the characteristic stereotypic hand movement of Rett syndrome. He quickly found another six similar patients and by 1966 was able to report on studies of 22 girls from the L. Boltzman Institute for Research on Brain-Damaged Children.[1]

The initial observations of Rett reported hyperammonemia which subsequent experience suggests is only rarely seen. Dr Rett contributed a number of further publications in the German-language literature from 1966 to 1969.[2] Because of the false lead of associated hyperammonemia and the lack of an English-language description, knowledge of Rett syndrome remained limited. In 1972 the syndrome was recorded as "Rett's syndrome" but again in a German-language publication.[3] In 1977 Dr Rett himself provided an extensive English-language account of Rett syndrome[4] which was not overlooked by Hagberg et al in their landmark account of 35 girls from Sweden, France, and Portugal.[5] This article confirmed the truly international character of Rett syndrome, awakened interest in the English-speaking world, and recognized Dr Rett's pioneering work.

The second international conference on Rett syndrome was hosted by Dr Rett in Vienna in 1984. At that conference 20 American cases were reported out of the world total of 125. Figure 1 depicts the fast pace of identification of cases in the United States from 1984 to 1987. By 1987 more than 650 girls with Rett syndrome had been identified in the United States with more than 1,250 cases reported worldwide (Kathy Hunter and the International Rett Syndrome Association, unpublished data, October 1987). The developing worldwide interest in Rett syndrome was both fueled and focused by an international workshop on Rett syndrome sponsored by the Kennedy Institute in Baltimore in 1985. Support for this event came from the National Institutes of Health and a number of private agencies including the International Rett Syndrome Association. Over 60 families were able to bring their daughters, providing a unique opportunity for interaction with one another, with the International Rett Syndrome Association, and with over 85 health professionals and researchers. The scientific sessions were a significant step forward in the development of research ideas and interest.

At the 1985 workshop a staging system for Rett syndrome was suggested by Hagberg and Witt-Engerström.[6] This scheme has been widely adopted. Figure 2 diagrammatically illustrates the course of typical or

From the Departments of Neurosciences and Pediatrics, University of California, San Diego.

Address correspondence to Dr Richard H. Haas, Division of Pediatric Neurology, H-815B, UCSD Medical Center, 225 Dickinson Street, San Diego, CA 92103.

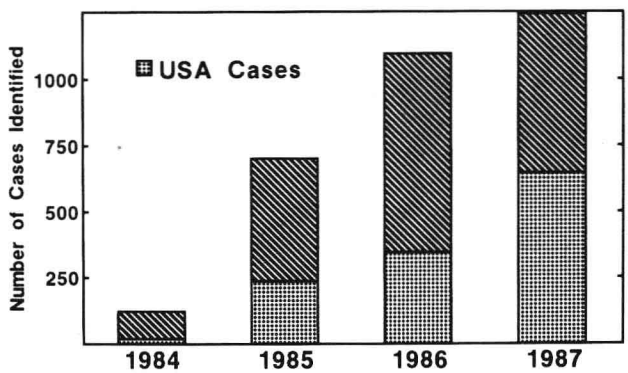

FIGURE 1
The rapid rise in worldwide identification of Rett syndrome.

classic Rett syndrome. Following a period of developmental stagnation (stage I), Rett patients suffer a rapid loss of previously acquired skills together with the onset of many of the characteristic features of the condition (stage II). Stages III (pseudostationary) and IV (late motor deterioration) represent the later stages as motor disability and orthopedic complications become more troublesome. Figure 2 extends the developmental course only to age 16. We do not know whether Rett patients continue to deteriorate slowly or whether in some cases an arrest of the disease occurs. Information on long-term outcome is of great importance to parents and health professionals alike. Several middle-aged Rett patients have been identified but they are relatively few considering the size of the Rett population. Is the life expectancy normal with adequate attention to seizure control, nutrition, and orthopedic complications? We do not yet know.

Rett syndrome presents by far the greatest challenge to the parents and families. It is remarkable how well integrated into the family group these severely impaired girls are. There is clearly a to-and-fro of social interaction which would not be expected by the casual observer looking only at the motor and language skills of the Rett child. The cognitive aspects of this unique disorder remain largely unexplored. To medical researchers, teachers, and health care professionals Rett syndrome presents many challenges. Figure 3 lists some of these. With so many different disciplines required to manage the Rett patient a team approach is essential.

Rett syndrome raises a number of intriguing questions. Why does Rett syndrome only seem to affect girls? Are there any male cases? To prevent omission of male cases the new recommended diagnostic criteria do not require female sex for diagnosis.[7] What is the nature of the disease process in the atypical or forme fruste patient. Is this presentation merely a phenotypic variant of the same disease process or can other disorders masquerade as Rett syndrome? Is the typical phenotype a homogeneous condition? Why are neuropathologic changes so limited in a disorder which so profoundly affects the central nervous system? The answers to these questions lie in the future but there is excitement for those of us interested in Rett syndrome in being involved with such a medical mystery. We owe a great deal to Dr Andreas Rett for the insight and clinical acumen which has given us the opportunity to help patients with this disabling disorder.

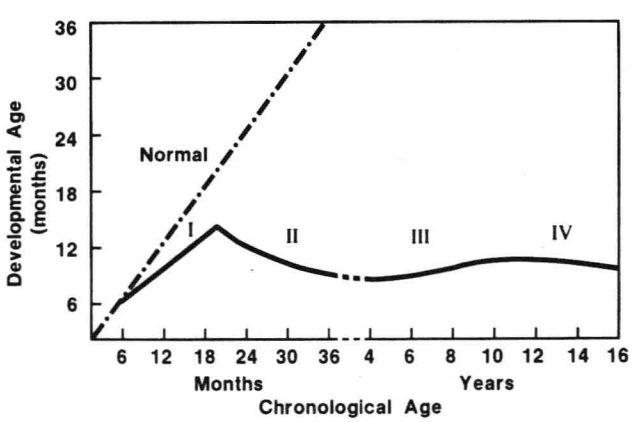

FIGURE 2
The developmental course of typical (classic) Rett syndrome. Roman numerals indicate Hagberg and Witt-Engerström stages.[6]

1. Medical - Nutrition
   Seizure Control
   Apnea
   Orthopedic Management • Scoliosis
   • Foot Deformities
2. Physical Therapists - Ambulation
   Spasticity
   Contractures
3. Educators/Occupational Therapy • Unlock the Dyspraxia - hand use
   • Communication
   • Music Rx
4. Psychologists • Reconsider Autism
   • Re-examine the "Autistic" Population
   • Therapeutic Approaches
5. Research - What causes this disease?
   Can we treat the primary disorder?

FIGURE 3
Challenges in Rett syndrome.

Acknowledgments

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References

1. Rett A: *Über ein zerebral-atrophisches Syndrom bei Hyperammoniämie*. Vienna, Bruder Hollinek, 1966.
2. Holt MC, Opitz JM: Rett syndrome bibliography. *Am J Med Genet* 1986;24(suppl 1):39–46.
3. Leiber B, Olbrich G: *Die klinischen Syndrome: Rett Syndrom*. Munich, Urban & Schwarzenberg, 1972, pp 763–764.
4. Rett A: Cerebral atrophy associated with hyperammonemia, in Vinken PJ, Bruyn GW (eds) *Handbook of Clinical Neurology*. Amsterdam, North-Holland Publishing Co, 1977, vol 29, pp 305–329.
5. Hagberg B, Aicardi J, Dias K, et al: A progressive syndrome of autism, dementia, ataxia and loss of purposeful hand use in girls: Rett syndrome: Report of 35 cases. *Ann Neurol* 1983;14: 471–479.
6. Hagberg B, Witt-Engerström I: Rett syndrome: A suggested staging system for describing impairment profile with increasing age towards adolescence. *Am J Med Genet* 1986;24(suppl 1):47–59.
7. The Rett Syndrome Diagnostic Criteria Work Group: Diagnostic criteria for Rett syndrome. *Ann Neurol* 1988;23:425–428.

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the research program has achieved international scope.

It is the hope of the organizers and contributors to this special issue that it will increase the understanding of this mysterious disorder and speed the time in which it can be treated or prevented. We wish to express special thanks to Dr Isabelle Rapin, recipient of the 1987 Hower award of the Child Neurology Society in recognition of her unique contribution in the study of autism. Dr Rapin solicited and edited the papers on autism contained in this special issue. Dr Michael J. Adams of the Centers for Disease Control provided the impetus for the epidemiological studies of Rett syndrome. Financial support for this special issue was provided by the Centers for Disease Control and the International Rett Syndrome Association.

References

1. Haas RH: The history and challenge of Rett syndrome. *J Child Neurol* 1988;3(suppl):S3–S5.
2. Trevathan E, Naidu S: The clinical recognition and differential diagnosis of Rett syndrome. *J Child Neurol* 1988;3(suppl): S6–S16.
3. Trevathan E, Adams MJ: The epidemiology and public health significance of Rett syndrome. *J Child Neurol* 1988:3(suppl): S17–S20.
4. Fontanesi J, Haas RJ: The cognitive profile of Rett syndrome. *J Child Neurol* 1988;3(suppl):S20–S24.
5. Haas RH, Love S: Peripheral nerve findings in Rett syndrome. *J Child Neurol* 1988;3(suppl):S25–S30.
6. Lieb-Lundell C: The therapist's role in the management of girls with Rett syndrome. *J Child Neurol* 1988;3(suppl):S31–S34.
7. Rice MA, Haas RH: The nutritional aspects of Rett syndrome. *J Child Neurol* 1988;3(suppl):S35–S42.
8. Hennessy MJ, Haas RJ: The orthopedic management of Rett syndrome. *J Child Neurol* 1988;3(suppl):S43–S48.
9. Allen DA: Autistic spectrum disorders: Clinical presentation in preschool children. *J Child Neurol* 1988;3(suppl):S48–S56.
10. Schreibman L: Diagnostic features of autism. *J Child Neurol* 1988;3(suppl):S57–S64.
11. Percy A, Zoghbi HY, Lewis KR, Jankovik J: Rett syndrome: Qualitative and quantitative differentiation from autism. *J Child Neurol* 1988;3(suppl):S65–S67.
12. Olsson B, Rett A: Behavioral observations concerning differential diagnosis between Rett syndrome and autism. *Brain Dev* 1985; 7:277–289.
13. Rimland B: Controversies in the treatment of autistic children: Vitamin and drug therapy. *J Child Neurol* 1988;3(suppl): S68–S72.
14. Percy AK: Research in Rett syndrome: Past, present, and future, *J Child Neurol* 1988;3(suppl):S72–S75.
15. Zoghbi H: Genetic aspects of Rett syndrome. *J Child Neurol* 1988;3(suppl):S76–S78.
16. Naidu S, Kitt CA, Wong DG, et al: Research on Rett syndrome: Strategy and preliminary results. *J Child Neurol* 1988;3(suppl): S78–S86.
17. Hunter K: Role of the International Rett Syndrome Association. *J Child Neurol* 1988;3(suppl):S87–S88.
18. Rapin I: Recruiting parents of children with a fatal disease as coinvestigators. *J Child Neurol* 1988;3(suppl):S89–S90.
19. Percy AK, Haas RH, Kolodny EH, et al: Recommendations regarding the postmortem examination in Rett syndrome. *J Child Neurol* 1988;3(suppl):S91–S93.

The Clinical Recognition and Differential Diagnosis of Rett Syndrome

Edwin Trevathan, MD, MPH; Sakkubai Naidu, MD

Abstract

Rett syndrome (RS) is characterized by progressive loss of intellectual functioning and fine and gross motor skills as well as development of stereotypic hand movement abnormalities, occurring after 6 to 18 months of normal development. Rett syndrome has been previously reported only in girls, but the possibility of the syndrome existing in male children cannot be currently excluded. Although the syndrome is thought to be relatively common, it was only described in the English literature 5 years ago. There is currently no marker for the syndrome; diagnosis is based on clinical criteria. The newly developed diagnostic criteria for RS are reviewed, with special attention given to the historical aspects of the diagnosis in the prenatal, perinatal, neonatal, and early childhood periods. Rett syndrome is characterized by a predictable, orderly progression of signs and symptoms. Four stages of RS have been described; each stage has special characteristics and offers different diagnostic challenges for the neurologist. Infantile autism is the most common incorrect diagnosis made for children with RS. The simultaneous regression of both motor and language skills, as well as the stereotypic hand movements, hyperventilation, bruxism, and seizures in early childhood are all typical in RS and help distinguish RS from infantile autism. (*J Child Neurol* 1988;3(Suppl):S6–S16).

More than 20 years ago Dr Andreas Rett noticed that two little girls sitting next to each other in the waiting room of his Vienna pediatric neurology clinic had similar behavioral characteristics, hand movements, and gaits; their developmental histories were also similar.[1] His systematic observations of these and other patients led to the description of a syndrome[2,3] that was later to bear his name.[4] Once thought to be relatively rare, clinical anecdotes[4–7] have suggested, and two epidemiologic studies[8,9] have indicated, that Rett syndrome (RS) is an important contributor to mental retardation.

In the absence of a specific biologic marker for RS, the diagnosis continues to be based on clinical characteristics of the syndrome.[10] Despite the lack of effective treatment, research efforts alone should not compel the clinician to identify patients with RS among patients with autistic features and mental retardation. Families and individual patients benefit from the clinician's specific syndrome diagnosis. A specific diagnosis helps families deal with the reality of the prognosis, plan for the future, cope with any guilt feelings, and obtain support from parent support groups such as the International Rett Syndrome Association.[11]

We review the diagnostic criteria[10] and describe the staging, clinical characteristics,[12] and the differential diagnosis of RS. We hope that this review will help clinicians evaluate patients with suspected RS.

From the Perinatal Environmental Epidemiology Branch, Division of Birth Defects and Developmental Disabilities, Center for Environmental Health and Injury Control, Centers for Disease Control, Atlanta (Dr Trevathan), and the Kennedy Institute, and the Departments of Pediatrics and Neurology, The Johns Hopkins University School of Medicine, Baltimore (Dr Naidu).

Address correspondence to Edwin Trevathan, MD, MPH, Division of Birth Defects and Developmental Disabilities, CEHIC, Koger Center, F-37, Centers for Disease Control, Atlanta, GA 30333.

Diagnostic Characteristics

Recently, an effort to develop diagnostic criteria for a physician survey of RS in the United States led to a consensus statement on the diagnostic criteria for typical RS (Table 1).[10] These diagnostic criteria were, in part, built on the foundation laid by experts at an RS conference in 1984.[13] The purposes of the new diagnostic criteria are as follows: (1) to provide guidelines that will enable investigators to define a relatively homogeneous population for clinical and

TABLE 1
Diagnostic Criteria for Rett Syndrome*

Necessary Criteria†
1. Apparently normal prenatal and perinatal period
2. Apparently normal psychomotor development through the first 6 months‡
3. Normal head circumference at birth
4. Deceleration of head growth between ages 5 months and 4 years
5. Loss of acquired purposeful hand skills between ages 6 and 30 months, temporally associated with communication dysfunction and social withdrawal
6. Development of severely impaired expressive and receptive language, and presence of apparent severe psychomotor retardation
7. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and "washing"/rubbing automatisms appearing after purposeful hand skills are lost
8. Appearance of gait apraxia and truncal apraxia-ataxia between ages 1 and 4 years
9. Diagnosis tentative until 2 to 5 years of age

Supportive Criteria
1. Breathing dysfunction
   a. Periodic apnea during wakefulness
   b. Intermittent hyperventilation
   c. Breath-holding spells
   d. Forced expulsion of air or saliva
2. EEG abnormalities
   a. Slow waking background and intermittent rhythmic slowing (3–5 Hz)
   b. Epileptiform discharges, with or without clinical seizures
3. Seizures
4. Spasticity often with associated development of muscle wasting and dystonia
5. Peripheral vasomotor disturbances
6. Scoliosis
7. Growth retardation
8. Hypotrophic small feet

Exclusion Criteria†
1. Evidence of intrauterine growth retardation
2. Organomegaly, or other signs of storage disease
3. Retinopathy or optic atrophy
4. Microcephaly at birth
5. Evidence of perinatally acquired brain damage
6. Existence of identifiable metabolic or other progressive neurologic disorder
7. Acquired neurologic disorders resulting from severe infections or head trauma

* Reproduced with permission from Trevathan et al.[10]
† Modified from Hagberg et al.[13]
‡ Development may appear to be normal until 18 months

epidemiologic studies; (2) to make the diagnostic criteria of practical use to practicing primary care physicians as well as subspecialists; and (3) minimize potential selection bias in clinical and epidemiologic studies of RS.

A basic assumption of the diagnostic criteria work group was that RS (in its typical form) is a unique disorder. To ensure a homogeneous patient population for epidemiologic and large-scale clinical research, the diagnostic criteria were restricted to include only typical cases.

The diagnostic criteria have been divided into necessary, exclusion, and supportive criteria (see Table 1). All nine necessary criteria must be observed in a given patient for RS to be diagnosed. Violation of a single exclusion criterion eliminates RS as a diagnostic possibility, even if all of the necessary criteria are met. For example, the presence of another well-defined neurologic disease that is known to cause or be an important risk factor for mental retardation, at present, excludes the diagnosis of RS. The supportive criteria are designed to help the clinician recognize potential cases of RS and provide additional confidence in the diagnosis once all necessary criteria have been met. The presence of any or all of the supportive criteria does not replace the requirement that all necessary criteria must be met. Rett syndrome may be diagnosed in the absence of all supportive criteria—especially in younger patients.

Some investigators have reported looking for

male children with RS within clinical series without finding a single case.[14,15] Based on these clinical series, some investigators have proposed an X-linked dominant mechanism of transmission.[3] Previously published diagnostic criteria included female sex as a necessary criterion for diagnosing RS.[13] Goutières and Aicardi, however, suggested that to avoid automatic exclusion of male children with RS characteristics, female sex should not be used as a diagnostic criterion.[14] Watanabe et al previously reported that three of 24 patients who presented with at least some of the features of RS were male children, although detailed evaluations of these patients were not discussed.[16] Female sex has not been included as a necessary criterion for diagnosing RS[10] for the following reasons: (1) limiting the possible diagnosis of RS to female children might introduce bias into clinical and epidemiologic studies; (2) due to the early stage of interest in this disorder, we cannot exclude the possibility of undiagnosed male cases.

All suspected male cases should have extensive diagnostic and cytogenetic evaluations to rule out other potential diagnoses (discussed later). We suggest that if any male children are identified as having RS, for research purposes they should be analyzed separately from the typical female cases, at least until a marker is identified. Once a marker is recognized for the syndrome, the male patients so identified may be found to manifest clinical characteristics different from those of their female counterparts.

Prenatal and Perinatal Issues

The first of the nine necessary criteria requires that there be no serious complications during pregnancy or the perinatal period (see Table 1). Evidence of perinatal asphyxia (or the syndrome of neonatal hypoxic-ischemic encephalopathy) excludes the diagnosis of RS (Table 2). A sharp distinction should be made between true evidence of perinatally acquired brain damage, as manifested by the clinical profile of neonatal hypoxic-ischemic encephalopathy,[17] and the unfortunate practice of some clinicians of attributing idiopathic mental retardation or cerebral palsy to "assumed perinatal asphyxia." A previous assumption that perinatal asphyxia must have occurred in the absence of clinical evidence of asphyxia or neonatal hypoxic-ischemic encephalopathy should not be interpreted as "evidence" of perinatally acquired brain damage and should not exclude the diagnosis of RS.

Deciding whether a particular complication during pregnancy or the neonatal period is significant enough to exclude the diagnosis of RS requires judgment; we offer some suggestions regarding these clinical decisions. In general, nonspecific, relatively minor problems during pregnancy that occur with significant frequency in mothers of normal children should not be considered exclusion criteria. For example, Naidu et al found that 30 of the 70 mothers of RS patients they interviewed reported various minor complications during pregnancy (Table 3)[18]; the significance remains unknown and we suggest that such minor complications should not exclude the diagnosis of RS. Rett syndrome patients may have had minor delivery complications such as forceps delivery without evidence of neonatal complications; the prevalence of minor delivery complications among RS patients is not known and should be studied using a suitable control population.

Mild hypotonia in the newborn period does not

TABLE 2
Clinical Features of Hypoxic-Ischemic Encephalopathy of the Newborn

First 72 hours
Deep stupor*
Initially hypotonic, then jittery
Periodic breathing or apneic spells
Seizures, often status epilepticus
Occasionally signs of renal or cardiac hypoxic-ischemic injury
Brainstem oculomotor and pupillary disturbances
After 72 hours
Persistent, but diminished stupor
Abnormal gag, swallowing, sucking, and tongue movements
Hypotonia progresses to hypertonia
Oculomotor disturbances may persist

Modified from Volpe.[17]
* Some infants who appear stuporous at birth to 12 hours of age may show apparent transient improvement at 12–24 hours.

TABLE 3
Minor Pregnancy Complications in 70 Mothers of Children with Rett Syndrome

Complications*	No. of Mothers
Clomiphene citrate (Clomid), diuretic, or medication for nausea	14
Medication for hyperthyroidism	1
Medication for hypothyroidism	1
Vaginal, urinary tract, or mild systemic infections	10
Minor surgery	3
History of decreased fetal movements	2
Preclampsia	3
Cesarean section (failure to progress)	1
Breech presentations	3
Oligohydramnios	1

Modified from Naidu et al.[18]
* In the absence of more severe complications of pregnancy, such as eclampsia or other severe systemic maternal disorders that were poorly controlled during pregnancy, abruptio placentae with hemorrhage, and suspected intrauterine asphyxia, these minor complications of pregnancy do not exclude the diagnosis of Rett syndrome.

exclude the diagnosis of RS and may be a common finding among those children with RS who had careful neurologic examinations during the newborn period.[18] We cannot consider the presence of mild hypotonia during infancy a necessary or supportive diagnostic criterion. Mild hypotonia in infancy is a nonspecific finding in many disorders.

Previous reports of clinical series have indicated that children with RS tend to be full-term neonates.[18,19] We suspect that among children with RS the rate of prematurity (<37 weeks gestational age) is similar to that of the general population (8.9%),[20] and we believe prematurity alone should not exclude the diagnosis of RS. Likewise, low birth weight in a premature infant whose weight is average for gestational age (AGA) should not automatically exclude the diagnosis of RS. Currently, we would consider the presence of any neurologic complication in the newborn period, including the presence of a symptomatic intraventricular hemorrhage (IVH),[21] to exclude the diagnosis of RS. Because very-low-birth-weight infants tend to have excessive neurologic complications in the newborn period,[22] we believe the diagnosis of Rett syndrome should be made in these children only if care has been taken to exclude previous neurologic complications (eg, IVH). The presence of intrauterine growth retardation excludes the diagnosis of typical RS (see Table 1).[10]

A history of minor neurologic complications in the newborn period associated with systemic disorders that are known to have a high risk of severe neurologic sequelae, such as bronchopulmonary dysplasia (BPD),[23] persistent pulmonary hypertension of the newborn (PPHN or PFC),[24] and severe Rh incompatibility with hyperbilirubinemia,[25] should generally exclude the diagnosis of RS. Infections of the central nervous system, including but not limited to a congenital TORCH infection before the onset of neurologic signs, excludes RS.

Late Infancy and Early Childhood Issues

Congenital microcephaly excludes the diagnosis of RS (see Table 1). Typically children with RS begin to have clear deceleration of head growth between 6 and 12 months, although deceleration of head growth may be apparent as early as 4 months (Figure 1).[5] No associated facial, oral, or cranial dysmorphisms have been reported in these children.

Virtually all children with RS acquire purposeful hand movements, including a pincer grasp, sometime before 18 months of age.[19] Some children develop the ability to drink from a cup, and others are even able to use a spoon before the purposeful hand use is lost. The loss of purposeful hand movements may occur as early as 8 months or as late as 4.5 years, but the most common time is during the 18- to 24-month age range.[4,18,19] The insidious loss of hand skills may be the single most reliable early sign of the syndrome,[26] and precedes the development of the characteristic stereotypic hand movements. Frequently, the loss of hand skills is temporally associated with autistic-like features (described later) between 8 and 36 months of age. The distinctive stereotypic hand movements, characterized by twisting or wringing movements, do not occur while the patient still has good purposeful hand skills (Figure 2). These hand movements are usually midline, but may also occur to one side or occasionally even behind the back. Often, the hand movements are virtually con-

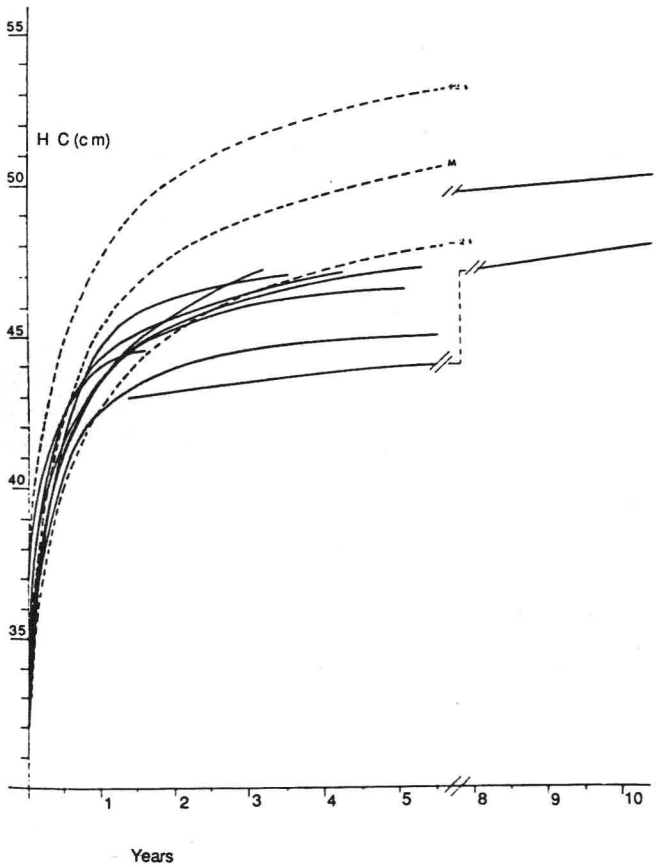

FIGURE 1
Head circumference growth curves in ten patients with Rett syndrome, demonstrating the deceleration of head growth between 6 months and 4 years. (Reproduced with permission from Hagberg et al.[4])

tinuous during waking, but disappear during sleep.

Marked irritability, often with screaming fits, occurs between 18 months and 2 years in most patients.[18,19] Yet by 4 to 5 years of age social interaction and eye contact improve, with resolution of the screaming fits. Autistic-like features have been reported during the first 6 months of life[5] in infants who were later diagnosed as having RS. These early autistic features, however, are usually not prominent until at least the age of 8 months.[4,18,19]

Crawling is almost always delayed, and is often abnormal in character, with a "crablike"[5] or "bunny hop"[18] crawl. Some patients never crawl but simply scoot themselves across the floor in an almost sitting position. Walking is usually delayed in these patients, occurring at about 19 months. Almost one fourth of the RS patients reviewed by Coleman et al never walked independently.[19]

Although the delayed and abnormal crawling and delayed walking is nonspecific and occurs in several disorders, the gait apraxia and truncal ataxia occurs consistently in RS children who are able to ambulate and is unusual in other disorders. The truncal ataxia has a jerky quality and is usually apparent when the child is sitting unsupported. The gait is wide-based and unsteady, usually with a jerky, stiff-legged swaying motion, and often with associated toe-walking.[5,18] Many RS patients benefit from leg braces to bring the foot down to the horizontal position. About one third of RS patients lose the ability to ambulate entirely, sometimes as early as 4 to 5 years of age.[19]

All children with RS function in the range of severe-to-profound mental retardation. Children with RS may develop language to the "mama and dada"

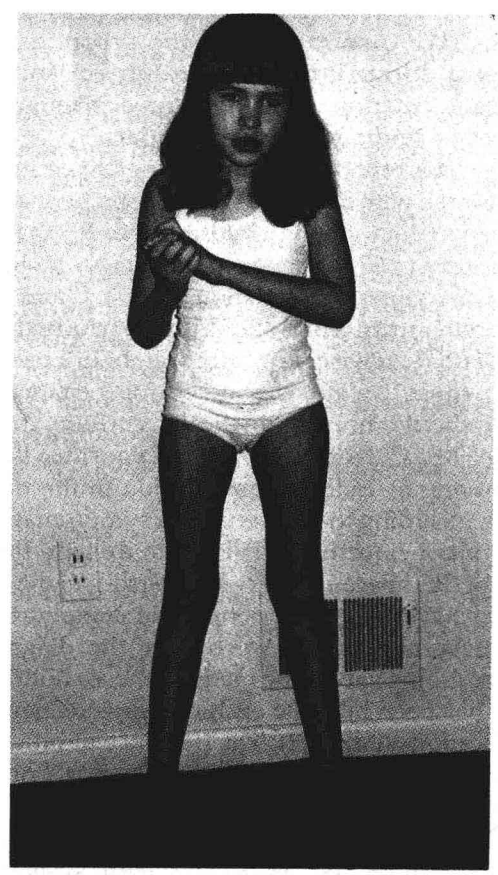

FIGURE 2
A child with Rett syndrome is shown at the age of 13 years. The hands are together in a wringing-like posture, the gait is wide-based, and intense eye contact is demonstrated (photo courtesy of the International Rett Syndrome Association).

plus two- to three-words level, but this language is lost between 12 months and 4 years.[4,18,19] Because of the loss or lack of language development, some RS patients have presented to the neurologist with a question of hearing loss. Virtually all expressive language is lost, although rarely some children may produce echolalic sounds and learn simple signing.[19] Evidence of minimal receptive language may persist after 4 years of age, but typically, children with RS lose all evidence of receptive and expressive language beyond the simplest level.

Seizures occur in about 70% to 80% of RS patients,[6,18,19] with onset of the seizures usually between 1 and 5 years of age. Generalized tonic, tonic-clonic, atypical absence, complex partial, myoclonic, and atonic seizures may occur. Multiple seizure types are common in many patients, and about 30% to 40% of RS patients may have poorly controlled or intractable seizures.[18,19] The multiple seizure types (including atonic seizures), the intractable nature of the seizures, and the EEG patterns have led clinicians to consider the diagnosis of Lennox-Gastaut syndrome in these children.[27] The seizures may be brought on by drowsiness or sleep. Based on our experience, we suspect that nocturnal seizures may contribute to the apparent excess of sudden unexplained death during sleep in these children. Several clinicians have reported that carbamazepine seems to be the most effective single anticonvulsant, especially among those RS patients with a predominance of complex partial seizures. Seizures often become less frequent and easier to manage during the second decade of life.

Among children with RS the EEG is abnormal in the majority of cases after age 2 years, though no specific abnormality has been described.[28,29] Glaze et al have reported a characteristic progression of changes in the EEG background, with slowing of the posterior rhythm after age 2 years, gradual disappearance of the posterior rhythm, and development of generalized background slowing;[29] this sequence of background abnormalities is similar to the evolution of background abnormalities seen in other progressive encephalopathies.[30] Rhythmical medium-voltage generalized theta activity during both waking and drowsiness has been reported to be prominent in many RS patients.[28,31] Between 3 and 10 years of age, paroxysmal abnormalities are prominent, even in patients without clinical seizures.[5,28,31] Multifocal spike and wave complexes, with atypical voltage predominance (ie, with voltage predominance over the posterior regions rather than the frontal regions as seen in Lennox-Gastaut syndrome), have been reported by Trauner and Haas,[32] while other authors have reported EEG paroxysmal abnormalities in Rett syndrome that are similar to the EEG patterns seen in Lennox-Gastaut syndrome.[28,33]

Epileptiform abnormalities may be activated by sleep in some patients, with slow spike and wave discharges sometimes being almost continuous during non–rapid eye movement (non-REM) sleep.[29] Sleep patterns are typically abnormal after age 2 years, initially with poorly developed spindle activity and later with absence of vertex waves and sleep spindles.[28,29,31] During the second decade of life the paroxysmal abnormalities are less prominent (as are the seizures), but the slow and somewhat poorly organized background abnormalities persist. Cranial computed tomography (CT) scans in RS patients have been reported to be either normal or to show mild generalized atrophy;[5,6,18] evidence of a large vessel stroke occurring before onset of the RS manifestations[34] should exclude RS.

Rett syndrome patients almost always have some type of breathing dysfunction. Hyperventilation with air-swallowing and breath-holding are usually prominent in these children.[4] These patients tend to have respiratory irregularity, often with intermixed apnea resulting in cyanosis during wakefulness, whereas respiratory patterns during sleep tend to be normal without reduction in oxygen saturation.[35–38] Polygraphic recordings during waking as early as 2 years of age have shown disorganization of respiratory patterns with central, obstructive, or mixed apnea in association with reductions in oxygen saturation below 60%.[37]

Blotchiness of the skin, especially reddish discoloration of the hands and feet, can be found in most RS patients.[4,18,19] By 5 years of age, hyperreflexia has developed in most children. Rigidity, which is initially pronounced in the lower extremities, later extends to the upper extremities and, in many patients, becomes diffusely prominent over the next few years. Joint contractures develop in some patients. Choreoathetosis and dystonia can be found in some children with RS.[39] Growth retardation, with decreased height and weight for age, in the presence of a normal (and perhaps increased) appetite, occurs as early as 2 years of age. Sexual development tends to be normal in girls with RS.[40] Beginning at about 5 years of age, there is an apparent progressive reduction in muscle mass.[4,18,40] Initially the feet predominantly, and later the hands, become small and appear hypotrophic. Scoliosis develops in at least half of these children beyond 10 years of age, and many require surgical correction to improve their lung capacity and respiratory function.

Atypical Rett Syndrome

Patients with RS-like characteristics who do not fulfill the diagnostic criteria as outlined previously[10] have been considered to have atypical RS.[14,41] Patients with perinatal asphyxia (case IV of Nomura et al[5]), normal development until 20 months, continued purposeful hand use and lack of stereotypic hand movements,[42] developmental delay from early infancy, absence of normal hand use before regression, and congenital microcephaly[14] have been included in discussions of atypical RS. Patients with well-defined neurometabolic disorders such as ornithine transcarbamylase deficiency[42] and neuronal ceroid lipofuscinosis have been described as having clinical manifestations similar to patients with RS. In addition, patients with clinical manifestations of RS but with other superimposed, well-defined neurologic syndromes, such as infantile spasms,[43] have been classified as atypical RS. Individual or selected cases of atypical RS may offer important insights into the disorder, but in the absence of a marker, we suggest that these atypical cases be analyzed separately in clinical and epidemiologic studies. Should a marker be identified in typical cases and be absent in other well-defined neurologic disorders, the presence of the marker might be considered sufficient for the diagnosis of RS and would help in recognizing the clinical spectrum of this disorder.

Staging of RS

One of the characteristics of RS is the orderly sequence of the appearance of clinical signs and symptoms at certain stages of the disease process.[3–5,18,43] Hagberg and Witt-Engerström have presented a staging system for RS.[12] This system provides a practical framework for describing the progression of clinical characteristics (Table 4). Although the duration and the age of onset of each stage varies from one patient to the next, the progression of clinical events is common to all patients. There is no clinically obvious transition between stages.

Although we acknowledge the usefulness of identifying the four stages of the disorder, the names of the stages may be misleading. For example, identifying stage II as the *rapid destructive stage* would be somewhat of a misnomer, as no pathologic data currently support the concept of an actual CNS destructive process associated with RS. Rather, stage II is characterized by a dramatic clinical regression of neurologic function in all areas. Likewise, the term *pseudostationary stage* is also confusing; although the autistic features tend to resolve, other clinical features, such as spasticity or rigidity, and scoliosis tend to progress. At present, we prefer to refer to the stages of the disorder without using the descriptive labels that have been previously suggested.

The diagnosis is frequently suspected during stage I, but usually RS is not formally diagnosed before the onset of stage II. The autistic features during stage II may obscure the diagnosis, but with the onset of stage III, the diagnosis should be clinically obvious.

Differential Diagnosis

The differential diagnosis of RS tends to vary with the stage of the disorder. Some of the key items in the differential diagnosis are listed in Table 4. The clinical characteristics of stage I are often so mild that they are not recognized. Beginning in stage II, the clinical presentation could be characteristic of several of the inherited metabolic disorders, such as infantile neuronal ceroid lipofuscinosis, and lysosomal or mitochondrial disorders. We suggest that all patients suspected of having RS should also undergo routine serum and urine screens for disorders of amino acid and organic acid metabolism. Cerebrospinal fluid from RS patients has been normal for protein, glucose, and myelin basic protein, and has not demonstrated oligoclonal bands.[18] CSF catecholamines have been reported to be low in RS patients,[44] but this has not been a finding in all RS patients. Although no characteristic findings on cranial computed tomography (CT) have been described for children with RS, CT scans should probably be obtained for all suspected cases of RS to exclude evidence of a previous large vessel stroke or a well-defined malformation. In addition, ophthalmologic evaluations should be obtained in a search for corneal or retinal abnormalities typical of other degenerative disorders. In children with suspected visual disturbances, both visual evoked responses and electroretinograms (ERGs) may be indicated.

Brainstem auditory, upper and lower extremity somatosensory, and pattern-reversal visual evoked potentials have been reported to be normal in RS patients between 2 and 15 years of age.[45] Among older stage IV patients with severe motor disability, somatosensory and brainstem auditory evoked potentials have been reported to be abnormal, with the somatosensory evoked potentials to median nerve stimulation demonstrating prolonged N13–N20 interpeak latencies in all patients, and most patients having prolonged N9–N13 interpeak conduction times.[46] Similiar findings have been reported by Pelson and Budden.[47] Based on the evoked potential findings in older patients, Badr et al suggested that upper spinal

TABLE 4
Rett Syndrome: Clinical Characteristics and Differential Diagnosis by Stage

Stages[12]	Clinical Characteristics	Differential Diagnosis
Stage I Onset: 6–18 mo Duration: months	Developmental stagnation Deceleration of head/brain growth Disinterest in play activity and environment Hypotonia EEG background: normal or minimal slowing of posterior rhythm	Benign congenital hypotonia Prader-Willi syndrome Cerebral palsy
Stage II Onset: 1–3 yr Duration: weeks to months	Rapid developmental regression with irritability Loss of hand use Seizures Hand stereotypies: wringing, clapping, tapping, mouthing Autistic manifestations Loss of expressive language Insomnia Self-abusive behavior (eg, chewing fingers, slapping face) EEG: background slowing and gradual loss of normal sleep activity; focal or multifocal spike and wave	Autism Psychosis Hearing or visual disturbance Encephalitis Epileptic encephalopathy Neurocutaneous syndromes Neurodegenerative disorders Various disorders of organic acid and amino acid metabolism
Stage III Onset: 2–10 yr Duration: months to years	Severe mental retardation/apparent dementia Amelioration of autistic features Seizures Typical hand stereotypies: wringing, tapping, mouthing Prominent ataxia and apraxia Hyperreflexia and progressive rigidity Hyperventilation, breath-holding, aerophagia during waking Weight loss with excellent appetite Early scoliosis Bruxism EEG: gradual disappearance of posterior rhythm, generalized slowing, absent vertex and spindle activity, epileptiform abnormalities activated during sleep	Spastic ataxic cerebral palsy Spinocerebellar degeneration Leukodystrophies or other storage disorders Neuroaxonal dystrophy Lennox-Gastaut syndrome Angelman syndrome
Stage IV Onset: 10 + yr Duration: years	Progressive scoliosis, muscle wasting, and rigidity Decreasing mobility, wheelchair-bound Growth retardation Improved eye contact Virtual absence of expressive and receptive language Trophic disturbance of feet Reduced seizure frequency EEG: poor background organization with marked slowing and multifocal spikes and slow spike and wave pattern activated by sleep	Unknown degenerative disorder

Modified from Hagberg and Witt-Engerström.[12]