CLINICAL MANIFESTATIONS AND STAGES OF RETT SYNDROME

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The presentation and clinical diagnosis of Rett syndrome at various ages and stages are reviewed. In addition to the classical form, variability in phenotype between different atypical Rett forms is given. Obligatory, supportive, and differential diagnostic criteria are summarized. Long-term follow-up findings in ageing Rett women are addressed.

Key Words: Rett syndrome; clinical manifestations; stages of disease

EARLY CLINICAL HISTORY

Less than 20 years have passed since Rett syndrome (RS) became internationally accepted as a unique and puzzling disorder affecting small girls previously regarded as “normal” [Hagberg et al., 1983]. Today, we know that RS is a condition found worldwide. It has probably existed for a long time in most if not all ethnic populations, although it has not been correctly interpreted and understood by clinicians. Between 1960–1980, I myself saw a number of these developmentally deviating girls with their curious and unexplained hand wringing which was not referred to in any textbooks. I was very puzzled! I saved their documents in a box and, from the family name of my first patient, I coined the provisional label of Vesslan’s (weasel) disease. The first step towards identifying RS occurred at the board meeting of the EFCNS (European Federation of Child Neurology Societies) in June 1981 in Manchester, hosted by Dr. Neil Gordon [Gordon, 1993]. There, I had the opportunity to present for discussion the clinical characteristics and oddities noted in my original series of 16 girls seen in Uppsala and Göteborg. In the discussion group comprising about a dozen experienced pediatric neurologists, the opinion was that the majority of them had seen these small girls but had not recognized them as belonging to a specific entity. Through the 1960s and 1970s, the disease was widely considered to represent another member of the rapidly-increasing number of previously unknown, rare and relentlessly deteriorating neurochemical brain diseases—a focus for neurobiological research activities. Within a short time, we had identified 35 girls with the condition in Sweden, France, and Portugal and had started to analyze this new syndrome for publication.

The second and most important step in my “Rett story” occurred during the process of writing a paper for publication in Annals of Neurology [Hagberg et al., 1983]. It started with an urgent call from Dr. Jean Aicardi in Paris. During a ward round when searching for conditions related to hyperammonemia in a large textbook, he and his collaborator Dr. Francoise Goutières had accidentally found a photo under that eponym illustrating a peculiar handwringing girl, one in a series of 31 such patients. The disease obviously affected only girls [Rett, 1966] and all our patients were girls, a curious fact which was underlined at a very early stage by Dr. Karin Dias in Lisbon. The author was an Austrian doctor, Andreas Rett, from Vienna. We immediately called him and learned among other things that the hyperammonemia had probably been due to some technical error. Otherwise, the clinical set-up of symptoms and signs appeared to be identical to that of the girls we were just in the process of describing for publication.

The third, and for me, quite unexpected, step occurred at the IASSMD (International Association Scientific Study Mental Deficiency) conference in Toronto in the Fall of 1981. At the end of my introductory presentation on the epidemiology of learning disabilities, an excited man suddenly rushed from the back of the lecture hall towards the chair and me, shouting in German: “Ich bin Rett, ich bin Rett, ich will jetzt mit Ihnen sprechen.” The man, Andreas Rett, underlined how important it would be for the Austrian Ministry of Health (where he had a consultant position), for his hospital, and particularly for him personally to have an opportunity to invite a small group of experienced neuropediatricians to an informal workshop in Vienna in order to see together and then discuss characteristic “Rett females,” from young girls up to women aged 30 and over. This was very successfully organized in April 1982 and became the extremely important start for the series of more strictly organized Rett conferences in Vienna in 1984 [Proceedings, 1985], 1986 [Proceedings, 1987], and 1988 [Proceedings, 1990]. The first workshop also became the background to important contacts with Japan, which was aware of the condition at an early stage [Ishikawa et al., 1978], and soon afterwards also with the US and with Professor Hugo Moser in particular. He and I in fact started a most productive RS dialogue shortly after the publication in Annals of Neurology [Hagberg et al., 1983]. The international family organization, IRSA, was successfully started by Mrs. Kathy Hunter and collaborators. A large international symposium was initiated and organized in Balti-
more, in November, 1985 [The Rett syndrome, 1986], with the participation of an impressive number of RS families, the majority with small RS girls at that time. This opened the door to a rapidly-extended international scientific and multi-professional network.

**CLINICAL FEATURES AND STAGES**

**Classical Rett Syndrome**

Rett syndrome is a clinical concept. In 2001, a diagnosis still has to rely on a battery of characteristic co-existing clinical criteria and a sequence of stages, combined with a procedure of differential diagnostic exclusions. The criteria (Tables 1 and 2) for classical RS, comprised by three quarters of cases, were agreed on in the 1980s [Hagberg et al., 1985; Trevathan and Moser, 1988] and those for atypical RS, comprised by one quarter of cases, in the 1990s [Hagberg and Gillberg, 1993]. One essential criterion for classical RS is a documented loss, usually at the age of 1–2 years, of early acquired developmental skills, i.e., fine-finger function/practical hand use, learned single words/babble, communicative behavior, and expected personality profile. The period of regression, which can last from months to a few years, is followed by a “come back” in a sequence of subsequent age-related stages (Table 3). This differentiates RS from progressive degenerative brain disorders. The classical RS was presented in great detail by Dr. Ingegerd Witt Engerström in her thesis [Witt Engerström, 1990] and was further developed by a Swedish team in a volume of *Clinics in Developmental Medicine* [Hagberg, 1993; Hagberg and Witt Engerström, 1992].

**Supportive Clinical Rett Manifestations**

**Stereotypic hand movements**

The almost continuous repetitive wringing, twisting, and clapping hand automatisms during wakefulness constitute the hallmark of the condition. In most patients, the patterns are midline motions, but some display patting or rolling stereotypes with their hands apart. Each girl has her own monotonously-repeated hand maneuvers.

**Intensive eye communication**

Intense staring to obtain eye communication, or express wishes, is a prominent feature in most RS girls. Usually, it appears after the end of the regression period. In schoolgirls and adolescents, this behavioral pattern has often become further strengthened. Well-functioning RS females even tend to develop a primitive yet sophisticated “eye pointing” language as a substitute for their loss of speech and fine motor communication skills. This has led creative teachers to develop useful methods of eye communication for use in habilitation programs.

**Episodic hyperventilation and breath-holding**

Peculiar and disorganized breathing disturbances are the rule. They usually consist of irregularly occurring episodes of intense hyperventilation, often disrupted by apneic breath-holding episodes usually lasting up to 30–40 seconds. The apneic pauses can be threateningly long and are often accompanied by Valsalva maneuvers. It is characteristic for the breathing abnormalities only to occur during wakefulness. Insights into hyperventilation in RS have recently been reviewed [Kerr and Julu, 1999; Julu et al., 2001].

**Bloating**

Air swallowing of a moderate degree is common. This kind of bloating is met extremely rarely in general pediatric practice. Some RS females (5–10%) demonstrate such extreme bloating that the abdomen may mimic the late stages of pregnancy. In the author’s experience, these prominent forms are only found in RS.

**Bruxism**

Bruxism is not pathognomonic, but it is a very characteristic feature. The

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**Table 1. Obligatory Manifestations in the Diagnosis of Classical Rett Syndrome. Adapted From Hagberg [1995]**

<table>
<thead>
<tr>
<th>Manifestation/Age</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Infant apparently normal initially</td>
<td>Pre/perinatal period as well as first 6 months of life or longer</td>
</tr>
<tr>
<td>Head circumference stagnation 3 months–4 years</td>
<td>Normal at birth, then a decelerating growth rate</td>
</tr>
<tr>
<td>Purposeful hand skill loss 9 months–2.5 years</td>
<td>Communicative dysfunction, social withdrawal, mental deficiency, loss of speech/bubbling</td>
</tr>
<tr>
<td>Classical stereotypic hand movements after 1–3 years</td>
<td>Hand washing/wringing or clapping/tapping</td>
</tr>
<tr>
<td>Gait/posure dyspraxia 2–4 years</td>
<td>Gait “ataxia” /more or less jerky truncal “ataxia”</td>
</tr>
</tbody>
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**Table 2. Rett Syndrome (RS): a Variant Delineation Model [Hagberg and Skjeldal, 1994]**

<table>
<thead>
<tr>
<th>Inclusion criteria: 1 A girl of at least 10 years of age with mental retardation of unexplained origin and with at least three of the six following primary criteria.</th>
</tr>
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<tbody>
<tr>
<td>A1 Loss of (partial or subtotal) acquired fine-finger skill in late infancy/early childhood</td>
</tr>
<tr>
<td>A2 Loss of acquired single words/phrases/nuanced bubble</td>
</tr>
<tr>
<td>A3 RS hand stereotypes, hands together or apart</td>
</tr>
<tr>
<td>A4 Early deviant communicative ability</td>
</tr>
<tr>
<td>A5 Deceleration in head growth of 2SD (even when still within normal limits)</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

Notes: Inclusion criteria according to the Diagnostic Criteria Work Group [Trevathan and Moser, 1988].

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"..."
bruxism in RS involves an episodic cracking sound similar to that heard when slowly uncorking a wine bottle. It appears to be produced far back in the tightly compressed jaw.

Night laughter
Sleep disturbances, mild or severe, are reported in the majority of cases and it is striking that 80–90% of preschool RS girls wake up laughing loudly during the night. Such curious episodes, sometimes continuing for hours, can be very disturbing. Episodic laughter is not constantly present through all ages and stages but tends to appear periodically and may persist in some subjects into adult life.

Screaming spells
Some RS girls, mainly in their teens and older, periodically have attacks of violent screaming, which may last for many hours. Such screams of horror are often suspected by parents and doctors to be associated with severe yet undefined body pains. This peculiar stereotypic symptomatology cannot be referred to any particular organ pathology but obviously to “pain in the brain.” Quite a few RS girls have been referred for acute surgery consultation, but thorough examinations and observations have not revealed any somatic abnormalities.

Hypoplastic red-blue cold feet
Many RS females display a disproportionate early deceleration in growth in their feet, more than would correlate to their frequently reduced total body size. Those with remarkably small, cold, bluish-red feet in adolescence tend to develop trophic skin and nail changes. In some, episodically occurring profuse sweating of the feet is also noted. It has been suggested that deranged autonomic regulation could explain the abnormal biology behind this [Kerr and Julu, 1999].

Back deformities
A scoliosis of neurogenic type with a double curve deformation is a very important and threatening deformity. A double curve of this kind appears, with large variations in severity, in many classical RS females. Characteristically, it develops successively from early school age and is more rapid and pronounced than in many other types of neurogenic scoliosis in childhood. The type of double curve most frequently seen has a longer upper curve (most often right convex) and a shorter lower one (then left convex). Early ominous signs, such as floppiness, neuromuscular insufficiency, and extrapyramidal asymmetries (dystonic features) indicate the threat of rapid development of the scoliosis. In such situations, active surgical corrections with spinal fusions should not be delayed. In contrast, in those without neurological asymmetries, deformities of the spine are usually much more benign. Among them, isolated high kyphosis deformities are not uncommon and surgical correction is then often not necessary.

Abnormal lower limb neurology patterns
Many RS girls develop successively, through school age, a complex distal lower limb deformative pattern. The feet become more and more fixed in a rigid supinated flexed position, hammering standing and walking. This obviously results from a mixture of slowly appearing, and progressive, distal dystonia which gradually conceals the original obvious yet milder lower limb spasticity. These dystonic features are very often asymmetric, usually with right-sided domination (unpublished observations). With increasing age, the asymmetric dystonia successively results in various patterns of inverted plantar-curved malpositions of the toes, sometimes grotesque in type.

Table 3. The Four Clinical Stages of Classical Rett Syndrome
[Hagberg and Witt Engerström 1986; Witt Engerström 1990; Hagberg 1995]

<table>
<thead>
<tr>
<th>Stage I: early onset stagnation</th>
<th>Later Additions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset: 6 months to 1.5 years</td>
<td>Developmental delay in age from 6 months to 1.5 years</td>
</tr>
<tr>
<td>Developmental progress delayed</td>
<td>Developmental delay in age from 6 months to 1.5 years</td>
</tr>
<tr>
<td>Developmental pattern still not significantly abnormal</td>
<td>“Bottom-shufflers”</td>
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<tr>
<td>Duration: weeks to months</td>
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<tr>
<th>Stage II: developmental regression</th>
<th>Loss of acquired skills: fine finger, active playing</th>
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<tr>
<td>Onset: 1–3 or 4 years</td>
<td>Loss of acquired skills: fine finger, active playing</td>
</tr>
<tr>
<td>Loss of acquired skills/communication</td>
<td>Loss of acquired skills: fine finger, active playing</td>
</tr>
<tr>
<td>Mental deficiency appears</td>
<td>Mental deficiency appears</td>
</tr>
<tr>
<td>Duration: weeks to months, possibly 1 year</td>
<td>Duration: weeks to months, possibly 1 year</td>
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<tr>
<th>Stage III: pseudostationary period</th>
<th>“Wake up” period</th>
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<tbody>
<tr>
<td>Onset: after passing stage II</td>
<td>“Wake up” period</td>
</tr>
<tr>
<td>Some communicative restitution</td>
<td>“Wake up” period</td>
</tr>
<tr>
<td>Apparently preserved ambulant ability</td>
<td>“Wake up” period</td>
</tr>
<tr>
<td>Unapparent, slow neuromotor regression</td>
<td>“Wake up” period</td>
</tr>
<tr>
<td>Duration: years to decades</td>
<td>Duration: years to decades</td>
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<tr>
<th>Stage IV: late motor deterioration</th>
<th>Subgrouping introduced</th>
</tr>
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<tbody>
<tr>
<td>Onset: when stage III ambulation ceases</td>
<td>Stage IV A: previous walkers, now non-ambulant</td>
</tr>
<tr>
<td>Complete wheelchair dependency</td>
<td>Complete wheelchair dependency</td>
</tr>
<tr>
<td>Severe disability: wasting and distal distortion</td>
<td>Severe disability: wasting and distal distortion</td>
</tr>
<tr>
<td>Duration: decades</td>
<td>Duration: decades</td>
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Deranged sensitivity to pain
Parents of RS girls often note a nociceptive derangement. It is, however, never total and usually not even very prominent. The nociceptive perception sometimes appears to be more delayed than absent. In a few girls, the time of pain reaction, adequate or inadequate, is surprisingly prolonged. One of our RS girls thus put her hand in a candle flame and initially only stared and then started to laugh inappropriately.

Feeding abnormalities—gastrointestinal symptomatology
This symptomatology is quite common and can sometimes be very alarming and threatening. Disturbances to the autonomic nervous system are considered to be of major importance as causative. Swallowing dysfunction and deranged mobility of the upper gastrointestinal tract have been well documented. Gastroesophageal reflux occurs frequently and constipation occurs in almost all RS girls. The manifestations have not been used in RS as supportive criteria, which in fact they are, as the clinical pattern is unspecific in type and has been difficult to delineate.
Atypical Rett Syndrome

Atypical RS creates diagnostic difficulties by deviating from the characteristic RS pattern in age of onset, sequences of clinical profile, severity/presence of expected signs, or in all of these domains.

Congenital RS

Congenital RS is very rare and should be regarded with skepticism. These girls should be broadly evaluated for various differential diagnoses and followed for years before a definite RS diagnosis can be accepted. Some children with rare chromosomal mental retardation syndromes may simulate RS in their early years. A definite loss of acquired hand skill is, however, not found in such non-RS cases, instead an improvement with age in their most primitive early bilateral hand use is seen.

Forme fruste RS

Forme fruste RS [Hagberg and Gillberg, 1993] comprises the most common group of atypical variants, around 80%. The characteristic is a pattern of quite discrete neurodevelopmental deviations, which is difficult to delineate precisely for diagnosis, but which nevertheless becomes compatible with RS, with increasing age. Within this group, there are some girls with remarkably well-preserved gross motor abilities and only subtle, odd, and easily missed neurological abnormalities. First at detailed evaluation, their more or less apparent hand dyspraxia is sometimes revealed. Such examples include a few Norwegian and Swedish RS teenagers who manage cross-country skiing, but are completely unable to use their hands for the sticks [Hagberg and Skjeldal, unpublished observations]. For forme fruste cases, an age of 8–10 years is currently considered to be a suitable lowest age limit for a final confirming clinical diagnosis. For them, as well as for other variant forms, the diagnostic RS variant system [Hagberg and Skjeldal, 1994], comprising basic inclusion criteria (group A criteria), combined with clusters of supportive clinical RS peculiarities (supportive B criteria), has been found helpful (Table 2). Today, we are inclined to require a somewhat higher number of combined supportive criteria for inclusion than in the original study, 6 rather than 5. This diagnostic schedule has also been useful for evaluating older females first suspected of having RS at a much later age. Their clinical profile may fit, but even basic developmental data from old records are too often lacking.

Preserved speech RS

Preserved speech RS is not as rare as was initially thought. It was first described by Zapella [1992] and some years later presented in a considerably larger series by Zapella and Swedish collaborators [Zapella et al., 1998]. This subgroup of girls is considered to represent either a subsection of the Rett complex or an entity linked to both RS and autistic disorders [Percy et al, 1990]. A precise location in either of these two groups is not currently possible to give [Gillberg, 1989; Gillberg, 1997]. Their complex RS features, their relation to communicative functions, and overall developmental levels have recently been explored and analyzed by a Gothenburg group [Dahlgren Sandberg et al., 2000].

Other rare variants

There are also additional types of fairly rare variants. One is “the late regression type” with the characteristic start of RS occurring late at preschool or early school age (unpublished observations). The complex issue of rare or even quite exceptional RS variants has been reviewed by Hagberg and Gillberg [1993].

Epilepsy Pattern From Infancy to Middle Age

From a representative Swedish series of 53 RS females, aged 5–55 years, a history of epilepsy was found in over 90% [Steffenburg et al., 2001]. Compared with the epilepsies in severe mental retardation in general, the median age of seizure onset was significantly later in RS (4 years versus 0.8 years) and partial complex seizures were noted to be considerably more frequent in RS (54% versus 23%). After the teens, the severity of the epilepsy tended to decrease in intensity, i.e., lower seizure frequency, and also to comprise more partial than general seizure types. It should be underlined that all fits in RS are not of epileptic origin. It is particularly important to avoid including so-called vacant spells [Cooper et al., 1998], as well as episodic laughing, crying, staring, and so on. At a long-term follow-up of RS women, it is necessary to analyze the following questions critically: a) are the reported fits any longer of epileptic origin? b) do the EEGs verify the presence of epileptic discharges? c) is it not time for a successive withdrawal of anti-epileptic medication?

Autistic Features

Communicative functions are always impaired to a greater or lesser degree in RS. Through the early regression stage, idiopathic variants of autism may not be possible to differentiate. Distinguishing features of RS may, however, already be traced from infancy [Gillberg, 1987]. After the “come back period,” in later preschool years, the special, somewhat odd type of communicative dysfunction is obvious [Dahlgren Sandberg et al., 2000]. One important distinguishing feature in RS girls is their unusually intense eye communication, preserved to adulthood. My preferred way to make contact with an RS female is silently to approach her with face-to-face, near, intense eye contact.

Ageing RS Woman

The increasing experience of ageing RS women has shown that quite a few—particularly those with preserved ambulation capacity—can live to an advanced age (the oldest I know of is a Danish lady, who is now 78 years old, in the series of Dr. J Bieber-Nielsen). In my experience, previously active and alarming epilepsy through preschool and school age calms down in middle age and sometimes completely disappears [Steffenburg et al., 2001]. Improved understanding, contact and communication may appear with age (even if to a modest degree). This is in contrast with gross motor activity, performance, and muscle strength that generally deteriorate from young middle age. In addition to the original abnormal RS neurology, a slowly progressive and marked muscle atrophic process is then repeatedly observed [Hagberg and Witt Engerström, 1987]. A prematurely aged, inactive, very small, thin and pre-senile woman is thus the long-term clinical profile that is so often met. It would now be of interest to try to elucidate in systematic gerontologic research this, and other premature geriatric features and their background in RS.

Concluding Remarks

Back at the end of the 1980s, the concept of RS as a degenerative encephalopathy could be abandoned from its clinical follow-up and disease profile. Today, less than 20 years after the first international publication [Hagberg et al., 1983], we know that RS is not a degenerative but a neurodevelopmental disorder with dendrito-synaptogenic and other brain construction errors of previously unknown pattern and distribution [Armstrong et al., 1995; Belichenko et al., 1997]. The delineation of the mutations in the MECP2 gene behind the large majority of classical RS patients was made through 1999–2001 and was a most relevant and important research step
towards an improved understanding of the complex clinical presentation and the abnormal biology behind RS. Today, however, mutations in the actual gene have been revealed in a much wider clinical spectrum than RS [Hoffbuhr et al., 2001]. No doubt it is currently important also to analyze this gene for mutations in patients with only fragmentary RS features, as well as in other developmentally odd presentations (Table 4).

The most important goal for combined clinical and neurobiological research would now be to try to elucidate—for the potential future prevention of RS—the basic neurodevelopmental dysfunction from the perinatal period through infancy and early childhood. Newborn screening for the inborn error in the defective MeCP2 protein structured by the MECP2 gene would perhaps not be overly unrealistic. Finding a functioning substitution therapy seems much more distant. Today, there is no effective treatment for RS and related disorders with MeCP2 mutations and subsequent MeCP2 protein deficiency. Nevertheless, important experience has been acquired from the research on and final prevention of PKU that was successively initiated in the late 1940s, the period when I started in pediatrics. In many countries like Sweden, clinically-defined RS in girls is three times more prevalent than PKU, while the wider MECP2 positive spectrum of phenotypes is even larger.

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