



WORKSHOP REPORT

An update on clinically applicable diagnostic criteria in Rett syndrome

*Comments to Rett Syndrome Clinical Criteria Consensus Panel
Satellite to European Paediatric Neurology Society Meeting
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Background and update

The worldwide increase in the clinical recognition of Rett syndrome (RS) and the advances in the neurobiology and molecular genetics of RS have underscored the need for systematic phenotype-genotype research of this unique disorder. In 2001, Kerr *et al.*¹ provided an ambitious effort to help those children with *MECP2* mutations and suggested a scoring system for facilitating comparison between various clinical profiles. Today, however, we know of an ever-widening pattern of clinical presentations associated with *MECP2* mutations. Many of them have clinical features, which are incompatible with RS. We need to underline the point that RS is a clinically and not genetically defined condition. Children fulfilling clinical criteria for RS may (80% or more) or may not have *MECP2* mutations. Conversely, as stated above, *MECP2* mutations may be seen in children who do not have RS. In addition, the catalogue of the required data set suggested by these authors seems too extensive, especially so for clinicians working in general clinics and hospitals where clinical evaluations are initiated. Further, atypical or borderline variants of RS, so important for extending

physician awareness and for increasing understanding of RS in the future would possibly be missed with too extensive or restrictive criteria.

One aim of the Baden Baden conference was to establish clinical guidelines which were as simple as possible in order to be of practical value to primary care providers who are likely to provide the first medical assessment, especially for those working in general clinics, health centres, or hospitals without the more comprehensive programmes of University centres. The present commentary presents the preferred basic evaluation points for establishing the clinical diagnosis of classic and variant RS. These are based on the original clinical criteria and the resultant clinical routines established during the 1980s and early 1990s at the outset of active clinical research in RS.

Following the initial clinical descriptions of RS^{2,3} clinical criteria (Table 1) were drafted and disseminated for general application in the evaluation of children presenting with neurodevelopmental disabilities.^{4,5} These criteria have been invaluable tools for advancing understanding of this unique disorder. For example, in the course of these clinical assessments, children fulfilling some but not all necessary criteria for RS were recognized. As such, variant criteria (Table 2) were developed⁶

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Table 1. Current diagnostic criteria for Rett syndrome**[a] Rett syndrome: diagnostic criteria for inclusion⁴**

1. Female sex
2. A normal pre- and perinatal period; essentially normal psychomotor development through the first 6 months, often 12–18 months of life
3. Normal head circumference at birth
Deceleration of head growth (and therefore by inference, brain growth) between 6 months and 4 years of age
4. Early behavioural, social and psychomotor regression (loss of achieved abilities); development of communication dysfunction and signs of dementia
5. Loss of acquired purposeful hand skills through ages 1–4 years
6. Hand wringing–clapping–“washing hand” stereotypies appearing between ages 1 and 4 years
7. Appearance of gait apraxia and truncal apraxia/ataxia through ages 1–4 years
8. Diagnosis tentative until 3–5 years of age

Criteria for exclusion

1. Visceromegaly, other signs of organ storage
2. Retinopathy or optic atrophy before age of 6 years
3. Congenital microcephaly
4. Perinatally acquired brain impairment

[b] Diagnostic criteria for Rett syndrome⁵**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 of age
9. Diagnosis tentative until 2 to 5 years of age

Supportive criteria

1. Breathing dysfunction
 - Periodic apnoea during wakefulness
 - Intermittent hyperventilation
 - Breath-holding spells
 - Forced expulsion of air or saliva
2. Electroencephalogram abnormalities
 - Slow waking background and intermittent rhythmical slowing (3–5 Hz)
 - 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
2. Retinopathy or optic atrophy
3. Microcephaly at birth
4. Evidence of perinatally acquired brain damage
5. Existence of identifiable metabolic or other progressive neurological disorder
6. Acquired neurological disorders resulting from severe infections or head trauma

and have been useful in delineating the spectrum of clinical expression associated with RS.

Since the initial criteria were established, remarkable progress has been made in our understanding

of the clinical, neurobiological, and molecular genetic characteristics of RS. Not the least of these are greater definition of the timing and pattern of clinical features,⁷ recognition of RS as a

Table 2. Current diagnostic criteria for variant Rett syndrome

Rett syndrome: a variant delineation model⁶

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 2 SD (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 lower limb neurologic abnormalities
- B7 Small blue/cold impaired feet, autonomic/trophic dysfunction
- B8 Characteristic RS electroencephalographic development
- B9 Unprompted sudden laughing/screaming spells
- B10 Impaired/delayed nociception
- B11 Intensive eye communication—"eye pointing"

Exclusion criteria according to the Diagnostic Criteria Work Group [5]

RS = Rett syndrome

neurodevelopmental disorder as opposed to progressive neurodegeneration and the identification of mutations in *MECP2* as the molecular basis for more than 80% of girls fulfilling criteria for classic RS.⁹⁻¹²

As the result of these important advances, significant interest has emerged in exploring the possible phenotype-genotype correlations Germany, 11 September 2001 as a satellite meeting across the spectrum of *MECP2* mutations. These efforts have led to a re-evaluation of the diagnostic criteria. The present progress report represents a clarification of these criteria based on our present level of knowledge and achieved through lively discussions held in Baden Baden, to the European Society of Paediatric Neurology meeting. While the nine essential clinical criteria promulgated earlier have been retained, the revised criteria clarify ambiguities in language, which could affect their broad application or implementation in the proposed phenotype-genotype correlation studies. The intent of the modifications contained in Table 3 is to make the criteria inclusive without sacrificing overall specificity.

In a similar manner, the variant criteria have been re-evaluated to allow greater inclusion. Specifically,

the inclusion criteria for age and gender have been removed (Table 4). Among the supportive criteria in the previous version (Table 2), concern was raised that information on the RS electroencephalogram (EEG) pattern could be missing for many individuals, thus, eliminating one feature from consideration. As such, RS EEG pattern has been replaced by sleep disturbance, a frequently noted feature of those within the RS spectrum.

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Commentary

It is essential to emphasize that RS is not synonymous with mutations in *MECP2* and at our present level of knowledge remains a clinical diagnosis. That is, RS occurs with and without mutations in *MECP2*, and, furthermore, mutations in *MECP2* have been identified in individuals who lack the clinical features of either classic or variant RS. As such, it is critical that consensus exist regarding the diagnostic criteria for classic and variant forms of RS. In order for the accurate conduct of phenotype-genotype correlation studies, these criteria must

Table 3. Revised diagnostic criteria for Rett syndrome**Necessary criteria**

1. Apparently normal prenatal and perinatal history
2. Psychomotor development largely normal through the first 6 months or may be delayed from birth
3. Normal head circumference at birth
4. Postnatal deceleration of head growth in the majority
5. Loss of achieved purposeful hand skill between ages ½–2½ years
6. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms
7. Emerging social withdrawal, communication dysfunction, loss of learned words, and cognitive impairment
8. Impaired (dyspraxic) or failing locomotion

Supportive criteria

1. Awake disturbances of breathing (hyperventilation, breath-holding, forced expulsion of air or saliva, air swallowing)
2. Bruxism
3. Impaired sleep pattern from early infancy
4. Abnormal muscle tone successively associated with muscle wasting and dystonia
5. Peripheral vasomotor disturbances
6. Scoliosis/kyphosis progressing through childhood
7. Growth retardation
8. Hypotrophic small and cold feet; small, thin hands

Exclusion criteria

1. Organomegaly or other signs of storage disease
2. Retinopathy, optic atrophy, or cataract
3. Evidence of perinatal or postnatal brain damage
4. Existence of identifiable metabolic or other progressive neurological disorder
5. Acquired neurological disorders resulting from severe infections or head trauma

Table 4. Revised delineation of variant phenotypes**Inclusion criteria**

1. Meet at least 3 of 6 main criteria
2. Meet at least 5 of 11 supportive criteria

Six main criteria

1. Absence or reduction of hand skills
2. Reduction or loss of babble speech
3. Monotonous pattern to hand stereotypies
4. Reduction or loss of communication skills
5. Deceleration of head growth from first years of life
6. RS disease profile: a regression stage followed by a recovery of interaction contrasting with slow neuromotor regression

Eleven supportive criteria

1. Breathing irregularities
2. Bloating/air swallowing
3. Bruxism, harsh sounding type
4. Abnormal locomotion
5. Scoliosis/kyphosis
6. Lower limb amyotrophy
7. Cold, purplish feet, usually growth impaired
8. Sleep disturbances including night screaming outbursts
9. Laughing/screaming spells
10. Diminished response to pain

be applied consistently. This seems self-evident. However, such is not always the case. Application of the criteria emerging from the Baden Baden meeting should obviate this issue.

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