

Commentary: Are Developmental Skills Acquired Normally in Rett Syndrome?

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Rett syndrome (RTT) is a rare neurodevelopmental disorder affecting females predominantly and associated in >96% of individuals with classic RTT with mutations in the methyl-CpG-binding protein 2 (*MECP2*) gene¹. The gene product, *MECP2*, is crucial for the development and maintenance of normal neuronal and glial, particularly astrocytic, function through the activation or suppression of many other genes, for example, *BDNF*, or brain-derived neurotrophic factor². RTT occurs in all racial and ethnic groups with an incidence of approximately 1:10,000 live born females³, that is, more common than phenylketonuria. From its first recognition, questions were quickly raised regarding the normal acquisition of developmental skills in RTT. The first publications of Rett⁴ and Hagberg et al.⁵ indicated that early development was normal, but already by the creation of diagnostic criteria in 1985 by Hagberg et al.⁶ and later by the CDC's Rett Syndrome Diagnostic Criteria Work Group⁷ the qualifiers "near normal" or "apparently normal" early development were added. These consensus criteria for RTT have been modified more recently based on the identification of the *MECP2* mutation type in 1999⁸ and further refined in 2010⁹. As such, the clinical profile has included the phrase 'apparently normal development' to characterize the earliest period in the ontogeny of clinical features in RTT.

The clinical profiles of individuals with RTT have a broad spectrum of severity ranging from significant limitations of gait and fine motor function, inattention, and overall clinical severity to relatively milder involvement with preserved gait, ability to manipulate food or other objects with a modified pincer grasp, and interact using iPads or specialized computer equipment. Atypical forms of RTT have also been identified with either higher or lower degrees of severity including the preservation of some interactive speech in the mildest form or very significant early onset-epilepsy or absence of many developmental skills in the most severe forms. Atypical RTT is associated with *MECP2* mutations in 76%¹⁰. This variation in clinical severity is related to a number of different factors including the specific mutation, the degree of X-chromosome inactivation (XCI) favoring the normal X-chromosome, the genetic background, the environment, and the variable distribution of the mutation within the central nervous system. Analyses from large databases have revealed a similar and convincing distribution of clinical severity based on the general type or position of the mutation in *MECP2*¹⁰⁻¹². However, when looking at two individuals with precisely the same

mutation, considerable variation in clinical severity may arise. This relates to the other factors noted. Large scale studies of XCI have not occurred. Initial findings suggested only limited XCI variability¹³, but this study contained a relatively small population of individuals with RTT. In an on-going, yet unpublished, study of this phenomenon in more than 200 participants with classic RTT associated with the US RTT Natural History Study, 11% demonstrated highly skewed X-chromosome inactivation, 26% moderately skewed, 51% randomly skewed, and 12% were uninformative (unpublished data, Friez et al.). Remarkably, the direction of highly skewed XCI was equally represented between the normal and mutated X chromosome. The overall genetic background (apart from XCI) is deserving of further investigations. The effect of environment and therapeutic interventions on overall health maintenance is remarkable. This is, perhaps, best exemplified by the difference in survival between the original group identified by Rett limiting overall survival to about 25 years and more recent studies of longevity suggesting average survival greater than 50 years¹⁴⁻¹⁶.

Beginning in the 1990's, formal assessment of development was initiated first by Kerr¹⁷ who assessed development in a survey of children with RTT in the United Kingdom and noted evidence of abnormal development in early infancy. This was later extended by Einspieler et al.¹⁸ and Marschik et al.¹⁹ using video analysis from fifteen children in the first two years of life with RTT, ten with classic and five with atypical RTT.

In 2014, Neul et al.²⁰ described the occurrence of developmental skills in more than 600 individuals with RTT, the largest reported to-date examined directly by teams consisting of a neurologist or geneticist and an experienced clinical coordinator. This allowed for a precise ascertainment of the timing of acquisition of specific developmental skills in this population. Of these, 542 had classic RTT and 96 had atypical or variant forms of RTT, 50 with higher functioning and 46 with lower functioning than seen in classic RTT. Although early developmental skills such as sitting, reaching for an object, or early speech are often acquired, the timing of this acquisition is beyond the normal age where this is accepted as normal in most individuals with classic RTT. This was particularly true for skills expected to be acquired after six months of age. Overall, the acquisition of gross motor and receptive language skills is superior to fine motor and expressive language. For the early skills, sitting, reaching for an object, fixing and following, and social smile, approximately 20% acquired the first three on time whereas the fourth skill was acquired on time by about 50%. The more complex motor and communication skill such as using utensils or multi-word sentences are generally delayed or absent. Further, greater acquisition of motor or communication skills is

associated with reduced clinical severity. These better outcomes are typically related to four specific mutation groups, the common point mutations R133C, R294X, and R306C and the 3' truncations. For atypical RTT, the higher functioning group was slightly better in acquisition of early onset skills whereas the lower functioning group was markedly worse. The pattern of developmental skill acquisition and subsequent loss, particularly those skills acquired in the first six months, and the declining head circumference percentile already in the first six months of life suggests that abnormally deficient *MECP2* has an adverse impact very early in post-natal life. It is known that the development of neurons and astrocytes is related to normal levels of *MECP2* such that the abnormalities described in the human brain are not unexpected²¹⁻²³.

As we enter a period of increased clinical trial activity in this population, it is important to achieve accurate diagnosis as early as possible. Currently, data from the RTT NHS indicates that the average age of diagnosis is 2.7 years, down from about 4 years in the initial years of the study. Still, to effect a treatment as early as possible, age at diagnosis must be reduced even further. Declining growth rate had been recognized in RTT from the initial studies of Rett and Hagberg with declining percentiles over time for head circumference, weight, and height through early childhood²⁴. The first clue is the decline of head circumference percentile which can be seen as early as 1.5 months of life. In addition, early infancy may be marked by inattentiveness or lack of response to the parents and the general realization that the infant is passive or too good. These should be clues to the primary care physician that identification of an underlying mechanism or cause should be investigated, either directly or by referral to an appropriate specialist. Coupling these factors with a closer examination of the abnormal pattern of acquisition of developmental skills adds further evidence for the possible establishment of a definitive diagnosis. The advancement of clinical trials and the possibility of identifying disease modifying or directly curative strategies bring further urgency to this diagnostic challenge. Ultimately, it could lead to the creation of a newborn screening program such as already in existence for so-many inherited disorders such as the previously mentioned phenylketonuria.

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