Overview of Rett Syndrome

The clinical features of Rett syndrome were first described in 1966 by Dr. Andreas Rett. Patients with these clinical features were subsequently given the designation of Rett syndrome in 1983 in recognition of Dr. Rett’s original report. Rett syndrome is still considered a clinical diagnosis based on specific developmental history and clinical criteria. These clinical criteria were last revised in 2010.

Initially, Rett syndrome was recognized only in females. It was hypothesized that Rett syndrome was lethal in males. This suggested that Rett syndrome was a sex-linked genetic disorder with the gene being localized on the X chromosome.

In 1999 it was reported that mutations in the MECP2 gene, located on the X chromosome, were associated with the clinical presentation of Rett syndrome. Since the ability to test the MECP2 gene has been available, there have been over 60 males reported with mutations in the MECP2 gene. A few of these males had a clinical picture consistent with the clinical criteria for Rett syndrome; however, most of these males presented with a different clinical presentation. Most males with mutations in MECP2 gene present with an earlier onset of symptoms, typically with significant problems beginning at or shortly after birth.

The diagnosis of Rett syndrome is still based on clinical criteria and the clinical presentation. Over 95% of females with classic Rett syndrome will have a mutation in the MECP2 gene. Mutations in the MECP2 gene by themselves are not sufficient to make a diagnosis of Rett syndrome. Patients with mutations in the MECP2 gene that do not meet the clinical criteria for Rett syndrome are given the designation of MECP2-related disorders.

Understanding the MECP2 gene

There is still much to be learned about the function of the MECP2 gene. It is a very important gene and acts as a regulatory gene for thousands of other genes. MECP2 can cause both increased expression and decreased expression of other genes at critical times in development. The MECP2 gene plays a critical role in brain development and brain function.

The MECP2 gene is located on the X chromosome, one of the sex chromosomes. Females typically have two X chromosomes and males typically have one X chromosome and one Y chromosome. Thus, all females typically have two copies of the MECP2 gene, one on each of their X chromosomes. Females with Rett syndrome have a mutation or a change in one copy of the MECP2 gene on one of their two X chromosomes. Because of a process known as X inactivation, only one copy of the MECP2 gene is active in any one cell in females. This X inactivation processes is random, so that in some cells the
MECP2 gene with the mutation is active and in other cells the MECP2 gene without the mutation is active. In females with Rett syndrome this means that roughly half of their cells have a normally functioning MECP2 gene and half their cells have a MECP2 gene with a mutation present that is not functioning normally. This is the typical pattern seen in Rett syndrome.

Males only have one X chromosome and, only one MECP2 gene. Thus, a male with a mutation in the MECP2 gene has that mutation present in their only copy of the MECP2 gene. Therefore, the function of MECP2 is affected adversely in all cells in the male. This is why males with MECP2 mutations present differently than females with MECP2 mutations. Males that have a mutation that is similar to the typical mutation seen in females with Rett syndrome present with early onset and more severe clinical problems than females with classic Rett syndrome.

Early on it was felt that males with MECP2 mutations were nonviable, thus, explaining the absence of the diagnosis of Rett syndrome in males. However, it was subsequently determined that most of the mutations in MECP2 are due to new spontaneous mutations in the MECP2 gene that occur during the division and formation of sperm, the male germ cell. Since fathers typically give their X chromosome to their daughters and their Y chromosome to their sons, this explains the low occurrence of males with MECP2 mutations.

Explanations for males with MECP2-related disorders

1. Males with Rett syndrome and Klinefelter syndrome: There have been rare males reported with the typical history of classic Rett syndrome. These males have also had an unrelated genetic disorder known as Klinefelter syndrome. In Klinefelter syndrome, males have two copies of the X chromosome and one copy of the Y chromosome; thus, they have an extra chromosome giving them a chromosomal designation of 47,XXY. Klinefelter syndrome is relatively common, appearing in roughly 1 in 500 males. Thus, it is not unexpected that occasionally an individual will have both Klinefelter syndrome and a mutation in the MECP2 gene as two unrelated events. Because these males have two copies of the X chromosome and undergo the same process of X inactivation that is seen in females, these males present with a clinical presentation that is very consistent with the classic Rett syndrome presentation. These males, will in addition to having the clinical features of Rett syndrome, also have features of Klinefelter syndrome, including underdevelopment of the genitalia and underproduction of sex hormones.

2. Mosaicism as a cause of Rett syndrome in males: Mosaicism basically is a term defining a mixture of two different populations of cells. There have been very rare reports of males with Rett syndrome on the basis of mosaicism. These males have a mixture of two cell types. They have some cells with one X chromosome with one MECP2 gene that is functioning normally. In other cells of the body they have one X chromosome with a MECP2 gene that has a mutation that is affecting the function of the MECP2 gene. Depending on the percentage of the mixture of these two cell types, these males will have clinical features similar to females with classic Rett syndrome. This mosaicism occurs by a mutation that occurs after conception but early in embryologic development. The timing of the occurrence of this mutation will determine the percentage of cells affected by the mutation.
It should be noted that basically, at the cellular level, all females are mosaic for the function of the MECP2 gene.

3. MECP2-related severe neonatal encephalopathy: Males that have one of the mutations that are typically seen in Rett syndrome usually present with earlier onset and more severe symptoms than females. Again, this is because this mutation in the MECP2 gene is affecting all the cells in the male. Most of these males present with early onset breathing problems, early onset feeding problems, and early onset seizures. Without aggressive medical care most of these males with typical MECP2 gene mutations pass away in the first year of life. However, with aggressive medical intervention, these males can survive into late childhood. They frequently require significant medical support, including nutritional and breathing support.

4. Males with MECP2 mutations and milder presentations (MECP2-related disorders): With increased sequencing of the MECP2 gene, males are being identified with mutations in the MECP2 gene outside of the regions of the gene that are usually associated with classic Rett syndrome in females. These mutations in the MECP2 gene may present with a male with intellectual disability or milder learning problems and behavioral problems, but not classic or atypical Rett syndrome. Some of these mutations, when seen in females, may present with no clinical features or very mild clinical features. It is thought that these mutations in certain regions of the MECP2 gene do not cause significant disruption of the function of the MECP2 gene, and, thus, result in milder symptoms.

**Life expectancy of males with MECP2 mutations**

The life expectancy and the medical complications in males with MECP2 mutations depends a lot on the underlying mutation and/or other associated genetic problems. Thus, males with Rett syndrome and Klinefelter syndrome together, will have a life expectancy more in line with that seen in Rett syndrome. These males may live a long life with medical complications. Males that are mosaic for a typical MECP2 mutation will have a life expectancy similar to females with classic Rett syndrome; thus, these males also may live a long life with associated Rett related medical complications. Males with only one X chromosome with a typical MECP2 mutation typically have shortened life expectancy. With aggressive medical intervention and dedicated families, these males may survive into late childhood; however, they may require significant medical support. Males with atypical mutations of the MECP2 gene, may have a normal life expectancy with problems in learning and/or behavior.

**Understanding clinical trials in males with MECP2 mutations**

Currently there are active clinical trials for Rett syndrome and plans for new trials in the future. At this time, all the clinical trials have been designed with eligibility criteria that are inclusive for females and have excluded males with MECP2 mutations from participating. This has generally occurred as part of the study design in attempt to have a uniform genetic background that will allow investigators to determine the safety and effectiveness of the medication for Rett syndrome. There are several factors involved in the design of clinical trials. The funding agency, typically a pharmaceutical company or a foundation, will frequently be involved in the design of the clinical
trial with the goal of maximizing the information that is learned from the clinical trial. The investigators involved in conducting the clinical trial may have some input into the design of the clinical trial, but are typically involved with conducting the trial as designed by the funding agency. There are also regulatory agencies, such as the FDA, which have stringent criteria for clinical trial design to ensure safety and proper conduct of trials. Lastly, the knowledge of the clinical condition being treated will impact the design of the trial and the selection of the compounds used in the trial.

**Challenges in including males in clinical trials**

1. Males with Rett syndrome or MECP2-related disorders are very rare. Recruiting sufficient numbers of males for clinical trials is a challenge. There are slightly over 60 male patients with MECP2 gene changes reported in literature, though there are probably more unreported males with MECP2 mutations.
2. Males with typical MECP2 mutations present earlier with more severe symptoms and a different clinical course than females with Rett syndrome. Including males in clinical trials for Rett syndrome creates challenges for interpretation of data, safety and efficacy.
3. Trial design and eligibility criteria typically exclude males with MECP2 mutations from the early clinical trials in Rett syndrome. This is partly due to the challenges of having essentially two different patient populations within the same clinical trial. The trial design may be different in a male population than a female population, including such factors as age of inclusion, outcome measures, dosage and safety parameters.

**Future for males with MECP2 mutations**

Current research and current technology allows the better identification of males with MECP2 changes. Males with MECP2 are eligible for the current natural history studies. Any success of the treatment trials for girls with Rett syndrome may be applicable to males with MECP2 mutations. Any approved therapy for Rett syndrome could be considered for compassionate use in males with MECP2 mutations. Rettsyndrome.org is committed to continue to fund research that will impact quality of life for both boys and girls living with MECP2 mutations. Rettsyndrome.org continues to support efforts to identify treatment for the symptoms of Rett syndrome, to identify best practices and therapies that will maintain or improve existing skills, and to identify a cure through protein replacement or gene therapy. All of these efforts are critical to a strategy that will accelerate research toward a cure for Rett syndrome and MECP2-related disorders.

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