RettEd Q&A: What IS Rett syndrome?
Webcast 01/30/2018
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DIAGNOSIS and GENETICS

My daughter was first tested in 2001 and no mutation was found. Is it worth getting her tested again now?

It is unlikely that full genetic testing for *MECP2* was done at that time. First, ask for complete sequencing study including exons 1-4. If this proves negative, then the genetic testing facility should do expanded testing such a MLPA to look for large deletions. The Greenwood Genetic Center or the Baylor College of Medicine laboratories will do these in sequence. If the test results remain negative, then you need to decide if whole genome sequencing should be done. A genetic counselor can help you navigate this.

Why is there normal development and then a loss of these skills if the deletion/mutation is there from birth?

This can be explained by the timing of when the *MECP2* gene becomes active in the development of synaptic connections in the brain (the forebrain and brainstem). This process does not accelerate until after birth such that abnormalities in development will not be evident. Remember that an infant does not learn to sit, pull to stand, or develop early communication until after 6 months of life.

What's the difference between classical and atypical Rett?

The difference is based on meeting specific criteria. In both forms, a period or pattern of regression of skills is required. For classic Rett syndrome, one must meet the four Main criteria: partial or complete loss of fine motor skills (hand function) and communication, develop hand stereotypies, and have abnormal gait or no gait. Many or all of the Supportive criteria may also be positive but are not essential for the diagnosis. For atypical Rett syndrome, after the regression, at least two of the Main criteria must be present and 5 (any 5) of the 11 Supportive criteria must be present. The full article *Rett Syndrome: Revised Diagnostic Criteria and Nomenclature (2010)* can be found here: https://www.rettsyndrome.org/document.doc?id=19

Difference in treatment for atypical and classical?

I would not treat the clinical problems that arise in these any differently. Depending on the features presented by the individual, I would address the

treatment options such as seizures, drooling, gastrointestinal issues such as reflux, stomach emptying, or constipation, scoliosis, and sleep, for example.

Are MECP2 deletions rare and is there a major difference in Rett symptoms/treatments with deletions?

Deletions can come in different sizes such as a single nucleotide, several nucleotides, a whole exon, or the complete gene. The relatively smaller deletions account for 15-20% of all mutations. The large deletions involving an exon or the whole gene make up less than 10% of all mutations. Thus, I would not say they are rare. Certainly, the position of the deletion can affect the clinical picture, but other factors may also influence the outcome. In general, the large deletions of the gene and the smaller deletions in the early part of gene may produce greater difficulties than deletions in the later portions of the gene. However, due to other factors such as X chromosome inactivation, overall genetic background, and environment, the outcome may be modified significantly. The requirements for treatment may vary as well.

How can one distinguish Rett syndrome from autism in very young children?

This would be based on fulfilling the criteria for Rett syndrome which may be problematic until at least 12 months if not longer. Indeed, girls with Rett syndrome often have a pattern of behavior during the regression when they do appear autistic. It is important for the child at this point to be seen by a qualified subspecialist.

Can prenatal testing be performed?

Yes, it can if the mother has a daughter with Rett syndrome. It could be done in a sibling of the affected girl, but this would be very unlikely to be positive (more than the 1:10,000 in the general population) if that daughter had a negative blood test. However, if it were planned, it would have to be done in the first trimester. The laboratory only has to check for the specific mutation involved.

Should female siblings be tested before having children?

This is an open question. The likelihood of other children being affected is very small. However, to be absolutely certain, when a female sibling reaches the age of majority, if she has specific questions about this, she should talk to a genetic counselor about her options. If genetic testing is decided, then only the mutation of her sister needs to be checked.

Not a question but a statement: we must find new verbiage to describe our boys/ men and girls/women with Rett Syndrome! It's hard to change from 'girls' only, but it is a must!

We do find Rett syndrome in boys who have a second disorder, Klinefelter syndrome which is 47XXY and results in two X chromosomes as in females. It also may be seen with somatic mosaicism, two populations of cells, one with a normal X chromosome, the other with a mutation in *MECP2*. We have identified a number of boys with features similar to Rett syndrome which we are proposing to call Male Rett Encephalopathy.

Can you tell me why girls with Rett have a higher incidence of siblings with autism?

I wish I could, but No, I cannot. However, autism with a frequency of 1 in 60-70 children is very prevalent making random overlap more likely.

Have any girls with Rett Syndrome ever had a successful pregnancy? If girls could be given gene treatment could they conceivably have regular children?

Pregnancy has occurred in only one instance that I know. The pregnancy resulted in the birth of a girl with Rett syndrome. Even if gene therapy were successful, I would still expect the germinal cells to have a mixture of the normal and abnormal gene such that the risk for inheriting the abnormal gene would still be 50%.

Can our girls have the x-inactivation blood test to know her skewing? We are part of the Natural History Study and they drew her blood already. What value does this information offer our family?

If your daughter was tested for X-inactivation, this information should be available (I would check with her physician in the natural history study). The information would help understand why your daughter demonstrates the features that she does compared with the specific mutation. It would not, however, alter anything else at the present time.

NATURAL HISTORY STUDY

How do we become part of the Natural History Study? What if we don't live in the U.S.?

At present, we have no requirement for place of origin, but you would have to travel to a site in the US to be enrolled. As we approach the next application for recurrent funding, this aspect will be addressed utilizing some electronic

mechanisms that are under discussion. This could lead to broader enrollment in this country and abroad.

RESEARCH

It was our understanding Phase 3 Trofinetide trials would begin early 2018. You said late 2018 or 2019. Why the delay. The pediatric trials ended almost a year ago. There were no reported side effects so what could be the reason for the long span between trials.

I cannot answer this question with direct knowledge as this is based on decisions made by Neuren, the relevant pharmaceutical company. One could imagine a number of issues including toxicity testing in animals, conversations with the FDA, working to design the trial to have the greatest likelihood for success, and others.

[We reached out to Neuren for an update. As of 2/5/18:

"Neuren has not yet confirmed the timeline, but there is a huge amount of preparation underway by Neuren and others to get ready for the trial, which is larger, longer and more complex than the previous two studies. Things are moving along nicely, but many different aspects have to be perfect before the trial starts, including approval of the protocol, manufacturing, trial sites, and logistics. All of these aspects are being worked on. Neuren will provide further updates in due course." Jon Pilcher, CFO & Company Secretary, Neuren Pharmaceuticals]

Can you talk about BDNF and positive effects for our girls?

BDNF is an important protein in brain development. It is known that BDNF levels are reduced in the brains of animal models of Rett syndrome and work with agents that mimic BDNF effects and that provide levels of improvement is emerging. The issue is finding a suitable and safe replacement as BDNF does not cross the blood-brain barrier sufficiently to treat by itself. Agents must thus be identified that fulfill the requirements for any pharmaceutical.

If it's been reversed in mice, how come it hasn't been tried on a child?

The animal experiments utilized a mouse model that had been engineered with the normal gene under the control of another biological marker. This specific experimental model could not be provided in humans. What is required is a means of transporting the normal gene to the body including the brain. While such studies are in progress and positive results are emerging, it remains to be shown that this is a viable mechanism for correction. I would anticipate that these studies will continue and clinical trials will begin. I cannot say when this will be ready.

Are there any plans to start clinic trials for our boys with RETT?

Dr. Neul and I suggested this to a gene therapy company and they are planning to have a conversation with us regarding this possibility.

If Rett is caused by a genetic mutation, what is the likelihood of a gene therapy solution from gene editing techniques like CRISPR/CAS9 that would be curative?

Gene editing techniques are exceptionally powerful. I do not know of specific testing of this methodology personally. Dr. Neul could, perhaps, offer his input on this.

What is the biggest barrier for advancement in the research towards a cure? Is it awareness, funding, government, etc? How can the parents and families help most efficiently?

The biggest barrier(s) to me involves all of these and, perhaps, more. Certainly awareness is important. The development of wide-ranging Natural History Study is critical. We have made remarkable progress, but more could be learned. Much is still to be learned on the basic science of this disorder and the many ramifications of any new discovery. This requires a substantial research investment. Thus, funding is always an issue. With up to 5-6000 rare diseases, many groups are clamouring for needed funds. Also, as rare diseases, the total number of those involved plays into a company's desire for investment. The rules of the FDA must be followed and the requirements met. This is a time-consuming adventure that requires patience and courage. FInally, if a treatment is identified, what would it cost, who would pay, and could everyone be given access? These are all major points for consideration.

Parents and families can help by spreading the word, participating in studies when requested, especially clinical trials, raising funds, communicating with elected representatives, and by participating, as you and others have, in asking questions.

A word about clinical trial participation: If no one participates, nothing will be approved. It is not wise to wait for the golden goose. We need to test products with promise as they become available.

Is it possible that any future "cure" for Rett, such as muting the abnormal x chromosome would be applicable for grown girls?

This is an important question. One does not know what or how much effect treatment would have at ever increasing ages. It is unlikely that treatments started later in life would reverse structural changes such as contractures or scoliosis or how long would the reacquisition of skills require to develop. This is all without answer at present.

Are there any trials for kids with FOXG1? And is there an expert we could see? We live in Canada.

I am unaware of a trial in *FOXG1* disorder. The person with greatest experience in this country is Dr. Alex Paciorkowski at the University of Rochester. However, many in the current US Natural HIstory Study are gaining experience with those affected by this disorder.

SYMPTOMS and MEDICAL

Our granddaughter rocks back and forth on her back and sitting, why?

The precise reason is not known. However, I would regard this as an inability to control body position, either because of poor voluntary motor control or because of a disorder of movement similar to the hand stereotypies. I personally favor the latter, but this remains an open question.

What is the best way to deal with sleeping difficulties? Our daughter wakes frequently looking scared and rigid.

Sleep is a common problem, either going to sleep or staying asleep. For the former, I recommend Melatonin, a naturally occurring hormone that aids in going to sleep. It does not necessarily maintain sleep. For the latter problem it is important to consider common problems first such as hunger, pain such as gastroesophageal reflux (GE reflux) or constipation. If these are not the issue, I most often use the medication, trazodone, which is an antidepressant that has the side-effect of sleepiness. In addition, others may use clonidine or clonazepam. I prefer not to use the last, clonazepam, as the effects may carry over through the next day. I ordinarily use these medications at bedtime or within 30 minutes of going to bed.

My child wakes in the middle of the night with what seem like night terrors and it can last up to an hour. What is going on and how can I help her?

Night terrors are common in the general population and may be particularly prevalent in the neurodevelopmental disorders. They usually occur a few hours after going to sleep.The individual will have no recollection of these events or no long term consequences. Our recommendation involves calming the child until they subside at which point the child usually returns to sleep without difficulty.

What is the best way to address the sleeping difficulties? Our daughter wakes up frequently seeming scared with eyes open and a rigid body.

Please see the answers above to sleep issues including night terrors and obstructive sleep apnea. The best way to address is to have an overnight sleep study from an expert in sleep medicine. This may be a pulmonary or neurology subspecialist.

What would you say the "awareness" level of girls with Rett Syndrome? It is clear there are delays, but how much do you feel people with Rett syndrome are processing on a day to day basis? Would you say it varies? (And if so, varies on what?)

I believe that these girls are generally very aware of their surroundings and can interact within them reasonably well with simple communication devices such as Yes/No cards, eye gaze in one direction or the other, or picture boards. Eye-gaze technology is also possible. I also believe that day-to-day variability in the level of awareness definitely can be detected or affected by a variety of external or internal factors such as pain or discomfort, level of interest, or other similar factors.

How old is the oldest woman with Rett that you are aware of?

The oldest woman I saw was 68. I am aware of another woman that Andy Rett saw in the Far East who was said to be in her late 70's. In the natural history study, women older than 50 have also been seen.

Do you typically see scoliosis in girls who are more wheelchair bound vs. those who can walk independently or with help?

The answer is yes overall to this question. Girls or women who have lower muscle tone and do not walk tend to have greater degrees of scoliosis and are more likely to undergo surgery for correction. These girls tend to sit unevenly or to slouch and ultimately tend to curve in this direction. We usually recommend fairly rigid pillows while sitting and standing in a standing frame to build or strengthen the back muscles. We also support the use of body jackets that may reduce the rate of scoliosis progression. On the other hand, girls who walk may still require surgery, just less frequently.

Can you talk about kyphosis and especially on impact in girls who are ambulatory?

Kyphosis or forward tilting of the spine (scoliosis is lateral tilting) is seen in Rett syndrome, but much less frequently. This can be addressed while sitting with straps to encourage a more upright posture. I am aware of surgery for this in one girl, but it is not common in my experience.

My daughter is 3.5 years, she can be very fussy at times, we were wondering if she has reflux. What are reflux symptoms?

Reflux symptoms are just as you describe: increased fussiness. Rarely one may see evidence of vomiting or more commonly, the results on the pillow case or bed after a night's sleep. These may follow particular meals including spicy foods, tomato sauces such as spaghetti or chocolate. Some girls simply have reflux from most foods, reflecting possibly a delay in normal stomach emptying. These may be treated empirically by your primary physician or may require a visit to a gastroenterologist.

If they do have Obstructive Sleep apnea (as my daughter does) what is your suggestion for remedy? Is surgery the best option? Are there other methods proven to be effective in Rett?

Obstructive sleep apnea may be treated simply if your daughter has enlarged tonsils or an enlarged adenoid. This will be determined by an ENT physician. Other times, it may be related to laxity of the upper or middle airway which may require modified sleep position or even the use of a CPAP device. This should be assessed by an expert in sleep medicine.

Can you please address metabolic acidosis in Rett Syndrome

Metabolic acidosis is relatively uncommon in Rett syndrome in my experience. A respiratory acidosis is more common from excessive breath-holding with an increase in carbon dioxide. If a metabolic acidosis is noted, this needs to be assessed by an expert in this area, usually provided by a nephrologist or possibly a gastroenterologist.

How common is Achalasia in Rett girls? My daughter is 20 and she had to have a PEG inserted 2 yrs ago. and she still struggles with choking and phlegm caused by her own saliva. Also is there a cure for Achalasia?

Achalasia usually refers to spasm of the esophageal sphincter making swallowing difficult. However, I am not certain that this the cause of her poor swallowing. Problems with swallowing are common in Rett syndrome and are related to poor motility of the esophagus rather than sphincter spasm. We commonly see these issues with saliva and phlegm. This can be troublesome to solve, but basically involves reducing salivation. We often use 1% atropine ophthalmic drops under each side of the tongue to reduce salivary gland production. If this is not possible, I would recommend seeing an ENT physician first off to see if any other suggestions are available. We tend to avoid robinul as it dries up everything, particularly making constipation worse.

Is there a way to know if our daughter is properly hydrated ?

The simplest way is to assess her mouth and her eyes to be certain that evidence of moistness is present. You can also assess the color and odor of her urine. Poor hydration is associated with dark color and stronger odor. Girls with Rett syndrome are commonly poor drinkers. We recommend adequate fluid intake by having at least 24 ounces of water throughout the day apart from water consumed at meals. A 25 kg (55 pound) girl should consume 1600 ml (>53 ounces) of fluid per day.This includes all foods that would have a high water content such as ice cream, yogurt, etc. In addition to promoting good hydration, this could alleviate some aspects of constipation or make Miralax optimally effective.

Girls with Rett have lower growth weight correct? We are looking into having a G-tube placed since our daughter is not gaining weight and sometimes does not want to eat. If we do the tube will it make her NOT want to eat by mouth? We don't want her to lose that ability.

A G-tube will not necessarily reduce the desire to eat. However, providing most of her G-tube feedings overnight by pump will allow her to be hungrier during the day, especially for lunch and dinner. Some girls are self-protective and rely on the G-tube because of an innate fear of choking and the food going down the wrong way. In this case, thickened liquids would be preferable. This can be determined by a feeding study.

My daughter is 39 and still mobile. She doesn't like looking at laptop so as to get her onto Tobii eye gaze. Is this usual for older rett ladies?

I do not have great experience with Tobii in the older women. I think that the lack of interest is due more to the lack of experience and the development of indifference to these devices. Other forms of communication may be used that do not require this more intense eye-gaze.

MISCELLANEOUS

How did you come to focus on Rett in your practice?

Interesting question. I began my interest in Rett syndrome more than 30 years ago as one of the first two or three physicians in the US at that time to meet a child with this problem. I was actually involved in basic biochemistry of the developing nervous system while fulfilling my clinical responsibilities mainly as the consultant to a child development clinic at Texas Children's Hospital and the Baylor College of Medicine. Seeing this young girl as part of my clinical

responsibilities captivated me and led me to focus on its understanding. I was intrigued by this difficult disorder about which little was known and dedicated my subsequent career to understanding its cause, which I thought had to be genetic, its features, and ultimately its natural history. I knew from other neurologic disorders of similar type, that the ability to bring these disorders to effective clinical trials was through development of an understanding of the natural history. The past 35 years have seen my laboratory career flourish less well, but my clinical research has resulted in promising results that, I trust, will pave the way for effective clinical trials.