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Managing Rett Syndrome: Building a Multidisciplinary Care Approach

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Dr. Tu:
This is CE on ReachMD, and I'm Dr. Jennifer Martelle Tu. Here with me today is Dr. David Lieberman. We're going to be discussing Rett syndrome, which is a neurodevelopmental condition that affects nearly every aspect of a patient and their family's lives. From seizures and feeding difficulties to communication and mobility, care is rarely straightforward. So how do we prioritize what matters most and build a management plan that truly supports both the patient and their family? Let's ground this discussion in a real-world case.

So here we're following a 9-year-old girl with classic Rett syndrome. She was diagnosed at age 3 after a typical period of early development followed by regression and confirmatory genetic testing. Over time, her care needs have become more complex. Currently, she has issues such as epilepsy, G-tube dependence, respiratory dysfunction, Rett spells, communication challenges, and at school she uses an augmentative communication device. She also receives PT, OT, and speech therapy.

So, Dr. Lieberman, when you're managing a patient like this with neurologic, gastrointestinal, and functional needs that are all evolving over time, how do you begin to prioritize the management plan?

Dr. Lieberman:
That's a great question, Dr. Tu. We want to start with the highest-impact domain, namely seizure control. Frequent seizures can impact daily life negatively, and we also want to prevent prolonged seizures that could lead to status epilepticus and could be potentially lethal. So seizure control is number one.

Looking at nutritional stability, we know that growth and nutrition are important over the lifespan, and adequate caloric intake is needed to provide for growth. We want to make sure the patient's also getting adequate fluid intake and that they're able to take their medications. So sometimes we have to place G-tubes, maybe in up to about a third of our patients, to help supplement their nutritional intake.

Respiratory management is also important. We look at breath-holding and hyperventilating episodes that can come on frequently and interrupt activities like eating and walking. We have some medications for that, so we can explore those as well.

In addition to seizure control, nutritional stability, and respiratory management, I wanted to bring up trofinetide, which is an FDA-approved medication for the treatment of Rett syndrome. It was first approved in 2023 in pediatric and adult patients 2 years of age and

older. It is the N-terminus of the IGF-1 molecule. It's a synthetic analog, and in preclinical studies it was shown to do a number of things. It increases synaptic plasticity by increasing dendritic outbursts, increasing spine density, increasing neuronal signaling, and increasing synaptic plasticity. It also decreases neuroinflammation so that you have less astrogliosis and less microglial activation.

There was a phase 3 LAVENDER study done in girls and women with Rett syndrome age 5 to 20 where they received either oral trofinetide twice daily or placebo for a period of 12 weeks. In this double-blind study, they looked at 2 outcome measures, the Rett Syndrome Behavior Questionnaire, which is a parent-derived measure, and the Clinical Global Impression of Improvement, which is a clinician measure. And in both those 2, and then in the third area, the Social Composite Communication Measure, there were improvements in the trofinetide group that were statistically significant compared to the placebo group. So there was no significant improvement in motor function or verbal communication, but this clinical trial did show that there was a large frequency of diarrhea in the patients, up to 80% versus 19% in the placebo trial.

Now, one of the issues is that most of these patients came in with constipation, so they were already on stool softeners, and so that may have contributed to the high rate of diarrhea, and also they were started at the weight-based goal dose, which could have also contributed to diarrhea.

There was an open-label extension study called the LILAC study. It was up to 40 weeks in the LILAC 1 study and up to 104 weeks in the LILAC 2 study. There was an improvement in the RSBQ score in the trofinetide group compared to the placebo group, as well as in the Clinical Global Impression of Improvement.

So this is the LILAC 2 study now, just the 32-month follow-up, looking at the RSBQ score, which showed a more significant improvement over time compared to where they were at the beginning of the LAVENDER trial, and the Clinical Global Impression of Improvement score also showed improvement to a minimal improvement. No new safety concerns were raised in this trial.

Dr. Tu, what is your approach to managing these comorbidities in a coordinated way?

Dr. Tu:
So you brought up some excellent points when talking about care for patients that have lots of comorbidities that evolve over time. I think there are just a few additional things to add on for these patients in general. And some of the things that we think about are things like rehabilitation therapies, getting their physical therapy, their occupational therapy, really trying to maintain and grow their skill sets.

There are a few other things to think about, like dentistry. A lot of these patients don't tolerate cleanings at home. Sometimes they need sedated procedures for cleanings or tooth extractions, cavities, things like that. So that's one piece that just to throw out there. We don't always think of top of the list, but we often have to consider in our patients with Rett syndrome.

A lot of our patients do have sleep disturbances. Sometimes they need medication. Sometimes we need to sort of revisit the whole sleep environment, just for safety reasons.

And then the last piece that I think is really important for these families is to bring in social work. There's a lot of resources available. It's a really challenging system to navigate, and so bringing in a little extra help to help families try and identify what resources are available, I think is a really nice thing to do for these families. It really adds to the care for these very complex patients.

Would you like to comment on any additional things that you would do for your patients?

Dr. Lieberman:
We just try to be supportive of the family's needs. The caregiver has a lot of emotional and sometimes physical stress taking care of these patients, and we want to be able to support their needs by providing any resources we can to the family.

Dr. Tu:
Well, this has been a great micro discussion, but our time is up. Thank you all for listening.

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