Clinical Laboratory Approaches for Diagnoses of Sleep-Disordered Breathing and ADHD-Like Behavior in Children

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Guests: Dr. Roland Valdes, Jr. is a Professor of Pathology and Laboratory Medicine and Dr. Maria Romelinda Mendoza is an Assistant Professor of Pediatrics, both with the University of Louisville School of Medicine.

Randye Kaye: Hello, and welcome to this edition of *JALM* Talk from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host Randye Kaye.

Over 25 million individuals experience obstructive sleep apnea in the United States. Impaired breathing during sleep may trigger several further clinical conditions, including cardiovascular complications, as well as behavioral symptoms similar to those observed in attention deficit hyperactivity disorder, or ADHD. As many as 25% of children diagnosed with ADHD may have obstructive sleep apnea syndrome as the underlying cause. Diagnosis of obstructive sleep apnea currently relies on sleep studies. However, these studies are inherently difficult and impractical to perform, particularly in children. Therefore, there's a need for the identification of relevant biomarkers and the development of noninvasive clinical laboratory tests for diagnosing obstructive sleep apnea.

The May 2023 issue of *JALM* features a review article that assesses the status of candidate biomarkers for the diagnosis of obstructive sleep apnea in children. If such tests could be appropriately analytically and clinically validated, they would have the potential to positively change the standard of care for management of ADHD in both children and adults.

Today, we're joined by two of the article's authors; Drs. Roland Valdes, Jr. and Maria Romelinda Mendoza. Dr. Valdes is a Professor of Pathology and Laboratory Medicine with the University of Louisville School of Medicine. He is both the former Chief of Clinical Chemistry and Senior Vice Chairman for the department. Dr. Mendoza is an Assistant Professor of Pediatrics with the University of Louisville School of Medicine, where she serves as Division Chief for Developmental-Behavioral Pediatrics and as the Medical Director of the Norton Children's Development Center. Welcome Drs. Valdes and Mendoza.

Can you start with expanding on the current conventional ways of establishing a diagnosis of ADHD and why it is difficult? Why do we need new biomarkers in this area, specifically for obstructive sleep apnea? Dr. Mendoza, let's start with you.

Maria Mendoza — Yeah, absolutely, and thank you so much for this opportunity. Well, ADHD, or attention deficit hyperactivity disorder, is a neurodevelopmenta,l neurobiological disorder characterized by a persistent pattern of hyperactivity, impulsivity, and/or inattention, that causes impairment in one's functioning in more than one setting and beyond what can be expected for the individual's developmental level. To establish the diagnosis, we clinicians must have evidence to support the criteria and these criteria are from the Diagnostic and Statistical Manual of Mental Disorders or DSM-5.

Essentially, there are two criteria clusters, one being the inattention symptom cluster and the other being hyperactivity impulsivity cluster. Each cluster will have nine symptoms listed, and you need at least six of the nine symptoms per cluster present, and significantly impacting functioning, to establish the diagnosis. ADHD can present as mostly inattentive, mostly hyperactive-impulsive, or a combination of both.

As a clinical diagnosis, its validity depends on the convergence of data from history taken from informants, observation of the child, use of questionnaires, and standardized interviews. We then analyze this information and we also are able to rule out by doing so any lookalikes or any what we call comorbidities related to this. A good number of individuals with ADHD have sleep problems and vice versa, and this bi-directional relationship between the two is what makes the clinical diagnosis more challenging.

Roland Valdes — Yes. If I could add a little bit to what Dr. Mendoza just commented on, I wanted to add to indicate that by adding that sleep disordered breathing has also been linked to several conditions, like cardiovascular disease that you Randye pointed out earlier in your introduction, and some reports actually suggest that stress due to sleep apnea can affect the immune system. So the clinical ramifications of sleep disorder breathing are actually many.

Now, the problem is that monitoring sleep related stress is difficult, with little progress in recent years. So developing laboratory-based approaches could provide a segue for clinical applications that go much beyond the diagnosis of ADHD.

Randye Kaye: — Thank you, Dr. Valdes. So let's stay with you for a second. Your review article discusses some candidate biomarkers for

obstructive sleep apnea, and some of these markers are measured in serum and some are measured in urine. Can you comment on the different considerations for serum versus urine testing in this context? Is one preferred over the other?

Roland Valdes: Certainly, Randye. For an overnight biomarker to be useful and the specimen be collected at home after sleep, drawing blood is not practical, nor desirable, particularly in children. So collecting a urine sample has many advantages in that it's noninvasive, simple to collect, and importantly, because the biomarkers accumulate in urine overnight, an average physiologic response is therefore monitored. I should also add that biomarkers in urine are not susceptible to physical movements, often a problem with both sleep studies or at-home monitoring devices.

So the bottom line is that likely a urine sample is the best and most rigorous option.

Randye Kaye: All right, thank you. And of the candidate biomarkers that have been explored in this area, which markers should our audience be aware of that maybe have the most promise?

Roland Valdes: Well, it's interesting to note that many researchers over the years have been searching for biological markers that may be related to sleep disorders, and they have done excellent work by these researchers in attempting to identify these sleep related biomarkers. We know that the best biomarkers in general are those that are linked directly to a physiologic response. So in the case of monitoring stress during overnight sleep as a result of intermittent hypoxia, for example, we suggest that the most promising two candidates to date are urocortin 3 and erythropoietin.

Now, both of these molecules accumulate in urine overnight in response to both stress and hypoxia, respectively. Urocortin 3, due to stress and erythropoietin due to hypoxia. They also have the advantage of representing an average response over time as biomarkers go, I believe that urocortin 3 may actually be related to stress, as C-reactive protein is to inflammation, but that remains to be seen. In any event, as we focus on discovery, we may very well find other markers for sleep apnea.

Randye Kaye: All right. Thank you, this is so interesting. Dr. Mendoza, if these biomarkers are demonstrated to work, how do you envision that healthcare providers can use the results of the tests?

Maria Mendoza: Oh, yes Randye. This can really be a game changer, because having biomarkers for conditions like ADHD can really improve access to care. For instance, if you have something

that you can use at the point of care testing, readily available at the general pediatrician's office, this will really cut down on wait times. So at this time, there are only 800 board-certified developmental pediatricians in the U.S. and it can take anywhere from 6 to 18 months before a child can be seen by us.

So if there's a way to screen those cases that will really benefit from intensive subspecialty evaluation, be it developmental pediatrics or pediatric sleep medicine, wouldn't that be amazing?

Randye Kaye: That would be amazing and that is a very long time to wait to see you. So finally, Dr. Valdes, as we look to the future, where is research in the field going?

Roland Valdes: Well, I tell you what. Speculation is always is exciting, and I always like to do this. Laboratory based biomarkers really open tremendous possibilities for monitoring stress conditions with simple urine tests, hopefully. Stress is a major problem, not often recognized because it's difficult to diagnose in any setting. Considering that sleep is the most relaxed time in a person's daily activity, it's the ideal time to monitor for latent stress conditions. So we envision reliable tests, useful in diagnosing and monitoring conditions like not only ADHD, but possibly post-traumatic stress disorder, PTSD, and other now overlooked stress situations that affect work performance.

So I think the future may hold for point-of-care tests that can be performed at home for screening and also suitable for more frequent testing at home to monitor treatment efficacy if needed. So, all being said Randye we highly encourage the discovery and development of sleep-related tests by our clinical laboratory community, and we hope that others will embark on this kind of novel discovery.

Randye Kaye: Well, thank you so much. Thank you, Drs. Mendoza and Valdes for joining me today.

Roland Valdes: Thank you, Randye.

Randye Kaye: That was Drs. Roland Valdes, Jr. and Maria Romelinda Mendoza from the University of Louisville School of Medicine discussing their *JALM* review article "Clinical Laboratory Approaches for Diagnoses of Sleep-Disordered Breathing and ADHD-Like Behavior in Children." Thanks for tuning in to this episode of *JALM* Talk. See you next time, and don't forget to submit something for us to talk about.