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VOICE OVER:

Welcome to ASA's Central Line, the official podcast series of the American Society of Anesthesiologists, edited by Dr. Adam Striker.

DR. ADAM STRIKER:

Welcome back to Central Line. I'm Dr. Adam Striker, your editor and host. And I'm looking forward to today's discussion. We're going to learn a lot about delirium markers from two experts in the subject, Dr. Tina McKay and Dr. Zhongcong Xie. We were informed by ASA's Committee on Geriatric Anesthesia that you were the right experts to discuss delirium markers with us. So we are thrilled to have you here on the show. Welcome to both of you.

Before we get to the research and the implications of delirium markers, I'd like you each to introduce yourself and tell our listeners a little bit about how you got interested with this particular subject. Let's start with Dr. McKay.

DR. TINA MCKAY:

Hi. Well, thank you again for the invitation to speak today. I'm Tina McKay. I'm an instructor at Mass General Hospital in the Department of Anesthesia, Critical Care and Pain Medicine. One aspect of our research is really focused on identifying and validating biomarkers that might be associated with the development of postoperative delirium in older patients, kind of with the goal to prevent cognitive decline. I'm originally from Oklahoma. I received my PhD in cell biology from the University of Oklahoma Health Sciences Center. My graduate work really focused on studying a corneal dystrophy called Keratoconus and evaluating some of the cellular and molecular features of that condition, as well as looking into systemic biomarkers. We also looked into studying wound healing and responses to hypoxia, and I moved to New England a few years ago to for a postdoctoral fellowship at Tufts University and Tissue Engineering and a research fellowship at Schepens Eye Research Institute, studying cell cell signaling. So my current research builds a lot on this training and trying to develop approaches to promote cognitive recovery following surgical stress. We're

trying to really understand which factors and pathways are important in cognitive resilience, and we think that identifying specific biomarkers associated with delirium might help with that.

DR. STRIKER:

Great. Dr. Z?

DR. ZHONGCONG XIE:

Yes. Again, thank you for the invitation. A truly great honor to have opportunity to speak out about the delirium after surgery and anesthesia. My name is Zhongcong Xie. Please call me Z. And I'm the anesthesia attendings at the Massachusetts General Hospital and Harvard Medical School. And I really enjoy doing that. But during my taking care of patient, we found some patient, and particularly very old patient, develop things called confusion during memory impairment. We call this post operative delirium. So bring that back to the study. We study that in humans, animals, even cell cultures. So I have a risk lab as well. And I'm also a professor of anesthesia at Harvard Medical School. So our lab focuses on study. Why? Why people develop the confusion, learning memory impairment after surgery. What's the potential reason? What medication or any other we can use to treat this kind of disorder?

DR. STRIKER:

Well, thanks again to both of you for joining us. This is a broad topic and something I know many anesthesiologists are well aware of. But just to set up the discussion, let's start with delirium itself. How well do we understand the pathophysiological mechanisms of postoperative delirium? Do we understand the causes? Do we know how to cure it? Let's set the stage as to where our current state of knowledge is right now. Dr. McKay, do you mind starting us off?

DR. MCKAY:

Sure. So we know that increased age is the major risk factor for the development of postoperative delirium, and this might be a result of some of the factors that underlie aging itself, like modifications to DNA, epigenetic changes that influence cellular responses to stress and nutritional sensing. And this can lead to mitochondrial dysfunction and cell senescence. But more specific to the brain, these aging factors may influence neuronal function and network connectivity at the molecular level, in addition to kind of the normal reductions in gray and white matter that accompany older

age. And this can result from increased oxidative damage to DNA lipids, proteins in the brain. And this is something we're kind of trying to investigate in our research.

Some of our biomarker work in delirium supports a potential role for increased inflammation in patients with delirium. So we've detected significantly higher IL six in serum from patients with delirium. Other groups have also looked at C-reactive protein, which is in acute phase protein as being associated with delirium.

In terms of treatments, I think the best course is prevention. There are a few factors that have been proposed to reduce the incidence of post operative delirium. So just optimizing perioperative pain management, adequate hydration, sleep, reducing polypharmacy. These are kind of all the factors that have been proposed to reduce the incidence of delirium. There are also things to improve cognitive recovery, so adequate hydration, having adequate staff or family support to permit reorientation and other soft measures like just ensuring that the patient has their classes and things like that. So we're still trying to investigate this, but these are just some of the things that have been proposed.

DR. STRIKER:

And Dr. Z, go ahead and give us your perspective.

DR. XIE:

Yeah, I actually agree with Dr. Tina McKay for this prospect regarding postoperative delirium. And obviously, it's very clear clinical disorder. But the reason is not clear yet. So we're thinking that due to inflammation, because inflammation after surgery can may be able to triggering neuroinflammation, the kind of inflammation in the brain causing the brain dysfunction leading to this confusion and memory impairment. However, almost everybody has kind of the post-operative inflammation after surgery, such as the fever, the increase of white blood cells, feel fatigue. But not everybody will develop post-operative delirium.

So how how that happens? So there must be something else which you also contribute to the pathology or the reasoning of the delirium change. And that's the reason we try to study what is kind of the pathology, what's kind of the biomarker for the patient. And we have any target intervention to mitigate or prevent these disorders.

DR. STRIKER:

Well, let's turn to biomarkers. Dr. McKay, if you don't mind explaining what is a biomarker specifically and tell us a little bit about how as a researcher you tackle this particular topic.

DR. MCKAY:

Yeah, sure. Thank you. So a biomarker is usually defined as a characteristic or factor that, first, it's objectively measured, it's quantifiable, and it can be evaluated as an indicator of a of either a normal or a pathological process. They can also be used to evaluate the effect of a treatment. So in the case of clinical trials as a surrogate endpoint biomarker. Biomarkers are really distinct from subjective measures like how patients as they're feeling, but they can be used in conjunction with those other measures to have a better picture of the clinical course. Generally, we think of molecular biomarkers like proteins, metabolites or lipids that are found in blood that may be associated with a disease, but they can also be other quantifiable objective measures like characteristics and might be identified during brain imaging. I really like to think of biomarkers as signposts that can kind of tell us where we're going, where we're at, and if we're there yet. But really, in order for a biomarker to be clinically useful, it has to be incredibly selective and specific for the condition of study. And this is really the challenge of most biomarker studies because there's often normal physiological range for specific factor. So associating a specific change in that level with a complex pathology like delirium can be kind of difficult.

And there are kind of different considerations that we put in place to identify what is a good biomarker. The first is it's got to be easily isolated. And so we usually most of our work focuses on blood or serum or plasma. But it also should be representative of the clinical condition that's distinct from other sorts of conditions. It should also be kind of stable so that other researchers can also detect it reliably.

There are different classes, so there are three basic classes of biomarkers that I'll talk about. Risk biomarkers which generally signal the potential for developing a condition and otherwise kind of normal, healthy individuals. And so an example of that would be certain APOE e gene variants that have been associated with a higher risk of Alzheimer's disease. Diagnostic biomarkers are another general class that can be used to detect or confirm the presence of the condition. So I think the most known case is HPA1C as a biomarker for type two diabetes. Prognostic biomarkers are kind of a third class that are used to identify the likelihood of a clinical event or a recurrence. So that's usually to study disease progression. And these sorts of biomarkers might be important in understanding potential links between delirium and later progressive cognitive decline. So these different types of biomarkers can help us to really understand the biological processes that underlie delirium. But there's still a lot that we don't know

about the pathophysiology, so we're hoping that biomarkers can help us tease out the important processes that are involved in delirium onset progression and resolution.

DR. STRIKER:

Well, I understand plasma biomarkers of Alzheimer's are correlated with postoperative delirium. Dr. Z, do you mind telling our listeners a little bit about the connection between those two?

DR. XIE:

Sure. Yeah. Certainly. So probably five years ago there's some studies showing that potentially there's some association between the hospital delirium and Alzheimer's disease. Specifically, we found the patient with Alzheimer's disease will have higher risk of developing post-operative delirium or any kind of delirium. And also the patient with delirium were higher risk to developing Alzheimer's. That's a very interesting but puzzling observation. And recently, we know that a biomarker called Tau protein phosphorylated at 217 and 181 other newly identified plasma biomarker for Alzheimer's disease. In other words, if you have increase of the two proteins, you will have a higher chance to developing Alzheimer's disease several years later. And in our recent study, we found, interestingly, this exactly seemed two proteins. We called tau protein, possibly at 217 and also at 181, also predictor of biomarker for delirium. And for the detail we found, if a patient has a higher level in blood of a P Tau at 217 and phosphorylated at 181 are actually associated with increased chance of developing with delirium after surgery. Also for increase severity of this productive delirium in patient. So you can see that both for the phenotype, for the observation, the clinical findings, there is a potential association. For the biomarkers, there's also a potential association that means the specific tau protein, the tau protein phosphorylated at 217 and 191 are both biomarker for Alzheimer's disease, also biomarker for post operative delirium in patient.

DR. STRIKER:

Well, we've been discussing associations, but Dr. McKay, is there evidence of an increased risk of something like Alzheimer's with delirium, or is this just are we still at association stage?

DR. MCKAY:

So there have been associations. I mean, delirium and Alzheimer's disease are considered, they're distinct conditions, but they're association evidence that an incidence of a delirium may promote accelerated cognitive decline during Alzheimer's

disease or related dementias. We still need to go do more further studies, really to prove that it's causation. It's been proposed also that someone maybe who has undiagnosed dementia will is more likely to develop delirium as well. But delirium, by definition is an acute condition with a fluctuating course. But persistent persistent delirium with kind of a progressive onset and long duration is a feature of dementia. So I think there's definitely strong parallels and one may be associated with another, but we need further research to kind of tease the causation out.

DR. STRIKER:

Well, it's a great segway to discuss the clinical implications and the practical implications for most anesthesiologists out there. So before we get to that, let's take a short patient safety break. Stay with us.

(SOUNDBITE OF MUSIC)

DR. JEFF GREEN:

Hi, this is Dr. Jeff Green with the ACA Patient Safety Editorial Board. OR medication errors such as syringe swaps can cause severe patient harm. Reduce the chance of a syringe swap by aligning the syringe and label on an IV stop cock so that the name and concentration of the medication is directly facing the anesthesiologist. If a manifold is being used to administer several medications, the syringes and their labels can be oriented in the same direction and placed in the order of their planned use, particularly during induction of anesthesia. While injecting the medication, the anesthesiologists should read the label, rechecking the concentration and calculated dosing as a quick and easy safety step. These simple steps can decrease risks by removing common causes of syringe swaps, such as failure to read the syringe labels using unlabeled syringes or relying on color coding or labels alone.

VOICE OVER:

For more information on patient safety, visit [asahq.org/patientsafety22](http://asahq.org/patientsafety22).

DR. STRIKER:

We're back, talking delirium and biomarkers. For anesthesiologists working to avoid delirium, what are the practical takeaways? For instance, can these biomarkers affect how we perform our pre-op evaluations or our interop course? Dr. Mackay, do you mind commenting a little bit on the practical implications of all this?

DR. MCKAY:

Yeah, so that's a great question. And I will say that's something our research is kind of trying to answer. As of now, there are no widely, I would say, accepted molecular biomarkers of delirium. We're working on it. Most of our biomarker studies have been in rather small populations, so we need to perform these larger studies. But there have been recurring themes. Biomarkers or pathways seem to be related to delirium. So Dr. Z mentioned neurodegenerative markers like Tau as being a biomarker of post operative delirium. I've also mentioned increased inflammatory factors. So that's a recurring theme as well. Another thing that we're kind of looking at in our research is looking at metabolic factors. And this may go back maybe to predictive risk if we can screen a patient at pre op and determine that there are a higher risk based on just metabolic factors in general. So we're currently conducting an observational clinical study to evaluate the relationship between inflammation, neurodegenerative factors, and metabolism during the perioperative period. And I think that's where it'll start to address maybe that question of clinical takeaways, but it really requires further work.

DR. STRIKER:

Well, Dr. Z, what does this tell us? How can we use these biomarkers to predict if a patient will face cognitive decline later in life or to optimize brain health, which has been a certainly a big topic in our specialty recently?

DR. XIE:

Yeah, that's a very good question. So actually showing that Tau protein may serve as a biomarker for postoperative delirium has been also reported before by many other labs. That's something consistently showing that potentially the proteins or any changes associated with Alzheimer's disease may be able to also contribute to the development or the ordering of this post-operative delirium. And what can we using biomarker to take care of patients? That's a great question, because so far we still do not have this magic bullet to even prevent or treat the delirium. But biomarkers can tell us several things. First, it can identify the high risk patient. A patient with high risk, the surgeons may come, may reconsider. Do we really need to have surgery now or wait a little bit time to make the patient be more optimized before the surgery? Secondly, biomarker can also be a good help tool for the clinical research who can using biomarkers to see whether any medications or any non medication interventions can take care of the patient by reducing the biomarker change. I think most importantly that the biomarker can also indicate maybe the changes in Tau proteins can be used as partially the pathology of the positive delirium. Then using this clue, we can bring more research into this delirium research to find out the exactly the underlying causes and also the intervention.

DR. STRIKER:

So kind of hard to imagine, but just suggesting that perhaps in the future ... we might postpone a surgery because of somebody who has an acute viral illness. But we never think about the brain health in terms of optimizing for specific procedure. But you're suggesting that with further research it might be possible when we look at these biomarkers to say, okay, we need to wait for the optimum time in terms of brain health to perform the procedure as well.

DR. XIE:

Yes, that's exactly true. So for elective cases, and we may be able to not only optimize the heart condition, liver condition, kidney condition, but also brain condition.

DR. STRIKER:

Well, that's fascinating. It's something that we're just so not used to thinking of as an anesthesiologist when it comes to the whole body. We're so used to the organ systems that are not the brain being optimized. The brain has always been somewhat of a mystery, but it's fascinating to think of it kind of rising to that level as well of optimization.

As long as we're talking about delirium. Is this specifically to certain patient population or does this apply to patients of all ages? Because we know delirium exists in young children as well as older individuals? Dr. McKay, why don't you give us your take?

DR. MCKAY:

Yeah. So in our research, we focus on older individuals because they're at much higher risk of developing postoperative delirium. So it's delirium is relatively common during hospitalization. I think estimates 20 to 30% depending on the patient population, but it's primarily affecting older individuals. And so when we say older, I mean older than 65 years old. I think some cases, some studies have reported 15 to 53% of older individuals will develop delirium while in the hospital. So this is kind of the patient population that our research focuses on. I think maybe the pathophysiology underlying pediatric delirium may be different than what we're thinking about here, but we'd have to study that.

DR. STRIKER:

And what's the typical time course that you're thinking of when you have older individuals, or at least individuals over the age of 65 that that have delirium post operatively.

DR. MCKAY:

So we usually focus on the first 72 hours. So post-op day one through three is generally what we we assess for. And then we've been looking at longer term outcomes like 30 days, 60 days, 90 days, and performing cognitive assessments to see if we can detect any differences from the pre baseline assessments.

DR. STRIKER:

Great. And Dr. Z, are there any other long-term patient centered outcomes as a result of this research specifically related to cognitive function?

DR. XIE:

Yeah. Well, Dr. McKay has a well said about this point. It is a potentially the patient who develop the delirium after surgery may also develop other kind of memory impairment. That has been well documented. And then regarding Alzheimer's disease, this is the potential association as well. But exactly the cause effect, association or relationship has not been formally established yet, you know, particularly due to that many clinical observation. That's the reason. So we have this observation now of the making of association between the delirium or Alzheimer's disease and non term memory impairment. Is that any cause effect relationship? We may need to bring this question back to the preclinical animal research to find out exactly the cause and effect relationship.

DR. STRIKER:

And I know most much of the research is early stage, but where do you both expect this research to take us? Do you think delirium will be cured? Well, that's always the goal, I imagine. Any kind of research is to to get to that goal. But for practically speaking, how do you both foresee this going? Dr. McKay, let's start with you.

DR. MCKAY:

Well, in recent years, there's been a lot of growth in developing platforms and different analytical approaches to detect kind of very lowly, abundant biomarkers in blood. So normally in the past we've had to deplete kind of the major serum proteins in order to

detect the really low abundant factors that are actually derived from the brain. And so I think these, the development of these other technologies have really accelerated biomarker work in general. For further development, I think using a systems biology approach is what we'll have to go to where we're trying to understand the Omega landscape, looking at not only proteins but metabolites, lipids, genetics, epigenetics that might be contributing to brain aging and health in general. So one aspect that we're working on in our research is really to identify a predictive biomarker signature. So I don't think it will be just one factor. It will likely be a number of factors that might indicate that a patient's at higher risk of delirium so that we can kind of optimize perioperative care to prevent it. A longer term goal is really to improve and extend brain health as we age, since we know that this can have dramatic effects on quality of life. I think the future is really bright, really in our search to identify targeted interventions to promote cognitive resilience. And developing therapeutics to actually do that requires a lot of further study, but something that we're working towards.

DR. STRIKER:

Dr. Z.

DR. XIE:

Yes, I agree with Dr. McKee. So the good news that many people realized we needed working very hard to identify the potential causes, the underlying reason and also the potential intervention to mitigate the impact of the delirium after the surgery. And what are they? We still don't know for for it yet. But in a lot of studies, there's a very many good laboratory of medical scientists are working hard and working together to in this area, try to identify the reason and the treatment. And I think that at the present time, we only try to optimize the old surgical condition before surgery, during surgery, after surgery for small things like temperature, hydration and controls. But maybe in the future we can develop the medications to treat the delirium. Meanwhile, we can also try to develop something called a long pharmacological treatment, some brain stimulations and some olfactory stimulations. And many other things can be used to really optimize patient's condition, particularly brain function, to mitigate the incidence or the chances of post-operative.

DR. STRIKER:

So let's let's tie this all together. Most of our listeners are not going to be bench researchers, myself included, so I want to tie this up for them. What do they need to know now going forward? Tomorrow they go in the operating room. They have a patient that may be susceptible to this. What are things they need to know going forward other

than just watching for the research? Are there things they should tell the patients or are there things that they should be cognizant of themselves as far as mitigating risk of delirium? Dr. Z?

DR. XIE:

Well, that's a great question. So I think that the biomarker research showing the potential vulnerability or the risk to developing the delirium will net both patients and doctors and the ... know that if you have a delirium, even though we call it post-operative delirium, it's not 100% associated with anesthesia. It also due to your internal risk or internal vulnerabilities. For example, you already have pretty higher tau proteins or P tau or ... proteins in your blood, suggesting your brain is already vulnerable to developing this disorder. So that's a combination of both external stimulations such as surgery and seizure and other factors. Also with surgery also is in combination of your internal reasons, such as you already have some pathology associated with Alzheimer's Disease, it's already there. So the combination of these multiple factors together can induce or leading to this prevent dysfunction are represented as the confusion and the memory impairment. We call it delirium after surgery.

DR. STRIKER:

Dr. McKay, do you have anything to add?

DR. MCKAY:

Yeah. So there are there have been a number of recommendations to improve long term cognitive health. And I think these maybe overlap with preventing possibly post-operative delirium. Some modifiable factors. I think that the patient can consider not just genetics but managing cardiovascular health. So managing hypertension has been shown to reduce the risk of dementia. So they may have relevance to delirium as well. Increasing moderate physical activity, maintaining sleep patterns. So there's been a lot of focus on sleep and sleep hygiene and delirium. And I think just engaging in social activity, cognitive stimulation, that's gained a lot of research, I think in recent years, continuing to learn new things and stay mentally active as we get older are also likely modifiable factors to consider when trying to optimize brain health before surgery.

DR. STRIKER:

And then finally, where would you both refer our listeners to go to learn more if they wanted to read specifically about not only your research but the topic of delirium and cognitive dysfunction after anesthesia in general? Dr. McKay?

DR. MCKAY:

So the American Delirium Society is a is a great community. They have a conference each year. They publish. They have an excellent website, I think, for referencing delirium research. There's also a number of kind of leaders in this field. So Dr. Sharon, Inuwe here in Boston, has written a number of really good review articles about postoperative delirium and delirium in general. So those are good kind of references to learn more about delirium and delirium biomarkers.

DR. STRIKER:

Great. Dr. Xie, anything more to add?

DR. XIE:

Oh, yeah. So in 2016, the American Society of Anesthesiologists has a brain health initiative, emphasize down to improve the brand conditioning of brain health before, during or after surgery. So thatwebsite, has some people to work on that we provide update information including the risk of publication and potential treatment. So that's a good resource to look out for the new information. And during every year, every year at the annual meetings of the American Society of Anesthesiologists, there are many lectures, discussions regarding this amendment, function change and confusing delirium of the surgery. That's always a good resource to get a new information. Overall, I think that it will take a village to make the work, and we hope that everybody this nowadays can pay attention, contribute, and really to enhance the health of patients during the surgery time.

DR. STRIKER:

Excellent. Thank you both. Great to have some resources for our listeners, great for all of us to have the tools to get the most up to date information. This is a fascinating topic. It's such a large one. Brain health is a huge issue. And just scratching the surface here, this whole discussion is fascinating and we probably don't spend enough time talking about brain health. But I want to thank you both for joining us today and sharing your expertise with us.

DR. XIE:

Great. Thank you very.

DR. MCKAY:

Much. Thank you.

DR. STRIKER:

Well, thanks to our listeners for joining us on this episode of Central Line. Please tune again next time. Take care.

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