



Defense Health Agency

Defense and Veterans Brain Injury Center
“Clinical Updates in Brain Injury Science Today [CUBIST]” Podcast
“Alterations in plasma microRNA and protein levels in War
Veterans with chronic mild traumatic brain injury”

TRT: 9:18

Host: Ms. Amanda Gano

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Gano: The views, opinions, and findings contained in this podcast are those of the host and subject matter experts. They should not be construed as official Department of Defense positions, policies, or decisions unless designated by other official documentation.

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Gano: Hi. Welcome to Clinical Updates in Brain Injury Science Today, or “CUBIST,” a podcast for health care providers about current research on traumatic brain injury, also known as TBI. This program is produced by the Defense and Veterans Brain Injury Center, otherwise known as DVBIC. I'm your host today, Amanda Gano.

In this episode of CUBIST, I'll be talking with Dr. Donald Marion. Dr. Marion is a neurosurgeon and senior TBI consultant at DVBIC. Don and I will discuss a study entitled: “Alterations in plasma microRNA and protein levels in War Veterans with chronic mild traumatic brain injury”, by Vikas Ghai and colleagues, and published in *The Journal of Neurotrauma*, February 2020.

Gano: Hi Don, thanks for bringing this article about biomarkers for TBI to our attention. What were some of the key findings?

Marion: Hi, Amanda, sure. There are two key aspects of the study that I want to emphasize. First, the study focused on biomarkers that might indicate a remote history of combat related, or blast, TBI. The mean time from the last TBI to evaluation for this study was 4.6 years. This deviates a little from our usual biomarker reports which focus on identification of mild TBI early, or within hours after the event. The second point is that biomarkers that were looked at were not the traditional protein biomarkers that most of us have focused on. These investigators looked at circulating microRNAs especially those encapsulated in extracellular vesicles and they used next generation sequencing to analyze microRNAs in plasma and plasma-derived extracellular vesicles.

The investigators identified 32 microRNAs in plasma and 45 microRNAs in extracellular vesicles that significantly changed in the chronic concussion cohort compared to control groups. This microRNA profile in the mTBI subjects was associated with significantly worse scores the PTSD checklist, the military version, or PCL-M, the Patient Health Questionnaire Nine, or PHQ-9, which is a quick assessment for depression, and the Pittsburgh Sleep Quality Index, or PSQI, compared with controls subjects. The plasma microRNAs they identified as well as two serum proteins could potentially be used as biomarkers of remote blast injury and provide insights into the molecular processes associated with long-term health outcomes associated with blast-related chronic mTBI.

Gano: That's really interesting Don. I am familiar with serum proteins like GFAP and UCHL-1, but not so much with microRNA and extracellular vesicles. What is a microRNA?

Marion: So, good question Amanda, and I'm sure you're not alone. I suspect a lot of our listeners are the same. MicroRNAs are small non-coding RNA molecules that negatively regulate gene targets by inhibiting protein translation or enhancing messenger RNA degradation. Typically microRNAs interact with specific messenger RNAs through complementary base-pairing to influence the translation or stability of the target messenger RNA molecule. So in general, a negative or degrading influence.

Gano: Ok, so, what is an extracellular vesicle?

Marion: Extracellular vesicles serve as carriers of biologically active molecules that can traffic to local or distant targets and execute defined biological functions. They are present in biological fluids and are involved in multiple physiological and pathological processes. They facilitate intercellular communication in diverse cellular processes such as immune responses and coagulation. Extracellular vesicles are a relatively newly described additional mechanism for intercellular communication, allowing cells to exchange proteins, lipids and genetic material.

Amanda, that was a lot of information, and I know it's technical. I think it is really important that our listeners have some familiarity with microRNAs and extracellular vesicles because I really do think they will be some of the most important TBI biomarkers in the next five to 10 years.

Gano: Yea, that's really interesting. They have a lot of different functionality. So, how exactly was this study done?

Marion: 27 Iraq and Afghanistan war veterans from the VA Puget Sound Health Care System, and that's in Seattle Washington, with blast-related chronic mTBI had physical and neurological examinations, behavioral assessments including the PTSD Checklist-Military version, Patient Health Questionnaire Nine for depression symptom assessment, the Pittsburgh Sleep Quality Index and the Alcohol Use Disorders Identification Test, or the AUDIT-C. Veterans with mTBI had at least one blast exposure with acute symptoms that met VA, Department of Defense, American Congress of Rehabilitation Medicine criteria for mTBI. The mean number of blast-related concussions was 14. Two separate control groups, 11 veterans deployed to Iraq or Afghanistan, but with no lifetime history of TBI, that is, the deployed controls, and 31 age-matched civilian controls or community controls, with no history of TBI, were also included and tested in the same manner. Lifetime history of both blast-related and impact-related TBI was obtained. Blood samples were obtained for all participants and analyzed for microRNA and extracellular vesicles. In addition, the plasma proteome was analyzed and showed the concentrations of C-reactive and membrane metalloendopeptidase were elevated in chronic mTBI samples. All participants were male. Females were eligible for study inclusion, but no female with blast-related mTBI was enrolled. And that's because they couldn't identify any females with blast related mTBI in their cohort.

Gano: So, what were the other limitations of the study?

Marion: The study, Amanda, only included 27 veterans with a history of mTBI. So the sample size is relatively small. It would have been informative if they would have correlated microRNA levels with PCL-M and PHQ-9 scores, they didn't really do a great job of that. In general, the manuscript was written at a very technical level and is not easily interpreted by most general practitioners.

Gano: So it's interesting they didn't do any specific screenings related to mild traumatic brain injury. It seems as if all of their screenings were specific to behavioral health conditions. Am I correct?

Marion: Yeah, that's correct. And in fact, as you well know, Amanda, the neuro-behavioral symptom inventory or NSI is sort of the standard or the routine screening measure that we use here at DVBIC for screening TBI patients and so yeah, that that was an additional shortcoming, I would think of this of this study.

Gano: What are the key take-a-ways from the study?

Marion: So, Amanda, this study shows that there continues to be evidence for brain injury years after the last known trauma, and that finding is consistent with recent MRI-DTI data that finds long term micro-imaging of the white matter after TBI. Technology now exists that allows for the reliable measurement of very small quantities of biomarkers, and has significantly expanded our understanding of the long term effects of blast injury. It will be important to follow these subjects for several decades to see if the elevated microRNA and extracellular vesicle levels correlate with the development of neurodegenerative syndromes akin to Chronic traumatic encephalopathy, Alzheimer's Disease, Parkinson's, or other diseases. It also will be important to correlate acute protective and prevention measures with levels of these biomarkers years after exposure to blast injuries.

Gano: Thanks Don, that's really interesting. That was a great summary of a really complicated topic. Unfortunately that's all we have time for today.

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"CUBIST" is produced and edited by Vinnie White and was hosted today by me, Amanda Gano. It is a product of the Defense and Veterans Brain Injury Center, led by Division Chief Captain Scott Pyne, Medical Corps, United States Navy.

Thank you for listening to this episode. Next time, we will discuss TBI research getting attention in the mainstream press.

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