



**Defense and Veterans Brain Injury Center “Clinical Updates in Brain Injury
Science Today [CUBIST]” Podcast**
“Concussion, Genetics and Alzheimer's”
Episode 101, Transcript
TRT: 11:51 min
Host: Inbal Eshel

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Inbal Eshel: Hi, and welcome to Clinical Updates in Brain Injury Science Today or CUBIST. We are a biweekly podcast for healthcare providers about current research on traumatic brain injury, also known as TBI. This program is produced by the Defense and Veteran's Brain Injury Center, otherwise known as DVBIC, and I'm your host, Inbal Eshel, a speech language pathologist with over a decade of experience treating civilians and service members with TBI. I currently craft clinical recommendations here at DVBIC.

In each episode I will interview DVBIC subject matter experts who will highlight current TBI research of particular interest to healthcare providers. Today I'll be talking to with Dr. Anneee Bunner who is a biologist and program analyst at DVBIC with broad clinical and laboratory research experience. She will talk about TBI research that has received significant media attention. In today's episode Anneee and I discuss mild TBI, also known as concussion, and Alzheimer's disease. Although we know that moderate to severe TBI is a risk factor for Alzheimer's disease, we know a lot less about whether concussion carries a similar risk. We'll explore a study by J. P. Hayes, who examined this relationship in Iraq and Afghanistan war veterans between the ages of 19 and 58, many of whom had TBIs. You can refer to the CUBIST SoundCloud page for the full citation and PubMed link.

All right. Let's get started. Anneee, what made you chose this paper?

Anne Bunner: So this article actually got a fair amount of press coverage, including a write-up in the UK paper the Daily Mail and EurekAlert!, which is a blog maintained by the same people who publish the scientific journal Science. And of course for the focus on veterans it was particularly interesting to me.

Inbal Eshel: Yeah. That makes sense. Maybe you could give us just a quick synopsis of the article so that we have kind of a starting point?

Anne Bunner: Sure. So the objective of the researchers was to look at the intersection between genetic risk for Alzheimer's disease, and traumatic brain injury history, and how that overlaps with Alzheimer's disease. And the way that they assess Alzheimer's disease was not by looking for diagnoses, because usually that happens when people are of advanced age, but really actually looking at neuroimaging findings that suggest that people might be on their way to the early stages of Alzheimer's, and then also looking at their performance on a memory test, which can also be very suggestive of the early stages of Alzheimer's disease.

Inbal Eshel: Okay. And what were they trying to really learn about this population?

Anne Bunner: They wanted to know whether people with genetic risk for Alzheimer's disease respond to traumatic brain injury differently. So does the genetic component alter how traumatic brain injury history contributes to the risk of developing Alzheimer's disease? Is there an interaction effect is what we say in clinical research. So if you have

one factor it may not increase your risk very much, and if you have another risk factor it may not actually have that much of an impact, but if the two factors combined have an impact we call that an interaction effect.

Inbal Eshel: And so can you tell us a little bit more about the kind of genetic risk, and how they would assess for that?

Anne Bunner: Sure. So listeners may be familiar with a protein called apolipoprotein E, which is a pretty well characterized gene in the world of Alzheimer's disease risk, and it's been investigated for its link to a number of other conditions as well. And so if a gene is like a grape, apoli, or apolipoprotein E has four different colors. Their grapes come in red, green, and black. Gene's come in different alleles. And apolipoprotein E has four alleles, one of which is high risk for Alzheimer's disease. But there are lots of other changes that happen naturally in our genomes as our population is diversified. So but there are many other small changes, small individual differences between people spread all across the genome. And researchers have done genome-wide association studies to look for small genome changes that happen to contribute to Alzheimer's disease risk. Because there aren't necessarily in these very well-characterized genes like apoli that can make headlines. So genome-wide association studies have found other genetic factors that when combined are more predictive of Alzheimer's disease than apoli alone. So this analysis can be used to calculate what's called a polygenetic risk score that takes into account small changes all over the genome that contribute to Alzheimer's risk.

Inbal Eshel: And so tell me what were the findings that relate to this polygenetic risk as far as this study goes.

Anne Bunner: The main outcome that they were looking at was cortical thinning, and they were looking at 14 specific brain regions that are particularly vulnerable to Alzheimer's disease. So seven regions on each side of the brain, right and left. So they were looking at the thickness of the cerebral cortex. And what they found was that people with both TBI history and a high polygenetic risk of Alzheimer's disease had more cortical thinning than people with neither of those factors or just one of those factors. So there was an interaction effect which is consistent with their hypothesis that people with this genetic risk respond more strongly to a history of TBI in terms of the development of some of these neurodegenerative features that are maybe indicative of the early stages of Alzheimer's disease.

Inbal Eshel: And so is this kind of a new or novel finding, or is this fairly consistent with the literature that is already out there?

Anne Bunner: So it's known that moderate and severe TBI are environmental risk factors for the development of Alzheimer's disease. Literature on concussion is much more mixed. So it is news that we now have identified a subpopulation that with mild TBI can experience an increased risk of Alzheimer's disease. And it's also consistent with previous research showing that there is a strong genetic component for Alzheimer's disease risk. This is novel because we're really looking at the interaction of those two factors, TBI history and polygenetic risk.

Inbal Eshel: So if I am a provider and I were going to explain this to my patient who let's say came into my office and said, "I had a TBI and now I'm going to get Alzheimer's." How do you think I as a provider could explain this interaction, this complex interaction?

Anne Bunner: So I think it's really important when patients are responding to media reports about these sorts of studies to really try to tone down whatever alarmism may have been present in the original journalism that they were exposed to. Because sometimes science reporting can be a little over the top, and it can't take into account things like limitations. One of the limitations of this study was that there was no one that was actually diagnosed with Alzheimer's disease. They were looking at memory tests and neuroimaging findings. Also, there were very few women in this study. So these results probably shouldn't be extrapolated to women. So but in terms of what to tell your patients, so if someone comes in with a mild TBI and they're scared about long-term risks, I think it's important to emphasize that we really don't know a whole lot about how mild TBI contributes to the risk of subsequent neurodegenerative diseases. Because the evidence is really mixed, especially with Alzheimer's disease. If we're talking about someone with moderate and severe TBI, then I think it's important to just be honest that the increase in risk is fairly modest. There's still a great deal we don't know and also to acknowledge that Alzheimer's disease risk has a number of different components, including lifestyle components. So people can stay healthy. They can prevent further traumatic brain injuries, and they can improve their cardiovascular health which can limit their risk for vascular dementia.

Inbal Eshel: That's really really helpful. So basically to kind of keep things in context and to recognize that the science hasn't evolved to this state where we could say anything definitive about any of these connections. But this article has brought to light that there do seem to be some interactions that I think we might want to just keep our eye on in the future as the research field continues to develop. Does that sound about right?

Anne Bunner: Exactly, thank you [inaudible].

Inbal Eshel: Okay [laughter]. Is there anything else that you think a provider might be interested in taking away from this article?

Anne Bunner: So I found it really interesting that the memory test that they use, which was a delayed memory test, which has been around for a number of decades. It was first published in 1989 and 1991 that it was able to distinguish with 90% accuracy between seniors who were in the early stages of Alzheimer's disease and healthy seniors. So the test involved hearing a list of words and then waiting 20 minutes and seeing if they could recall-- how many words they could recall. And this had very high levels of accuracy. So this might be something that providers might not know about.

Inbal Eshel: It's nice to know that there are some tools out there that, at least in their research, have shown to be so effective at distinguishing between these two groups. And it'll be interesting to follow and track future research to see whether there might be some clinical implications or whether that could be useful in the clinical setting.

Anne Bunner: Yes, absolutely.

Inbal Eshel: All right [laughter], great. All right. Well, thank you so much, Anneee. That's all we have time for today. We hope you found this episode informative. You can stay up to date on future episodes by subscribing to [Cubis?] on iTunes, Stitcher, or wherever you listen to podcasts. If you have any questions about the podcast or about DVBIC products or programs, please feel free to email us at info@dvbic.org. That's info at D-V-B-I-C dot org.

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Inbal Eshel: CUBIST is produced and edited by Terry Welch and Deborah Bailin and is hosted by me, Inbal Eshel. It's a product of the Defense and Veterans Brain Injury Center, commanded by Army Colonel Geoffrey Grammer and the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury, commanded by Navy Captain Mike Colston. Thanks for listening. We'll be back in two weeks with neurosurgeon Dr. Don Marion. Dr. Marion is a senior clinical consultant at DVBIC. We'll be talking about current concussion research. See you then.

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