Cyberseminar Transcript

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Series: Mild TBI Diagnosis and Management Strategies

Session: Cerebral Microhemorrhage Following Chronic Blast and Blunt-Related Mild Traumatic Brain Injury – Imaging Findings

Presenter: Eyal Lotan, MD, PhD

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Dr. Ralph DePalma: It’s a pleasure today to have with us Dr. Eyal Lotan he’s MD, PhD, Graduate of Tel Aviv University in 2006 where he also got Master of Science and PH Degrees. He is a Clinical Assistant Professor of Radiology and Neuroradiology specifically at New York University Langone School of Medicine. His topic today is one of great interest and that is the definition of, possibly the definition of chronic blast and blunt-related mild traumatic brain injury imaging findings. Go ahead, Eyal.

Dr. Eyal Lotan: Thank you very much, Ralph. Thank you for the introduction and thank you very much for inviting me. I will talk as Ralph said about imaging findings and most specifically about microhemorrhages in mild traumatic brain injury. So the outline will be first talking about definition of mild traumatic brain injury and then both mild TBI in the U.S. and the Army at the cause of morbidity. Then I will talk about different mechanisms of TBI with emphasis of on blast-related TBI and then I will talk about different imaging findings in mild TBI. And in the end I will talk specifically, can you do next slide please.

Whitney: Yes, give me one second we’re\_

Dr. Eyal Lotan: Are you with me?

Whitney: Yes, yes. We’re running into some issues on my end as well give me a minute please.

Rob: Whitney you need to click into the slide on your, there you go.

Dr. Eyal Lotan: So and then I will talk about specifically about cerebral microhemorrhage in MRI and the significance. Next slide.

So also it’s common only defining mild TBI is a challenge. There are multiple criteria of different agencies like the World Health Organization, the Department of Defense, there’s American Congress of Rehabilitation Medicine. Some clinical criteria of mild TBI clues goes down remarkably structured MRI loss of consciousness, so less than 30 minutes so transient neurological deficit at the time of injury or post-traumatic amnesia less than 24 hours, or a Glasgow Coma Scale score of 13 or higher in the time of injury. Next slide. The other direction.

So, how big is the problem? This is a question it has a, the audience needs to answer.

Rob: Yes sir. And we’ve launched that poll. The question is, how many emergency department TBI-related visits, hospitalizations, and deaths occur in the U.S. annually? Answer choices are; point five million, one million, three million, and five million. Please select one. And Dr. Lotan the answers are streaming in, we have about half of your audience having made their choices already. So we’ll leave it open for a little bit longer until things level off and I will close the poll at that time and read the results to you. It looks like things have pretty much leveled off so I’m going to go ahead and close the poll and I will share out the results to the audience members and then I will read the results to you sir. And\_

Dr. Eyal Lotan: I see, I see it.

Rob: Okay.

Dr. Eyal Lotan: So most of the audience think about, said three million and it’s quite correct. So next slide.

So TBIs can demand the major [unintelligible 04:19] mortality and morbidity with about 2.9 million emergency department visits, hospitalization, and deaths in the United States. Alone in 2014 with 5.3 million persons that currently live in the U.S. with TBI-related disability. Next slide.

So the United States Army very considerable interest in the study of military head trauma due to the ongoing and past military deployments of the world. Especially in the Middle East in Afghanistan and the number are indeed high with over 400 service members who returned from this countries area and were diagnosed with TBI between 2000 and 2019. Next slide.

You can see that the majority of the military traumatic brain injuries were classified, are classified as mild TBI. Next slide.

So it was estimated that the incidence of TBI during the conflicts in Iraq and Afghanistan transformed 12% to 35% soldiers with approximately 80% of them, of the injuries were involved blast exposure. Many times more than one exposure for blast and these were more commonly younger males, junior in rank, and significantly more likely to report high combat intensity and hospitalizations during the deployments. Next slide.

So diagnosis of mild traumatic brain injury is clinical and it is important to make a better management in care of the patient. The symptoms are not limited to typical cognitive or motor deficits that usually associated with more severe brain injury. They might include complex combination of symptoms like mental health issues, sensory defects, chronic headaches and pain, sleep disorders, and as well as metabolic and endocrine dysfunction. The cause is usually [unintelligible 06:51] about two months and 85 to 90% of patients but some deficits for life leading to disability in many areas of their life. Next slide.

To us, to the challenge of the clinical study mild TBI has wide spectrum of injury mechanism including a direct blunt hit to the head, acceleration or deceleration mechanism such as in car accident that can cause the focal coup lesion and distal contrecoup lesion. We can see it in the middle figure. And also blast injuries from explosions that represent a unique injury mechanism. Next slide.

This is a description of the blast forces following explosion. After the explosion the [silence 07:56-08:06] followed by a drop in atmospheric pressure to below normal resulting in reverse blast wind the arrow in number three or blast under pressure, the negative phase in the middle. Then after the blast subsides the atmospheric pressure returns to normal. Next slide.

This is an illustration of the different injuries that can be seen after blast explosions. It can describe by itself to see all the effects. Primary blast injuries for those changes of the blast wave and the atmospheric pressure. The blast wave is followed by a blast wound this is a longer, which is a longer phase which can put object into motion causing ballistic penetrating trauma as the second effect. And then trauma from solid objects at the third order effect. The fourth and fifth order of blast injuries result from the other explosive products and toxic materials. Next slide.

From an imaging perspective CT is the standard of care for emergent evaluation of acute TBI regardless of severity. In case of negative initial or follow-up CT MRI may prove useful as a more sensitive modality as it may reveal the most at their injury and improve short-term outcome. However in effecting long-term outcome for mild TBI the result of imaging by conventional CT and MRI are frequently normal. Next slide.

There are several MR methods that have shown promise in demonstrating evidence of subtle brain injury in mild TBI that is not apparent at conventional imaging. This can be divided into three main categories based on the ability to characterize the brain’s structure, function, and metabolism. I will talk on function and metabolism in the beginning and then I will be concentrating structure. Next slide.

So functional MRI is a technique based on the detection of level of oxygen extraction of specific brain tissues providing that evidence of blast flow and local brain activity. This allows for detection of specific areas of brain activation doing different tasks. In this study for example patients with mild TBI had decreased activity in the walk and memory network that can be seen in the lower images of mild TBI patient with less activation in the bilateral frontal and parietal lobes as compared to the control subjects in the upper images. Next slide.

Metabolic changes can be examined by using proton MR Spectroscopy to assess neuronal injury decreases in any of the values of these three metabolites; N-acetylaspartate, creatine, or choline can be evidence of neuronal injury. Here for example we see a decrease in the value of NAA as compared to the heads of controls that’s what collate we say PCS positive or post-concussive symptoms as compared to a matched control. Next slide.

We can use a variety of segmentation techniques to assess the macrostructural changes. Patients with mild TBI have been seen to have cortical changes with thickening in the acute phase, presumably related to edema as can be seen marked by one and two here. And in the frontal and parietal region the results are evidence of seen in the more chronic stages after mild TBI. And the results evidence of volume loss both in the white matter and gray matter in chronic stage. And this is greater than what we see in matched controls. Next slide.

Microstructural changes in mild TBI include diffuse traumatic axonal injuries that can be hemorrhagic or non-hemorrhagic and also include cerebral microhemorrhages that’s a hemorrhage smaller than 10 millimeter and can be seen in the microvascular or axonal injury. So the cause can be both vascular or because of diffused axonal injury. As you can see in the diagram both diffused axonal injury and cerebral microhemorrhage are more common in patients with moderate to severe TBI. Next slide.

Regarding the physiology of cerebral microhemorrhages. In this recent study from Brain the source of the traumatic microhemorrhages pigments on MRI appear to be iron-laden macrophages in the perivascular space that we see there dysteleology [unintelligible 14:45] expressing. And this is the right here present traumatic injury to the microvasculature along the vascular trees. In this study the pigment of the axonal injury has been histology for the microhemorrhages also that was expected based on the current literature. And their conclusion in this study is that the presence of microhemorrhages may be biomarker for vascular-related interventions after TBI. Next slide.

In the appropriate clinical settings microhemorrhages can be considered a marker for TBI. Indeed we can detect microhemorrhages in traumatic brain injury and this can explain focal neurologic deficit and can correlate with injury severity as can be seen in the diagram on the right. We see microhemorrhage more in the moderate to severe traumatic injuries. Next slide. Next slide.

It has been presented, so positive relationship between location of the microhemorrhage and specific clinical symptoms. This patient had major abnormality and we see that the microhemorrhage involves the region of the left postchiasmatic optic radiation. The results suggesting microhemorrhages in the cerebral peduncle. Next slide.

The same article saw in Brain, it was prospective study with more than 400 participant and we see that the presence of both linear and traumatic in the [unintelligible 16:59] TMB, on the left you see TMB and this is traumatic microbleeds. So the presence was a significant clinical predictor of outcome. They found that those with microhemorrhages were twice as likely to have disability post-injury. Next slide.

Another diagram in mild TBI that shows that the number of microhemorrhages in the frontal, parietal, and temporal lobes is associated with depression. Next slide.

Here the researchers found that the presence of microhemorrhages showed neuropsychological deficits in shortened memory that is measured by digit span. Next slide.

So detection of microhemorrhages we can use both susceptibility-weighted imaging or SWI and also we can use T2 star gradient echo. The hemorrhage can be identified due to the high iron concentration in different blood products. This allows for detection by MRI because of the paramagnetic properties in the iron that help to differentiate the microhemorrhage from the sound in brain [unintelligible 18:37]. SWI is considered much more sensitive than T 2 star. For example here in the right image we see [unintelligible 18:47] microhemorrhage that is clearly better seen compared to the right image. Next slide.

This is the patient three weeks after motor vehicle accident. We can use phase map to differentiate diamagnetic calcification as we see in the choroid plexuses in the left lateral ventricle in the red arrow. Also hemorrhagic paramagnetic microhemorrhage that is marked by the blue arrow. We see that the microhemorrhages have different pigment in the phase map and the calcification of the [unintelligible 19:34]. Next slide.

So another question.

Rob: Yes sir, before I launch that poll I’m going to leave this image up for a moment because you do use imagery here. But the poll question is typical locations of CMH? The corpus callosum, gray-white matter junction, dorsal brainstem, or all the above. And now I launched the poll question and it’s just the questions. And the answers are streaming in slowly. We’ll give people another maybe 10 or 20 seconds to make their choices. Okay and it looks like things have leveled off Dr. Lotan so I’m going to go ahead and close the poll and share out the results. And I see that you can see them so I won’t bother to read the results to you.

Dr. Eyal Lotan: Yes, thank you Rob. So you’re right these are all areas that are most vulnerable to traumatic brain injury. In this brain slide, can you bring back again the\_. Thank you. So we see in the brain slide the small hemorrhages being the corpus callosum marked by the arrow. The left frontal and superior temporal are cervicomedullary junction and also in the basilar aspect of the brain in the middle. Next slide. Next slide.

So this is the case of a 25-year-old patient six months after motor vehicle accident. We can see multiple microhemorrhages in the cranium of the corpus callosum and in the gray-white matter junction, in the occipital lobes. Look how it can be easily seen in the SWI image but not in the conventional FLAIR or T2 images. These are typical location of traumatic microhemorrhages. Next slide.

And we can see in a different patient, the other one, no. Can you go back please, another, no back? Back. You’re going\_

Whitney: Sorry I don’t know what’s going on with the slides.

Dr. Eyal Lotan: Yes.

Whitney: All right.

Dr. Eyal Lotan: No, another one back.

Whitney: Okay, sorry about that. Are we going back one more, is this\_

Dr. Eyal Lotan: Yes. One more.

Whitney: Okay.

Dr. Eyal Lotan: One more. Okay. So we can see here the dorsal brainstem location that sometimes we see more severe cases. Okay, next slide.

Just to show that the microhemorrhages are presently present in the frontal and temporal lobe and less in the corpus callosum and posterior fossa the FP. And the posterior fossa close to brainstem. Pay attention that SWI is much more sensitive than the T 2 star. Next slide.

Here we see in A, a microhemorrhage detected at the left posterior subcortical white matter in a patient after trauma as opposed to a volunteer in B where we see microhemorrhages in the left putamen. This is the typical center location for spontaneously hypertensive microhemorrhage. Both these example to show that the clinical correlation is important because sometimes microhemorrhages have overlapping patterns like there are other causes of microhemorrhages such as the hemorrhagic [unintelligible 24:35], amyloid angiopathy, cavernous malformations, [unintelligible 24:40] and hemorrhagic [unintelligible 24:44]. Next slide.

Just because we are all in this pandemic here is a recent example of microhemorrhage in a critically ill ventilated COVID-19 patient. We see that he has the right side of the paracentral [unintelligible 25:11] hematoma as well as microhemorrhages and vestibular diffusion bilateral white matter presumably because he had hypoxic encephalopathic which is hemorrhagic and also ischemic [unintelligible 25:31] seen by the diffusion. Next slide.

Please skip please.

Can you skip. Okay. Thank you. So in a recent AJNR study we summarized the recent literature regarding prevalence of microhemorrhage and relationship to mechanism of injury. The mix, the different cohort military or civilian and the time since injury. Two things are clear from the table. First and most studies were performed in the civilian population following blunt-related mild TBI with results in prevalence of microhemorrhage as high as 28%. Probably around 20%. The second thing that we can see from the table is that this particular civilian status were performed in the acute or subacute phase. However we can see that in recent studies in the military members from 2016 that included also blast TBI patients. There were only three to four percent prevalence of microhemorrhage. And, okay there’s also the time since the last TBI in these patients was also [unintelligible 27:11]. Next slide.

And also we used a cohort from NYU Cohen Veterans Center. And we included 146 Veterans who experienced blast-related mild traumatic brain injury. Approximately nine years prior to the including in the study or to the imaging. We excluded patients with blunt-related TBI. Our cohort had approximately 50% two or more blast episodes of explosion. Next slide.

However our results showed no cerebral hemorrhage. So in our cohort no subjects had cerebral hemorrhage. Maybe that’s opposed to more prevalent to microhemorrhages that resulted following blunt-related mild traumatic brain injury in the civilian population. Next slide.

Possible explanations. The blast mechanism of the mild TBI that supports the volume idea that blast-related mild TBI has not only a unique mechanism of injury but also a unique pathophysiologic that may distinct from blunt-related TBI. The second possible explanation is that the time intervals from their last injury to the MRI imaging. In our cohort went from one to 51 years which means a median of nine years. Next slide.

So what we’ve just mentioned, also the recent study that included the military cohort were done in the chronic stage. Next slide.

So 2003 there was a report on 20% reduced detection of microhemorrhages after two years. You can see that the hemosiderin [unintelligible 29:49] seen in the right cranium of the corpus callosum in the bilateral frontal lobes were almost undetectable after two years. Next slide.

Here we can see that the evolution of microhemorrhages of SWI in patient who underwent full up imaging in [unintelligible 30:14] intervals. It is clear that the microhemorrhages decreases in size and becomes less conspicuous over time. When patients who have classified into four groups of the basis of time since injury as we see in the table. The detection rate of the microhemorrhages in patients who underwent imaging more than one year after injury was much lower than in those who underwent imaging in aerial stage 5.2% compared to 24%. This was a mixed cohort. Next slide.

This study they also showed it, this fact 20-page release demonstrating the reduced volume and decreased total number of the microhemorrhages over time for all patients. Next slide.

In a very recent study the authors evaluated the progression of microhemorrhages for up to five years following blunt-related traumatic brain injury. They have not a lot, they didn’t have a lot of participant but they showed that in 15 out of 18 percent patient and there was persistent low signal related to the microhemorrhage over five years timespan. And there was, they did see a reduction in the overall volume as can be seen in these image. But they didn’t do a quantification of the results. Next slide.

So to conclude what I just briefly showed to you it seems that the microhemorrhages are most common, more common in patients with TBI at the acute stage due to the blunt mechanism. And it is likely that the blast product in the brain becomes less distinct over time due to a complex [unintelligible 32:58] process. And the ability to use imaging to monitor the evolution of these microhemorrhages could provide important information regarding disease progression or recovery with implication to patient care. And thank you very much for inviting me.

Rob: Thank you Dr. Lotan. Dr. DePalma do you have comments or questions at this time or would you prefer that I ask the questions [unintelligible 33:33]\_

Dr. Ralph DePalma: No, I think, you know I’d like to say that we really appreciate this presentation from New York University and specifically radiology and artificial intelligence. I think there’s 127 participants and I’m sure looking at all the technical pictures they have questions.

Rob: Yes, sir.

Dr. Ralph DePalma: But the results of the study seem to be quite dramatic. So go ahead with your questions please and we’ll give Lotan plenty of chance to answer.

Rob: Thank you, sir. With these changes detected on neuroimaging is there evidence of dose response regarding number of injuries?

Dr. Eyal Lotan: So you’re asking about if I understand, if the number of injuries correlates with a clinical outcome? This is what I understand. So I say, I think I mentioned there are several even recent studies that show the correlation with the number of or the dose of the microhemorrhages and the clinical outcome. However there are also [unintelligible 35:08] particles that show no correlation only correlation in a certain lobe and that’s the temporal lobe. So it depends, as we saw in the severe and moderate TBI we see much more rare findings. So probably there is that correlation but and sometimes if the microhemorrhages are in this specific location it can cause the symptoms as I showed in with the visual abnormality example. You have another question.

Rob: Yes sir. This person asks what is the source and timing postinjury of microbleeds? And then they go on to ask venous arterial capillary endothelium disruption leakage.

Dr. Eyal Lotan: So I really like the recent brain study from 2019 that I showed. And I think it’s a very good and convincing study because he had the one patient that fortunately it’s a bit crude, the patient unfortunately died so, but the family agreed to do a postmortem. They accrued the correlate the imaging findings to [unintelligible 36:56] findings. And as I showed they saw that the source of the low [unintelligible 37:09] signals was microvascular injury. They saw microphage in the [unintelligible 37:18] vascular space along with vascular tracks and that the microphage with iron and in their study they didn’t see any evidence of axonal injuries. Prior research was, didn’t do the distinction between the [unintelligible 37:47] axonal injury and cerebral microhemorrhage. The literature was, when you see cerebral microhemorrhage it means that the patient has a diffused axonal injury and this status from brain shows that it’s not only the case it can be both microvascular injury like vascular injury to the vessels on the [unintelligible 38:17]. And also they didn’t see but of course at least the results diffused axonal injury that as I said can be hemorrhagic or non-hemorrhagic. And actually the diffused axonal injury is more common than hemorrhagic diffused axonal injury. And this diffused axonal injury, find them difficult to assess in the acute stage of the traumatic brain injury. If it’s hemorrhagic we can see, sometimes seeing fatigue but usually we don’t do, especially in the military, we don’t do MRI in the acute setting and so sometimes it’s missed. And in the acute setting we can see some diffusion abnormalities with diffusion and this can be attributable to the axonal disruption. But after like in the subacute and chronic stages the diffusion distinction we don’t see it anymore. And all we see sometimes is just [unintelligible 39:38] abnormalities. And this abnormalities of course they have effected a typical location in the splenium or in the cortical region of the brainstem but implication is overlapping with other maturities for where white matter changes such as microvascular systemic changes. And if we don’t have MRI before the injury we sometimes cannot say for sure if it’s an axonal injury or not. So I think I expanded my answer. But I hope I answered.

Rob: Thank you, sir. Next question this person writes while these are interesting research findings and some classic case examples, in general it’s difficult to see the clinical utility to these imaging techniques. What is the take-home message for primary care and specialty care clinicians from these techniques?

Dr. Eyal Lotan: I agree that sometimes these technique they’re not doing in the conventional and the regular work and of course each patient there should be a collective collaboration between clinician and our geologies. And then there are disadvantages of this technique is that many of the status is showed a compassion between a research group and between a healthy control group and a group with mild TBI but the changes was not for [unintelligible 42:04]. So when we [unintelligible 42:09] changes can be visualized in any number of comorbidities there is the demographic evaluation and sometimes we cannot tell accurate as definite answer. As I said sometimes we [unintelligible 42:37] abnormality in a typical location but we cannot say for sure if it’s because diffused axonal injury or not. But we need to consider all relevant clinical information. We can compare different sites, different hemisphere, we can then develop a certain typical range of values in TBI so cortical thickness also sometimes it’s very clear that we have traumatic injuries a typical location for encephalo- [unintelligible 43:26], the frontal and temporal lobes and so and we fix in specific location that is impacted by the patient symptoms. So when imaging is very important to compliment of the management of each patient. But I agree that it’s not 100% definite.

Rob: Thank you, doctor. Do you think your data and information has implications for how we should classify injury severity?

Dr. Eyal Lotan: So I’m not sure if I’m the right person to answer regarding this small, each has limitation of the different [unintelligible 44:35] for traumatic brain injury. And what can be said is that no question blast station has less prevalence to cerebral microhemorrhages. So we should estimate different clinical element there in this patient. Because the fact that we don’t see cerebral microhemorrhages in this patient doesn’t mean anything about the severity of the other injuries. So they can have the different injuries. So I’m not sure this fact of less preventative cerebral microhemorrhage can change the severe, how we measure, how we define the severity of, for TBI.

Dr. Ralph DePalma: Yeah. Thanks Lotan. You know these are tough questions. I, you know I’d like to respond to the person that asked what’s the take-home message for a clinician. So the take-home message was you might see two different patients; one that fell down and hit his head in combat and was temporarily unconscious and another that was exposed to a blast and just had slight confusion. The question that you asked is what should the clinician do and when should they take pictures and if so, what kind of imaging should they use? And the whole point is that answer is not clear. But it comes a little more clearly to say that it is likely that with the blunt injury you’re likely to see microhemorrhages which may relate to severity. May relate to the number of injuries particularly inertial injuries like impact and with a blast where we’ve been shown now that there’s no inertial injury. The head, we’ve been showing that with low-intensity blast the head doesn’t move so the brain doesn’t move and you know you don’t see anything on the standard scanning. You only see it with DTI as he pointed out. So it’s a very difficult issue and it’s something that we’re struggling with you know to what, how to advise our clinicians. And I know that Dave Cifu is looking at it very carefully.

Dr. Eyal Lotan: Thank you, Ralph.

Rob: Thank you.

Dr. Eyal Lotan: I agree with what you’re saying.

Rob: Well thank you for the clarification Dr. DePalma and Dr. Lotan that was the final question that we have at this time. Would you like to make closing comments before I close the webinar?

Dr. Eyal Lotan: Thank you very much. And I think that research is just only, only continuing and we see much more new and exciting research and results. And I hope very much that we can say more individualized things about patients and their progress to precise medicines in this regard, so of traumatic brain injury.

Rob: Thank you very much sir. Dr. DePalma if you have nothing more to say I’ll just go ahead and close the webinar.

Dr. Ralph DePalma: Well I would like to ask Lotan what he plans to do now.

Dr. Eyal Lotan: The plans for what?

Dr. Ralph DePalma: What are you planning to do?

Dr. Eyal Lotan: Oh regarding\_

Dr. Ralph DePalma: Yes, regarding MTBI.

Dr. Eyal Lotan: So clinically we are, I don’t have any plans in this regard to continue with blast [unintelligible 49:42]. But we’ll continue to collect the information from the Cohen Center in NYU and then, and probably we will continue to do the research but I don’t have now specific projects.

Dr. Ralph DePalma: Thank you very much.

Rob: Well Dr. Lotan thank you\_

Dr. Eyal Lotan: [unintelligible 50:15]

Rob: \_for preparing and presenting today, I’m sorry to interrupt go ahead sir.

Dr. Eyal Lotan: No I’m just saying thanks, thank you.

Rob: Great. Attendees when I close the webinar momentarily you’ll be presented with a short survey. Please do take a few moments to provide answers to those questions. We count on your answers to continue to provide you high-quality Cyberseminars such as this one. And with that I’ll just wish everyone a good day. Thanks everyone.

[ END OF AUDIO ]