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Battling Gulf War Illness: A Look at Treatments & Research Efforts

Dr. Lisk:

Gulf War Illness is a chronic condition characterized by physiological and psychological symptoms, including cognitive dysfunction, memory problems, and depression. But what is currently known about this debilitating condition that affects nearly 30% of Gulf War veterans? Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Jerome Lisk, and joining me to help shed some light on Gulf War Illness is Dr. Ashok Shetty, who is a Professor in the Department of Molecular and Cellular Medicine, as well as Associate Director for the Institute of Regenerative Medicine at Texas A&M University College of Medicine. Dr. Shetty, welcome to the program.

Dr. Shetty:

Oh, thank you very much. It's my pleasure.

Dr. Lisk:

So, let's just dive right in, Dr. Shetty. As we know, the Gulf War took place over 30 years ago. So why are the cognitive problems associated with Gulf War Illness still prevalent in veterans today?

Dr. Shetty:

To answer this question, I need to give you some background about the potential causes of Gulf War Illness. So initially, when veterans displayed symptoms after the war, it was thought to be all because of war-related stress. But later on, epidemiological studies have suggested that the illness is because of exposure to multiple chemicals during the war. And this includes insecticides, pesticides, and also the nerve gas, prophylactic drug, pyridostigmine bromide. So, during the war, the service personnel took pyridostigmine bromide against the possible nerve gas attack. But pyridostigmine bromide is approved for treating myasthenia gravis, for example. So, it does not enter the brain because of the blood-brain barrier, but in the presence of significant exposure to other chemicals, such as pesticides or even the war-related stress, PB can enter the brain because of the leaky blood-brain barrier. So once it enters the brain, it can mediate adverse effects, particularly hyperactivity of neurons sensitive to acetylcholinesterase inhibitor. It can increase the concentration of a particular neural class which is called acetylcholine. And that can activate neurons, so neurons can fire like crazy with really high levels of acetylcholine. So, the next effect of multiple chemical exposures is the hyperactivation of neurons in the brain, which can increase oxidative stress. So oxidative stress is basically accumulation of harmful reactive oxygen species, also called free radicals. So, when you have very high levels of reactive oxygen species, it can trigger acute inflammation. So now acute inflammation after injury or infection is good for removing dead cell debris or invading pathogens.

So, cells that mediate acute inflammation in the brain are called microglia. So, these cells are basically the resident immune cells in the brain. However, the problem is, when the trigger for acute inflammation is sustained in the case of Gulf War Illness, it happened because of continuous chemical exposure for a certain period of time – the microglia become chronically activated, so when that happens, they never go back to the resting state. So activated microglia continuously secrete the harmful chemicals called cytokines – these are the pro-inflammatory cytokines – so they can maintain sequence-like behavior. So that is what is likely happening in Gulf War Illness. So, animal studies have shown that exposure to Gulf War Illness-related chemicals leads to persistent chronic inflammation in the brain. So, the persistent inflammation in the brain appears to be the main reason for never-ending cognitive problems in veterans with Gulf War Illness.

Dr. Lisk:

Do you know why this affects some veterans over other veterans from the Gulf War?

Dr. Shetty:

This is another issue that I've been debated a lot, and I think it is mainly because of the variability in exposure to different chemicals that

cause Gulf War Illness. For example, service personnel stationed in battlefield areas, they were reported to being exposed heavily to many pesticides and insecticides, in addition to the drug pyridostigmine bromide, but those stationed away from battlefield areas had regularly less exposure to pesticides and other chemicals. So then, a subgroup of veterans most likely exposed to low level neural gas that was released into the atmosphere after the demolition of some buildings during the war. So overall, it appears that the extent and the type of chemical exposure played a role in developing Gulf War Illness with distinct symptoms. So, it's quite severe in some veterans, not so severe in some veterans.

Dr. Lisk:

For those just tuning in, you're listening in to *NeuroFrontiers*, on ReachMD. I'm Dr. Jerome Lisk, and I'm speaking with Dr. Ashok Shetty, about Gulf War Illness in veterans. So, Dr. Shetty, based on everything you discussed earlier regarding the underlining mechanisms, how do we currently approach treating Gulf War Illness in veterans today?

Dr. Shetty:

In animal models of Gulf War Illness we and others have tested several antioxidant and anti-inflammatory compounds. And many of these studies have shown the ability of these compounds to reduce both neural inflammation and cognitive problems in Gulf War Illness.

So some of these compounds are actually natural dietary supplements, such as resveratrol, which is an extract of red grapes, and curcumin which is an Indian spice. Both resveratrol and curcumin, they are being tested in veterans with Gulf War Illness in clinical trials. Our recent study had also shown that even moderate exercise can reduce neural inflammation in the brain and improve cognitive function in animals with chronic Gulf War Illness. So, a simple lifestyle change, like exercise, can improve cognitive function in veterans with Gulf War Illness. However, the severe exercise may not be suitable for veterans with Gulf War Illness because some veterans with Gulf War Illness also have chronic pain. But in those who do not have chronic pain, simple exercise can modulate those activated microglia and improve cognitive function.

Dr. Lisk:

Okay, and are there any promising therapies for Gulf War Illness on the horizon?

Dr. Shetty:

So far, cognitive behavioral therapy has shown some benefits. The resveratrol, curcumin, and other drug trials, they are still ongoing, so the results are yet to be published. But based on the results in animal model studies, beneficial effects are expected with dietary supplements such as resveratrol and curcumin.

Dr. Lisk:

Are there any preventative therapies moving forward, in such situations for veterans that are exposed?

Dr. Shetty:

Yeah, I think the one important thing is to minimize exposure to pesticides and insecticides because during Gulf War, it was heavily used. Chronic exposure to pesticides and insecticides are very harmful, particularly for brain function. So that's one thing one can take care of using some other methods to compounds like DEET, some other compounds which can repel insects could be used. In terms of drugs, I would think that dietary supplements like resveratrol and curcumin will be beneficial, because they have antioxidant and anti-inflammatory effects. So, during day-to-day exposure to the compounds that cause inflammation, you can prevent it by taking such dietary supplements.

Dr. Lisk:

Now we're almost out of time for today, Dr. Shetty, but before we close, can you share with us what's next for your research focusing on Gulf War Illness?

Dr. Shetty:

Sure. We recently found that a drug used for treating asthma called montelukast reduced neural inflammation and improved cognitive function in a model of Gulf War Illness. Again, this is an animal study, but based on these cyclical results, my research group, and the research group headed by Dr. Drew Helmer at the Baylor College of Medicine, Houston submitted the collaborated clinical trial planned proposal to the Department of Defense. So, this proposal is now approved for funding, and Dr. Helmer will be recruiting veterans for this clinical trial, and my lab will be studying changes in neural inflammation. So, this is our next project, actually.

Dr. Lisk:

Well, all this has been very interesting, and I for one hope to speak to you again once those results are available. And that brings us to the end of our program today. I want to thank my guest, Dr. Ashok Shetty, for joining me today. Dr. Shetty, it was great having you on the program.

Dr. Shetty:

Thank you very much, it's my pleasure.

Dr. Lisk:

I'm Dr. Jerome Lisk. To access this and other episodes in our series, visit ReachMD.com/NeuroFrontiers, where you can Be Part of the Knowledge. Thanks for listening.