Kessler Foundation Podcast Transcript: Cancer Related Fatigue. Part 5 of 5 – A Research Perspective

Recorded September 2019. Listen to it here.

DIDIER ALLEXANDRE: 00:05	[music] You know, these large studies have shown that cancer-related fatigue reduced during treatment by as much as 80% of the population.
ANNOUNCER: 00:13	Welcome to the 2019 third annual cancer conference, Beyond Rest: A Rehabilitative Approach to Managing Cancer-Related Fatigue, sponsored by Kessler Institute for Rehabilitation, and Kessler Foundation. Cancer-related fatigue is an issue that often develops during treatment and can last for months or even years. The conference podcasts will focus on the impact, screening, and management of the physical, physiological, emotional, and cognitive sequela. Listeners will gain understanding of the various evidence-based therapeutic interventions and the overall benefits of a multi-professional approach. Topics to be discussed will include current research in practice guidelines as well as the unique role that rehabilitation can play in managing and reducing signs of cancer-related fatigue. This presentation was recorded, produced and edited by Joan Banks-Smith, creative producer for Kessler Foundation on Thursday, August 8, 2019, at the Kessler Institute for Rehabilitation, West Orange campus, New Jersey. Be sure and check out the conference playlist to listen to all of the other session podcasts. The link to the playlist is in the show notes. In this lecture podcast, Didier Allexandre, research scientist at Kessler Foundation, presents Cancer-Related Fatigue: A Research Perspective.
ALLEXANDRE: 01:42	My name is Didier Allexandre. I'm a research scientist at the Kessler Foundation. Our research interests at the Kessler Foundation, which is next door, in cancer-related fatigue is really to try to understand the underlying neuro-muscular mechanism of it. But what I want to try to do today is to try to give you a sort of overview of the state of research. What does research knows and found about cancer-related fatigue? My talk is going to be divided in three different sections. The first one I'm going to be describing what research has found in terms of the prevalence of cancer fatigue as well as the impact that it has on daily activities and quality of life. The second part of my talk will be to describe the mechanism or at least what research has tried to unravel, and trying to understand the mechanism of cancer-related fatigue. And finally what I'll do is cover, as well, treatment. What research has shown as being effective, in which condition, and which one seems to be most effective in general? And I will, as well, quickly review the possible mechanism of action of those intervention.
ALLEXANDRE: 03:23	So prevalence and impact. Early in the research, there's been some small studies that have been done, but in the past 10 years there's a few nice studies that have been large studies that are [locked?]. But before we will look at the prevalence and the impact I think it's critical to better understand how to define cancer-related fatigue, and I'm sure this has been covered before, but the incident guidelines defines CRF as a distressing, persistent, subjective sense of physical, emotional, or cognitive tiredness, or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Why I'm bringing that out? Because in order to understand fatigue it's really important to understand

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how to define it. It's not an easy symptom to understand because it's usually subjective and everyone has different ways to describe it. Even the same type of symptom could be described in different ways. So first, it should be distressingly persistent, which is important. Second, we realize that fatigue can have different dimension, can be physical, emotional, or cognitive. And it can be manifested in different way as being tired, even without doing any kind of activities, or when you're doing activities, you feel more tired and exhausted in doing so. And it has to be related to cancer and cancer treatment, and we will cover a little bit about comorbidity that could be associated with that. And, as it says, it should be-- let me see if I can find a pointer here. Okay. So the fatigue should be not proportion to recent activity, which means that it's not by doing heavy exercise that you would normally get fatigue. In this case, people with cancer-related fatigue would have more fatigue and would be more exhausted.

ALLEXANDRE: 05:43 So in terms of prevalence, these large studies has shown that cancer-related fatigue is experienced during treatment by as much as 80% of the population, and that is fatigue in general. And that is one of the most prevalent symptom compared to all the other symptoms that is felt during treatment. Another study I kind of looked at cancer-related fatigue in a large sample again which combined different type of cancer, breast, lung, post [inaudible] and colorectal cancer, and found that 45% of the population felt moderate to severe fatigue before treatment, but, as well, after. Even after complete remission up to 30% still experienced fatigue. This study has kind of tried, looked at using a meta-analysis. So they basically look at all the studies that have looked prevalence and finding out what kind of factors in terms of type of cancer stage or treatment is more related, or is more associated with fatigue. And in this case, they found out you have about 23% of the population that have-- this is considered severe, by the way. So severe fatigue, experienced severe fatigue. And the risk is higher for stage two and three compared to zero and one. It's higher as well for those who has chemo versus no chemo. And it's, as well, higher for those that have combined treatments. So when you have surgery, chemo, or radio versus-- and even more you have an increased risk of fatigue when you have all four type of treatment combined.

ALLEXANDRE: 07:55 Now in terms of interference in daily activities there is several studies that I've looked into about this. This is one of the largest and recent studies which show a direct correlation between the level of fatigue from, you see here, mild to severe with all kind of impact on quality of life in relation, mood, enjoyment, walking, general activity, and work. So it definitely affect every aspect of life. So in summary, cancer-related fatigue is perversive, affecting all cancer type. It's present before, during, as well after treatment, and in cancer-free patients. It's most present in those doing chemo than not and receiving multi-treatment. And is present in those, we think, chemo and radio-free and combination, but also with hormonal therapies. So I'm highlighting this because there was a earlier thinking, and I'm going to cover that earlier, but fatigue was mainly related to toxicity of the treatment. Mainly chemotherapy and radiotherapy, but it's seen as well in hormonal therapy, and it does serious impact on physical, psychological, mental, and social dimension of quality of life.

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ALLEXANDRE: 09:28

So what are the mechanisms? What leads to the development of cancer-related fatigue? It's complex as you can see. And don't be scared. I know it's kind of late, and you might be a little fatigued yourself, and you think, "Oh, my gosh, what did I sign up for?" And usually, when you ask a scientist to come in they make things very complicated, but no worries. What I'll do is I'm going to walk through the main mechanism that is believed to lead to cancer-related fatigue. So early on researchers, as I mentioned, thought that cancer-related fatigue was mainly due to the toxicity due to treatment, mainly chemotherapy, and radiation. In essence, treatment is really harsh on the cell, not just the cancer cell, and this lead to DNA damage. [We took?] a mitochondria damage as well which affect cellular function and leads to muscle function alteration, but, as well, centrally in the brain, neuro-degeneration. It affects the nervous system as well so we see, as well, peripheral neuropathy in some patients, especially with agent, chemo agent like [Taxane?], [Taxol-based?] chemo agent. And all of this is believed to lead to fatigue.

ALLEXANDRE: 11:14

However, as I mentioned before, cancer-related fatigue is not just present in radiotherapy or chemotherapy, but it's present as well with people on hormonal therapy. But more importantly, it is seen that even before treatment people experience fatigue. So this led to [think?] that this couldn't explain the whole origin of cancer-related fatigue. That there should be something else. And now the primary mechanism that people believe is responsible for cancer disease is inflammation. And that is it's sort of a direct biological pathway. And how that works is that the cancer, or the cancer treatment, leads to cell damage or inflammation, and the inflammation releases cytokines such as [TNLF?], TNF Alpha, Il-6 CRP which has basically signal protein, signal protein that communicate with the rest of the body. And the cytokines triggers a series of cellular changes throughout the body. One is that it reached the brain and leads to neurotoxicity. It basically create neuro-inflammation at the brain level. [The internal?] neurotoxicity. It, as well, affect the central nervous system function, especially the dopamine which is highly related to fatigue. And that's kind of a sort of pathway for central origin of fatigue. What it does as well is inflammation and cytokines can as well trigger dis-regulation of the HPA axis. The hypothalamic-pituitary axis are related to Cortisol which further increase inflammation, which further would lead to affect at the brain level as well the autonomy peripheral nervous system. You know, change in the autonomy nervous system the same way which leads to increased inflammation, and again, effect on the brain. And it can lead, as well, to mitochondrial damage which would be related to the dysfunction in energy function of a cell. And that directly leads to muscle function impairment. So that would be more sort of a peripheral pathway by which we would have fatigue where the muscle don't activate, or they're not recruited as well as before.

ALLEXANDRE: 14:37

Now this is what I would call the direct pathway, but there is, as well, an indirect pathway. And direct pathway would be that the cancer treatment, the disease or the treatment itself, can lead to sort of a change in behavior of psycho-social changes, and obviously, such a disease can lead to stress, depression, and that by itself and impaired sleep-- the treatment has great impact on sleep impairment. And all of that leads to change, and change in the HP axis, dis-regulation, and inflammation. It has, as well, a sort of a pathway to affect the brain that way too, or peripherally. Sorry. And

those factors have all been shown to correlate with the severity of fatigue. So it's an important aspect to remember.

ALLEXANDRE: 15:49 The other pathway would be that due to cancer or the treatment, people would not be active as much so we would have a sort of de-conditioning. And the lack of activity can have a similar effect. It would lower the resistance and it would [persuade?] an increase in inflammation, and, again, a neurotoxic effect on the brain. Similarly, cancer and cancer treatment can lead to muscle loss known as [cachexia?] due to the ability to eat in some ways, or to biological changes [or cures?] that can precipitate muscle loss.

ALLEXANDRE: 16:45 Now one interesting aspect that I wanted to emphasize is that this whole inflammation and neuro-inflammation at the brain level and the cytokines' effect is known, and this is shown in animal as well as human, that cytokine release, or administer of cytokines, you automatically see it change what would be called sickness behavior. And the sickness behavior is basically a clustered symptoms that has very similar signature as the one we see in cancer-related fatigue or in cancer in general cancer patient. And that include stress, depression, impaired sleep, and cognitive disfunction as well as fatigue. So as you know, people have a cluster of symptoms, and they are always very correlated when people see cancer-related fatigue. Sometime, in most cases, we see, as well, cognitive dysfunction. We see impaired sleep, sometime depression, and it [feel as?] cluster, and that could be explained by this neuro-inflammation and neurotoxicity as a common factor related to release of cytokines.

ALLEXANDRE: 18:19 So this is an example of evidence that they show that the total fatigue score we studied has been done in breast cancer survivors-- that the total fatigue score is directly related to inflammation [Leukocyte?], so that the more fatigue the more [Leukocyte?] you have as well as a particular cytokine, CRP in this case. And the greater the amount of CRP, the more fatigue. So this is kind of sort of a support for neuro-inflammation as one source of cancer-related fatigue.

ALLEXANDRE: 19:02 This is another example of a study, but I looked at Cortisol. And they show that technically Cortisol decrease during the day. It's high in the morning and decrease during the day, and for cancer patient they found out that it doesn't decrease as much. And we know that an increase in Cortisol is pretty much similar symptom that we see when we see effect of anxiety, and increased Cortisol is basically considered to be a HPA dis-regulation that trigger an inflammation response that would lead to, in this case, cancer-related fatigue.

ALLEXANDRE: 19:50 So okay. So now one thing that we were interesting in our lab is to better understand the relative contribution of central brain level. The source of fatigue at the brain level versus peripheral at the muscle level. So in our lab, with my mentor, Dr [Yue?], we have done several study, and in this particular case we have done a study in 16 cancer patient referred to palliative medicine. The stage three, stage four, so these are really advanced cancer patient, and we recruit, as well, [age-match?] control. And we asked them to perform effective task. So basically what we do is we measure their maximum force and we tell them, "Okay, we want you to hold that 30% of that maximum, and we provide a visual feedback for that. And we want you to sustain as

long as you can until you can no more sustain that." And when we see that they're no longer, even with verbal encouragement, they were no longer able to sustain that force, then we considered that they-- we considered task failure where they get fully fatigued. So when they are at 30%-- so in this case what we do, this population, as you can see in black here, this is a brief fatigue inventory has a higher score overall which is about moderate to severe fatigue compared to healthy control which is mild or non-existent fatigue.

ALLEXANDRE: 21:34

And it's a mixed diagnosis by the way. They have different type of cancer. Lung, thyroid, ovarian, all kind of different cancer. And when we measure, we measure brain activity, force, and muscle activity. So typically what happen is-- as you can see this is the force. They're trying to maintain the force, and then they no longer can and they just drop. And this is the duration. How long they are able to sustain. So as you can see, they are able to sustain, for healthy, about six minutes, where for cancer patient they are not able to sustain more than three minutes or five minutes. Actually, it's five minutes versus about nine minutes. So they are not able to sustain, and they fatigue faster. Now in order for us to find out whether it's peripheral versus central, what we do is we stimulate the nerve that enervate the muscle that is activated. So if we're able, if the muscle is not fatigued, if we trigger we should be able to generate an additional force. Does it make sense? So you hold the force. If you ask them to increase the force more they should be able. If they're fatigued they're not able to increase the force. So what we do is we basically stimulate the nerve and see how much reserve they still have in the muscle. And the more the force, we called twitch force, we have, the more the reserve there is. If there's no more reserve the twitch force is zero. We're not able to produce any more force out of the muscle during the task.

ALLEXANDRE: 23:18

So in this case, as you can see, as it gets fatigued the additional force that can be generated decrease over time because the muscle gets more fatigued. And the same way for the control in the circle here. But what you see is that at time of task failure that in the control the muscle is much more fatigued than it is in the cancer patient. Mean that we are able to generate, at the time when they say, "I can no longer do this, that's it. I can't do this anymore," the activity, the muscle force is much stronger. Means that they have much more reserve in their muscle than in control. So this would suggest that their inability to sustain the task is mainly due to central origin. Meaning that they get more fatigue at the brain level, and it tells them, "I can't do it anymore," rather than at the muscle level.

ALLEXANDRE: 24:29

What we can do as well to look at muscle fatigue, you look at EMG. So when the muscle is no longer able to maintain the force, so it starts failing. What the brain is trying to do is trying to excite more of the muscle to try to generate more force. And so you have a increase in the electrical activities in the muscle, and what we find out is that for the control we're able to increase that muscle activity more than in cancer patient which means that you have the muscle is definitely more fatigued. Similarly, we look at brain activity. So during the task-- so we measure brain activity during the whole task, and why we see so different-- we use electrical encephalogram, and what we're able to measure, and this is mainly in the two area that control the muscle, the motor area. And cell works at different frequency, and the beta band is basically a

frequency which kind of tells you the ability for the brain to improve excitability. So in a sense what happened is that the brain-- when you don't do any movement the brain has tendency to have a [inaudible] [inhibition?] and when we see that we see high beta. As soon as you want to do a movement you have to decrease that inhibition, so beta decrease and you're able to do the movement. So in this case what we see is that cancer [inaudible] patient, patient with fatigue, are not able to decrease their beta as much as control. So there is a brain abnormality in terms of activity here. And we find that this inability to decrease beta is directly related to the twitch force which means that the less they're able to decrease their activity to promote movement the less peripheral fatigue there is. So in a sense the source of fatigue is mainly at the brain level.

ALLEXANDRE: 26:54 Similarly, we looked at a different band which has different function. We find out that they have abnormal activity at baseline, and they are not able to recover. So the red line, you see this is what it is at baseline is much higher, and at the end of the task they are not able to get back to their normal values at baseline. Where, in control, in blue, they are able to get back to their base line value. So this lack of recovery, this would be a sort of a lack of brain activity recovery, [so I know?] that it's directly related and correlated with the level of fatigue score.

ALLEXANDRE: 27:33 So all of this is to say that the measure of central fatigue is supported by abnormality that we see at the brain level. One other way to look at this is to look at what we call brain to muscle coupling. The more the brain and the muscle are coupled, the more they are able to generate a force. And we found out that in cancer fatigue the brain and muscle are less coupled especially either before and after, which means that the brain is not able to drive the muscle as well. It's not as efficient to drive the muscle and drive force compared to control.

ALLEXANDRE: 28:25 So in summary, we found that cancer patients are fatigued earlier, and the early fatigue has a central brain, rather than a peripheral origin. And this seems to be caused by the inability to increase motor output as by the brain as muscle fatigue. So now this was done in, as you see, in a particular population, so we don't really know how much this generalized to other population in breast cancer. For example, with lower stage. So this we need to kind of be explored in other population. Yes?

ALLEXANDRE: 29:05 Yes. I'm going to skip a few slides. So the other thing I wanted to point out is that neuro-inflammation doesn't come on its own. As you know, there are patients that gets fatigued from the beginning, even before treatment, all the way through treatment, and after. And some don't even experience any fatigue at all. And so there is really huge variability in respond to the treatment or the cancer. And researchers are recently suggesting that there is a host of risk factors, or that would explain that difference between patients. So, for example, there is some behavioral risk factors. If people before they even start cancer and they start the treatment have childhood adversity, depression history, [inaudible] anxiety, or catastrophizing tendency, which means the tendency of having a negative attitude toward their treatment or the outcome, or a sleep disturbance, they would have a higher correlation of fatigue which means that this would be a higher risk factor for developing this chain of event that will lead to cancer-related fatigue. Similarly, people that are inactive, obese, have

a tendency to as well have a higher risk of developing fatigue. So in that sense, this is another risk factor. The other risk factor is biological, which is more genetic, and they found out that people that have, due to cellular aging, [inaudible] comorbidity, or what we call a small genetic variation in cytokine, will have a higher tendency to trigger that inflammation response and fatigue. So without getting too much into the detail, this shows that the more you have this genetic variation, the higher the severity and fatigue.

ALLEXANDRE: 31:34 So in summary, the specific mechanism [inaudible] remains poorly understood. It's basically mainly based on association. It most likely involve multiple systemic [inaudible] peripheral [inaudible] cytokine, HPA dis-regulations, [skeletal?] muscle wasting. The inflammation is believed to be one major and important pathway that leads to cancer-related fatigue. And the wide variety in cancer affecting symptom experienced by cancer patient may be due to individual variation in the risk, or predisposition.

ANNOUNCER: 32:08 [music] For more information about Kessler Foundation go to kesslerfoundation.org. Follow us on Facebook, Twitter, and Instagram. Listen to us on Apple podcasts, Spotify, SoundCloud, or wherever you get your podcasts.