Einat Engel-Haber, MD, Discusses Evolving Definitions and Challenges of Central Cord Syndrome
Northern New Jersey Spinal Cord Injury System Lecture Series

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Welcome to our Northern New Jersey Spinal Cord Injury Model Systems Lecture Series. In this podcast, Dr. Einat Haber, Associate Research Scientist in our Tim and Caroline Reynolds Center for Spinal Stimulation at Kessler Foundation, presents Defining and Decoding Central Cord Syndrome.

EINAT ENGEL-HABER, MD: 00:21

This is my current title. This work was done as part of my fellowship at the Spinal Cord Injury Research Center, and it was with Dr. Stephen Kirschblum, Dr. Snyder, and Buddy Chell. I was actually thinking of a different title for this talk, Everything You Always Wanted or Did Not Want to Know About Central Cord Syndrome, but were too afraid to ask because I think after this talk, you'll understand why I call it this way. Exactly three years ago, Dr. Kirshman, which couldn't be here today, presented me with a challenge of coming up with a more accurate definition for central cord syndrome, more accurate than the ones we have today. And this took us on a journey, which I will tell you about today. And as often in the stories, the actual journey became more intriguing than the end result, which is also very interesting. But I will tell you about our journey. And I will show you today what we learned, what we still need to learn, and why all of this is important. The plan for today would be, first, we will show the rationale for this work. Two, I will talk about the existing literature, the existing definitions. Three, will be a discussion of the new definitions, what we are proposing to do. And four would be the summary. Central Chord Syndrome, abbreviated CCS,, was originally defined by Schneider in 1954. There is disproportionately more motor impairment of the upper than of the lower extremities, bladder dysfunction, usually urinary retention, and varying degrees of sensory loss below the level of the lesion. This definition is somewhat vague. What is disproportionate? definition is somewhat vague. What is disproportionate? In the literature, a large spectrum of injuries is collectively called CCS, from patients with mild weakness in their hands to patients with complete atroplegia. In the clinic, it's usually pretty straightforward for us to say, you know, to tell who has central cord syndrome. But that's not really the case in research, and this is what we will see today. There is variability in the criteria used, which leads to huge variation in the numbers reported, and it makes prognostication almost impossible. There are some studies that exclude all individuals with central cord syndrome because of the presumable favorable recovery, with central cord syndrome because of the presumable favorable recovery, and other studies include cases which we might not actually consider as CCS. What makes this syndrome particularly interesting and important? I will go over these in more depth, but in a nutshell. So it is the most common and the most controversial of the spinal cord injury incomplete syndromes. Now, with the changing demographics in recent decades, it is becoming even more and more common. But the numbers reported exhibit such a substantial variability. For example, there is a study showing a frequency of 6% and just another study showing 32%. Also, our understanding of the

pathophysiology has also changed in recent decades. Actually, even the name of the syndrome, central cord, is not really correct. But finally, and this is important for also the clinical audience, it's not only about research, it's not only about numbers, about mechanisms, there are also major clinical implications. For example, there is a big debate on the timing of surgery, early versus late, or even if there should be a surgery. Demographics of acute traumatic spinal cord injury are changing in recent decades. The age is increasing. 50 years ago, average age was about 28, and today it's 43. The etiology is changing with falls now becoming more common. It was 21% in the year 2000 and 32% today. And also, there is much more incomplete tetraplegia nowadays. Now, it went from 30% 20 years ago to 47% now. So nearly half of injuries are incomplete tetraplegia nowadays. Now, it went from 30% 20 years ago to 47% now. So, nearly half of injuries are incomplete tetraplegia. Now, all of this goes hand in hand with the increase in CCS, in central cord syndrome, because CCS is a syndrome of incomplete tetraplegia, typically occurring in individuals, in older individuals, and it's usually due to falls. So these numbers really correlate with that. And these numbers and these figures come from the National Spinal Cord Injury Statistical Center. When we first started, we were actually quite amazed to see the huge variability in the numbers reported for this syndrome. And there are several reasons for that. One of them is just the changing demographics that we discussed a minute ago, but it actually plays a relative small role in that. The main reason for this incredible variability is that there is no consistent definition, no consistent quantifiable definition for central cord syndrome. And one of our first steps in this journey was a paper that we published last year, and we reviewed the existing literature. Originally, we only planned to focus on central cord syndrome, but actually it made more sense to discuss all of the major incomplete syndromes because they are often reported together and they sometimes overlap. So we also included Brown-Saquard syndrome and anterior cord syndrome in this review, starting with central cord syndrome. Now, we are looking at the entire traumatic SCI population, so it means complete, incomplete injuries, tetra, and paraplegia. We see a range of between 6% to 32% incidence. But actually, the most quoted number is this 9% by

ENGEL-HABER: 06:06 most quoted number is this 9% by McKinley, a study from 2007. But if you look at the inclusion criteria for central cord in that study, you would see a lesion characterized by sacral sensory sparing and greater weakness in the upper limbs than in the lower limbs. But again, upper extremity weakness can be very mild or very significant. We don't know which cases were included here. Also in that study, they included an individual with AIS-B as having CCS. And that actually can't be so arguable.

ENGEL-HABER: 06:43

Now, additionally, there are these three recent studies, including our own study, the one at the bottom, on the bottom, and these were using a specific measurable criteria, which we will discuss soon, but just note these three. In that paper, we also reviewed the numbers for Brown-Seguard and anterior cord syndrome, reviewed the numbers for Brown-Sequard and anterior cord syndrome. And these syndromes are not as common, and therefore, there are also fewer studies for them. And again, when it comes to the clinic, usually those that have marked syndromes are easy to recognize. But in research, we need a consistent criteria, which was at all unavailable for ACS and Brown-Sequard. And therefore, in our study, which also we had the largest sample compared to previous studies, we provided quantifiable definitions for both Brown-Sequard and anterior cord syndrome. But since this is not the focus of this presentation, I'm not going to discuss that, but you can view it in our study of incomplete syndromes and along with some examples. So this was a table of incidents within the entire cohort sample of traumatic SCI. But actually, there are studies that measure the frequency only within incomplete tetraplegia. And here, the variability is even higher. It ranges, the reported incidence for CCS ranges from 18% of incomplete tetraplegia to 70%. And you can say that the 70% is a study from 50 years ago, but actually it is still often quoted. So huge variability here. And as for the other syndromes, I also wanted to point out another interesting observation, anterior cord syndrome, which has weakness and impaired pain and temperature sensation and sparing of light touch and proprioception. This syndrome is considered relative rare in the Asia booklet. But if you look here, it has been described in up to 60% of incomplete

ENGEL-HABER: 08:45

tetraplasia. So you pretty much see my point here, and it really is a jungle out there. We will try to be Katy Perry. Going back to central cord syndrome, this is an old drawing from Netter, which is pretty much the Bible of medical illustrations. And much of our understanding has since changed. And yes, it's often a hyperextension injury due to falls in the older individuals as depicted here in the picture, but also it can occur in younger individuals due to a high-velocity typical flexion injury. Our understanding of the pathophysiology has completely changed. We no longer think, we no longer believe it's a somatotopic organization of the corticospinal tract. And also, we no longer think it's a central hemorrhage. So, with a little more detail about the pathophysiology, originally described by Schneider as a hemorrhage in the central aspect of the cord, affecting the medially placed fibers of the corticospinal tract. Now, this motor tract was thought to have a somatotopic organization, that is, the more medial parts of the tract were supposed to control the upper extremity, and the more lateral, the farther parts, were mainly for lower extremity, and the more lateral, the farther parts were mainly for lower extremity. And therefore, when you have a central lesion, it affected mainly the medial part of the tract, and that's why it was believed to cause hand weakness. But we actually no longer believe that, as today it is recognized as an injury to the lateral columns and the corticospinal tract

rather than the central cord. So really, if we were to rename this syndrome today, we wouldn't call it central cord syndrome. I mean, the name stuck, and we will use that, but it really is not central cord. Also, the corticospinal tract is not somatotopically organized. You can see here in this drawing, it's a mix, but it is especially critical for hand function, which are the big H, and it's less critical for lower extremities, which go through different tracts. And this is actually also, I also, when I was taught this, I was originally taught and I was, in my exams, everything was about the original description, but the original pathophysiology, but really the knowledge has now changed. So there's an update. As I said, it's not only about research. There are major clinical implications. research, there are major clinical implications. There is a fierce debate on the timing of surgery.

ENGEL-HABER: 11:34 Originally, there was a widely held belief that the natural history of this condition is favorable and operative intervention may lead to poor neurological recovery. So originally, maybe no surgery at all. But then more recent evidence suggested that early operative management of patients with CCS undertaken within 24 hours of injury may be safe and effective at improving long-term neurological and functional outcomes. But then again, just recently, and other evidence shows that it really doesn't matter, and it doesn't matter as much. And early surgery does not result in meaningful neurological improvement. So that's one big debate on central cord syndrome. Okay, so this would lead us to the second part of the talk, but I hope that the previous slides really elucidated the need to discuss central cord syndrome, to define it, to understand what the incidence is. And now let's talk about definitions. There is no universally accepted quantifiable definition for central cord syndrome. There are various interpretations. Therefore, in different studies, use different definitions. And that's why we see such huge variability. So in a second paper, we published a literature review on this subject. This is part of the literature review. So this is the EMSCI criteria was proposed more than a decade ago. EMSCI stands for European Multicenter Study about Spinal Cord Injury. Although there is no universal criteria, this one is the most commonly used today in research. The total motor strength in the lower extremities, LEMS, is greater than the upper extremities, UEMS, by at least 10 points. A large number of studies have used these criteria, and in this review that I already showed you with the frequencies of central cord syndrome, the three studies that are highlighted actually used the Emski criteria. There is still some variability, but not as big. And maybe accounting for that is the time difference. And also, POW, the first study, used a European database. Furusawa used a Japanese registry. And we were using, in our work, we're using the United States Schemes database. Going back to these criteria, it does have several limitations, which we will see in a minute. And also, it may not be the right criteria to use in prognostication of outcomes, as also noted by its authors. We'll go back to that. And there are variations of these criteria in the literature. Some studies even considered any difference in favor of the lower extremities to be indicative of central cord syndrome. So even one

point difference in the lower extremities, in favor of the lower extremities to be indicative of central cord syndrome. So even one point difference in the lower extremities in favor of the lower extremities could be central cord syndrome according to these studies. And on the other end of the spectrum, another study used a 19-point difference between lower and upper extremities. It really is a mix. And I would like to show you, this is the 10-point criteria. I want to show you some considerations in central cord syndrome, and I will be showing it with actual examples from the model systems database. So these are actual cases. Now, here you only see the motor scores of the INSKE exam. And over the next slides, you will see that there really isn't a classical CCS case because it's so variable, but these cases are as classical as it gets. All right, so let's look at these. And they easily fulfill the 10-point criteria because there is a difference of more than 10 between the lower extremities and the upper extremities. For example, the first case, lower extremities is 40, upper extremities is 18. So we see here in both cases significant upper extremity weakness compared to the lower extremities. In most of these cases, there is typically more pronounced weakness of the distal upper extremities, hands and fingers innervated by C8 and T1. And, well, we just discussed the pathophysiology, so it actually makes sense that we see more weakness in the distal part of the upper extremities. However, there is also some proximal upper extremity weakness, as we can see in these cases as well, so for C5 to C7. Often seen in these cases are individuals with intact lower extremities, such as here. So only the upper extremity, the hands and fingers and the arms, are affected by CCS in these cases, and it's a subset of CCS. Also, cases classified as central cord syndrome are often asymmetrical. And for example, here, it's not very pronounced, but you still see some difference between the left and right side. Now, these cases were pretty straightforward, these two, and I think we would all agree also in the clinic that these are central cord syndrome. But what about the ones I'm going to show you now? These also fulfill the Emski 10-point criteria, but would you call them CCS? In this case, we see CCS pattern only on the left side. And on the other side, the right side, it's zeros from top to bottom. But there are still 15 points in the lower extremities and zero in the upper extremities. So according to that criteria and others, it is considered central cord syndrome. The second example is a very mild CCS case, but still it has a 10-point difference between the upper and the lower extremities, so it still qualifies as central cord syndrome. Now, you would agree with me that the course of rehabilitation and prognosis of such cases would be completely different, but existing criteria do not differentiate between them. Now, should these cases even be considered as central cord syndrome? I don't know. I'm not saying that they should, but we really need to discuss these scenarios, and we shouldn't automatically include them when using a quantifiable criteria such as the EMSCI. But you see, it's very difficult to find an accurate criteria in research here. Other than the EMSCI criteria, many studies don't actually use a specific definition, and the diagnosis of central cord syndrome is subjective and based on clinical impression. Now, again, that's what we do in the

ENGEL-HABER: 18:12 we do in the clinic. It's a clinical impression, but that's not the case in research. We need consistency.

ENGEL-HABER: 18:20 And I do want to share with you another definition. It was depicted by two unrelated studies, and they quantified the strength of the central cordiness. They call it CCS-ness. I think we call it CCS-ness. They just qualify the strength. But there was a range between 0% to 100%. So it's a continuum. And 0% is no CCS at all, and 100% is full CCS. So these studies suggest a threshold of 10% or 20% to define CCS. And also, they only include the average of the upper extremity motor scores below the level of injury. Because why would you include intact segments in your calculation of upper extremity weakness? I'll show an example in a second. So in this actual case, there is significant weakness in the distal upper extremities. As you can see here, it's all zeros in C8 and T1. But the Emske criteria does not consider this case as central cord syndrome because look at the lower extremity motor scores. It's 24. It's actually less than the upper extremity motor score, which is 30. Now, it's 30 because of all fives in C5, C6, and C7. So it doesn't qualify as central cord, but there is significant distal upper extremity weakness. The NLI, neurological level of injury in this case, is C7. And now using this definition, when we look at the average upper extremity motor score below NLI, it would be zero because it's just the average of C8 and T1 on both sides. So basically in this formula, we would get 1 minus 0 times 100. We would get 100% CCS for this case. So this definition could be useful to delineate CCS in specific cases of distal upper extremity weakness.

ENGEL-HABER: 20:09 could be useful to delineate CCS in specific cases of distal upper extremity weakness. It could be useful, but in reality, this is not a typical case because usually we do see some proximal upper extremity involvement. When I say proximal, I mean C5, C6, or C7. And this involvement may be motor or it may be sensory. But in that case, the neurological level of injury would also be higher. And then you get pretty much the same results for this formula as you get for the Emski criteria with their strength and get pretty weaknesses. much the same results for this formula as you get for the Emski criteria, with their strengths and weaknesses. So it's not useful enough. And by the way, the definitions that we are proposing and we will now see do take these cases into account. I will show you it later. So these were some of the primary elements in the description of CCS. We already saw the top three considerations, distal versus proximal, asymmetrical weakness, and disproportionate weakness. We discussed that a little bit. But let's look at the bottom row. This was also part of our review. We noticed that many studies about central cord syndrome do include an AIS grade, Asia Impairment Scale grade, in their definition of CCS, with A being a complete injury, B, C, D. The range is usually between A and D. When D is incomplete, typically individuals that won't. It is worth mentioning, okay, so they do use AIS in their studies, but we would assume that only motor incomplete injuries, those with AIS-C or D, would be included in these studies because if you have AIS-A, which is complete, or AIS-B, which is still motor complete, you're not supposed

to have CCS. But actually, there are quite a few studies that considered individuals with AISA and B as having central cord syndrome. Another consideration we want to note is that some studies actually have a specific inclusion criteria for central cord syndrome that really uses, incorporates the imaging or mechanism of injury or pathophysiology into their definition. So for example, a recent review actually includes any type

ENGEL-HABER: 22:34 review actually includes any type of acute sensory or motor deficit localized to the cervical spinal cord. So they are specifically noting in the absence of fracture or dislocation. So that's a specific inclusion criteria. Another study includes radiographic and or clinical presence of a cervical SCI without ongoing compression and in pre-existing spondylosis and the narrowed canal.

ENGEL-HABER: 23:03 and the narrowed canal. Now, they're not only describing CCS, they're really saying we are only including individuals and we're calling them individuals with this inclusion criteria, and only these are considered CCS in our study. So again, it's different classifications here. So again, it's different classifications here. What we have so far is a huge variation, and we understand there needs to be a better way to delineate between the different subtypes and characterize who should be included or excluded from a study. We're not the only ones calling to revisit this syndrome, and in recent papers, there were several calls advocating for revisions.

ENGEL-HABER: 23:50 And actually, one of the authors of these papers, I just presented with a course on central cord syndrome in East Coast last month. So this is the third part. Now we have already discussed the existing data, and I want to show you our recent work. We're going to submit it for publication very soon. So in this next step of the project, really taking into account all the information presented so far, and I'll remind you, the original question Dr. Kirshblom asked me was, can we find a more accurate, a better definition for central cord syndrome? But taking all of that into account, really, it took us a long time. But we understood that one definition just wouldn't work for all. In the first few months, we were working on it. We were just trying out different definitions. But after a while, we understood that there's just no one definition for this syndrome. It consists of several. So we understood that with such variability within these criteria, the first step for us would actually be to describe this variability and describe it not only by showing the examples that we just did, but also quantifying it, showing that these are not rare examples, showing what the actual incidence of the different variations is. And these were our objectives, to define different clinical variations of central cord syndrome that would improve our understanding of the term, assess their frequency, and compare neurological and functional outcomes. Following IRB approval and utilizing the US Spinal Cord Injury Model Systems, which is SCIMS database, our inclusion criteria consisted of individuals 16 years and older with a complete neurological examination and motor-incompleted traplegia. So it's cervical injury with severity of AIS-C

or D. We only included these individuals in our sample. We ended up with a sample of 14, 19 individuals. The statistical analysis was mostly descriptive, along with some comparisons.

ENGEL-HABER: 25:58 We are proposing these new clinical subsets of CCS, and we're specifically focusing on the critical aspects of distal upper extremity weakness and symmetry. Let's discuss that for a minute. Although the original Schneider study and subsequent clinical and pathophysiological studies highlighted the prominent involvement of the distal upper extremity, the hands and the fingers, in CCS, it has not been translated into actual definition. We address this gap by comparing the distal upper extremities to the lower extremities in our criteria. As for the symmetry element, although most studies imply bilateral involvement in CCS, and this is also what we expect, CCS to be bilateral, it has not been consistently included in existing studies and existing criteria in research. And this is significant, as weakness, we've seen that can range from complete symmetry to substantial asymmetry resembling Brown-Siquard syndrome. And I will go into more details over the next slides, but in general, these are the three criteria. Full is bilateral significant weakness in the hands and fingers compared to the lower extremities.

ENGEL-HABER: 27:18 Unilateral is also significant weakness, but only on one side. Borderline is some bilateral hands and fingers weakness, but to a lesser extent than full. I want to stress, I want to highlight here that the general concept here is more important than the actual threshold that we used. The threshold was needed as you do need a threshold to be able to quantify any of that. But we're not saying that this is the threshold that should be used. It is just, we needed something to be able to show the incidence of these syndromes, of these variations that I just showed you all these examples of. Let's go into a little more detail about these variants. This is full CCS. And again, I'm using here actual cases from the SKIMS database. And I'm again, using here actual cases from the SCIMS database.

ENGEL-HABER: 28:01 Full CCS is the more classical type with a difference between the this is the the average lower extremity motor scores. average, calculation, So this is L2 to S1 and distal upper extremities, C8 to T1, of at least two on each side. For example, on the right side, these averages are 4.6 in the lower extremities and zero in the upper extremities. So the difference here between lower and upper is greater than two. And it's the same on the left side. This definition focuses on distal upper extremity weakness, but I do want to say that most cases have some proximal weakness. It could be mild, as seen in this case, which has mostly fives and fours, but it could also be significant. The key to this definition is that it must have significant distal upper extremity weakness. For unilateral CCS, only one side fulfills the criteria of a difference of at least two. In both these examples, only the right side actually fulfills it. For example, the first example is 4.2 minus 0.5, so it's greater than two. The other side, on the other hand, can be very strong, even intact, or extremely weak. So there is still significant variability here.

And it is really arguable whether these cases should even be considered as CCS. But again, both cases here fulfill the existing Emski criteria. And there are many more of these cases. It is therefore important to identify this form of clinical presentation and differentiate it from others. For borderline, the difference is between one and less than two on both sides. So the distal upper extremities are still weaker compared to the lower extremities, but not by a lot. And again, there is a huge difference between the cases here. The first case we've seen before is very mild CCS. The second case is also just very weak altogether, but both are considered CCS by the 10-point criteria. And therefore, we need to account for these cases, although not sure in the clinic or even research we would want to call them central cord syndrome.

ENGEL-HABER: 30:30 Within our cohort of motor incomplete tetraplasia of the 1490 individuals, we identified 17% with full, 25% with unilateral, and 9% with borderline CCS, together accounting for more than 50% of the study sample.

ENGEL-HABER: 30:47 Going back to the Emski criteria, it is the most commonly used, so important to discuss. There were 582 cases classified as CCS according to the Emski criteria, and this is not related to our proposed criteria. It's just a 10-point criteria. Now, we already saw some overlap between our criteria and the Emske criteria using those examples. And you can also see this in the donut figure. So we can see the breakdown of the 582 cases identified with the Emske criteria, but this time it's using our different subsets. 40% of these 582 were full CCS. 42% were unilateral. 11% were borderline. So we see a significant overlap. But in reality, this overlap is only partial. So while the Emski criteria includes all of the subsets that we described, it only includes them in part. For example, the Emski criteria, although it includes many unilateral cases, there are still 36% of unilateral cases that are identified by our definition that are missed by the Emski criteria. So the bottom line here is that there is a problem, the Emski criteria. So the bottom line here is that there is a problem because either a criteria should include 100% of a subset or not included at all. Right now we see that the Emski criteria sort of includes everything but only part of it. They include unilateral but not all unilateral cases, same for full and same for borderline. I will not go into too much detail

ENGEL-HABER: 32:24 not go into too much detail here, but I do want to describe the main characteristics, the main details of the characteristics and outcomes. And I will share the most salient findings with you. In this comparison, I will show you the difference between individuals we identified with full CCS to those that did not fulfill any CCS criteria. And the reason I'm doing it is that the other cases we identified of unilateral and borderline CCS criteria were typically somewhere in the middle within these numbers and often not too significant, so I'm not going to present them here. numbers, and often not too significant, so I'm not going to present them here. One of the reasons for that, actually, for unilateral and borderline is that still our criteria is, although it's much more specific than the criteria that existed until now, it still includes a large range of cases. Those with full CCS were older, more likely to have

an AISD injury compared to non-CCS. Naturally, those with full CCS had lower scores of the upper extremities on admission, but after a year, they were almost intact. This is different from non-CCS, who had lower scores of the lower extremities to begin with, and these remained relatively low even after a year. With regards to functional differences, there were some between these subsets, but the majority were not statistically significant. We were actually quite limited with the functional outcomes because we only had functional outcomes at discharge. functional outcomes because we only had functional outcomes at discharge. The one-year follow-up data is only partially available in the model system. Using the one-year discharge, I'm sorry, using the discharge data, we can tell that individuals with full CCS were more dependent in feeding upon discharge, but we suspected that the one-year follow-up, they will be similar to others. but we suspected that the one-year follow-up, they will be similar to others.

ENGEL-HABER: 34:28

That was these subsets that we just presented. And we now have a proposal to describe the clinical subsets of CCS. These variations often present differently from those not classified with CCS, but we did not see significant functional differences. This is an important question. All of these subsets combined, they accounted for more than 50% of motor incomplete tetraplegia, and that's a lot. It's also difficult to compare to other studies, as each had a different inclusion criteria, as I just showed you. But just for reference, with the EMSCI criteria, it's 39% with CCS. So we have, with our combined criteria, more than 50% with CCS. And also, in our analysis, we saw that two-thirds of the entire cohort, of the entire motor incomplete cohort, had more weakness in the upper extremities. So that really raises the question, should we even consider central cord syndrome separately from motor incompletetraplegia? The majority of individuals with motor incompletetraplegia actually have more weakness in the upper extremities. Maybe we should always just discuss motor incompletetraplegia and not central cord. I did discuss these limitations despite we didn't have the one-year functional data. And also, despite the introduction of these new clinical subsets, there were still notable variations, especially in the unilateral and borderline categories. But there is only a limited number of subcategories that we can really include and define. We advise also including injury level and severity while describing these subsets. The take-home message, there may not be a good reason to exclude individuals with central cord syndrome from studies.

ENGEL-HABER: 36:25

from studies. These definitions should enable researchers to clearly define their criteria and allow clinicians to more accurately describe injury patterns. Thank you.

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