Advanced imaging to better understand myelitis and pain in children and young adults

2017 Rare Neuro-Immune Disorders Symposium
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00:00 Everybody. So, my name is Nadia and my job for the next 15 to 20 minutes is to convince you that spinal cord imaging is a fascinating field. OK.

00:15 So here we go. I'm going to start from the very beginning. Right. So, when you have a neurological problem you go see a neurologist. Right. So, the neurologist let's say. Who can I pick on let's say Dr. Benwell. She you know she does her magic all her neurological examinations and at this point she has a pretty good idea of what's going on. Right. So, then she goes on and orders an MRI of your spine with without contrast. And then what the result she gets is high. What is that hyper signal intensity, C4 to C6, and sometimes that correlates with the clinical functions. The clinical symptoms sometimes it doesn't sometimes it's negative MRI. Sometimes it takes a while for MRI to actually show lesion.

01:11 So what conventional MRI does not tell us is what the focus is of this talk. OK. So, I'm going to share with you a story on how I got involved in transverse myelitis research. I was actually doing my Ph.D. dissertation in traumatic spinal cord injuries in Philadelphia and I met an 11-year-old boy who was diagnosed when he was seven and four years later he came to us because he wanted to participate in our research project. He had notable motor impairment had difficulty walking. And so, when I scanned him and I compared his and I use this technique called diffusion tensor imaging which I'll explain in a bit. And I compared his data to our controls healthy controls. He was significantly different from all of them compare them to the traumatic injuries. He was also significantly different.

02:09 So he was somewhere in between. And but as part of the study I was supposed to meet with a radiologist who is blind to whether this subject is a patient or a control. But his job is to tell me control patient. So, this guy says The MRI is negative. This is a control subject. Now I was an engineering student and I know we have some engineers in the audience right. As an engineer, you tend to trust a $5 million MRI scanner over the human radiologist right. So, I didn't believe anything he said. So, I want to get a second opinion right. This time from a much younger radiologist. He also said the MRI was negative. OK. So, I didn't stop there. Right. So, I waited two weeks went back and tried to trick them. So, I said I have a new data new subject.
What do you think of this line. He says negative MRI control subjects showed him again to the younger radiologist. He said the same thing. So, in statistics right. This is what's called enter an intra radar agreement and you can't argue with that. So finally, you know we published that. So, this is his MRI right. So, no lesion showed showing on the T2. And this is that technique I mentioned called diffusion tensor imaging also. So, we went on to publish that as a case report and we turned that into a grant application and we get some money from NIH to do the project. So anyway, so this is how I got involved in transverse myelitis about five years ago. OK. So, what MRI doesn't tell us is actually the underlying microstructure of the spinal cord.

It doesn't tell us how far the lesion extends. It doesn't tell us what's going on in the tissue above and below the injury. And just because tissue does look hyper doesn't have that hyper intense signal doesn't mean that it's healthy. Right. So, we're looking for ways to assess what's happening in the spinal cord in a quantitative way and assess that tissue that may look healthy on an MRI but actually it's not. OK so what is diffusion Tensor Imaging? It's gonna get a little technical for two slides. And I know Saturday afternoon when you guys don't want to hear about science we're just hang in there okay. So, diffusion tensor imaging is MRI based. Additional time in the scanner. In that 1.5 Tesla or three tesla scanner it's what it does is it measures the movement of water molecules in the spinal cord.

You know we're all made of water molecules moving around. That's actually my failed attempt at drawing in axon and molecules inside of it. And this movement or this diffusion. Is not the same in all directions? And what's with that we try to model that use in using this technique. And how many of you in the audience know what a tensor is.

One person OK of course. Of course, it's you Dr. Emanuel. OK. So, it turns out I actually didn't know.

So a tensor is nothing but a mathematical way to model or represent diffusion. That's all it is. And you guys know MRI is actually three dimensional. Right. So, when you take a picture with your phone you're looking at a two-dimensional image and it's made of little squares called pixels and MRI. We're talking about voxels which is a pixel with a thickness or pixel with a volume. So, what these geniuses did was find a way to represent diffusion in each voxel of an MRI. Didn't make sense a little bit. OK. Kind of cool. So, in a spinal cord water movement is happening further along the axons than a cross. And that helps measure by how they move up and down versus left and right or front to back. And I think this will this will put it all together very nicely.
06:19 So this is the cross-sectional image of a spinal cord and you see how it's made of little cubes kind of. So, each one is a voxel each voxel is represented with a tensor. And in each tensor water is moving in all kinds of directions. And that's what we're measuring with diffusion is how by how much water moves in each single voxel of an MRI. OK. Did that make sense. It wasn't so bad right.

06:46 OK. Perfect. Perfect. OK. So, if DTI is so fascinating why isn't it used in the clinic every single day for every single patient. OK. So, this is a little bit challenging. OK. It's this is especially the spinal cord in the brain. I found out actually from Dr. Benwell that it's used in the clinic but in the spinal cord hasn't made it to the clinic yet. OK. And I went and did a little research on to see just how many publications are there for each eye and the brain. In the last 10 years, we have here five thousand. OK. Any guesses for spinal cord.

07:28 Three hundred. OK. Pediatric spinal cord.

07:36 Alright. So, OK. Remember your numbers OK. I have that answer but at the end of the pediatric spine is actually a whole different world. To image it's much much more challenging. And again, like I mentioned it's one of the challenges the size right the spinal cord is much smaller and to obtain a certain resolution you actually have to scan for a longer time.

07:57 It's also adjacent to the lungs in the heart. So, it suffers from all this motion. And also, you know in pediatrics you know kids move. Right. And we can't sedate for research. So, we just have to say don't move and hope that they won't.

08:13 We have an added challenge in pediatrics. So, you guys see what the problem is with this image. Like I said this is a patient we had he's acute TM patient. I think he was about nine years old and you see that big black hole. That's one of his braces. So, if we get this a lot from what we know with our pediatric population the braces retainers and his lesion which is an upper cervical area I was so close to where his signal dropout is. And unfortunately, DTIs even more sensitive to metal than conventional MRI. So I don't think we're going to be including his you know for this study. OK. So, for DTI to make it to the clinic here I have to do a list for us for the scientists. We have to improve our imaging protocol, we have to make them standard across all centers. Also, I found out that clinicians love pushbutton technologies. Right now, it takes me an hour to analyze one data set one spine.

09:17 So I don't think the clinicians have that much time on their hand right. So, we have to come up with ways to make this automatic for them.

09:26 Also hardware improvements that you guys hear about FDA approved in seven Tesla scanner very recently I think it just happened two weeks ago. So now we
can use seven Tesla scanners for clinical use so that means higher resolution faster scan time.

09:43 But I know that some of our pediatric neuro radiologists are hesitant. You know they don't want to put the kids in there but we'll see. And finally, and I think this is the most important part is we need stronger data. We need these imaging techniques to show or to be able to predict disease severity and monitor how patients respond to treatment. And I think this is the most important part for this to make it to the clinic. OK. And I think we even have to put the agenda even further and find ways to differentiate between myelin lost versus Axon a loss. Everybody's familiar now with what an axon is what myelin is but we don't have ways right now to differentiate between the two. Also, I think there's a talk later about remyelination. So, the question is can we use these imaging techniques to measure remyelination.

10:41 So there's a lot to do. Certainly, more questions than answers. And you know I added this because you know this wise man said that if we knew what we were doing and wouldn't be called research. So, it's a lot of questions. A lot a lot of questions. OK so now I'm going to move on to what the study that currently going on at Children's Hospital and how we're trying to answer some of these questions in our pediatric cohort. This is done at the Center for Pain and the Brain, still fighting with City Hall to have spine somewhere in there. So, we'll see how that goes.

11:21 So right now the goal is pretty simple to develop an image protocol that is sensitive to detecting loss of myelin. Different stages of the disease from acute subacute to chronic. Additionally, define if there is there's a relationship between these imaging measures and the clinical symptoms and especially pain. A typical study so far. So, we're we were enrolling ages 7 to 21 different stages of myelitis and I mentioned 30 patients, 30 matched controls. We matched by height age and gender and we matched by height because we want to make sure that we're covering the same levels spinal cords in both groups. And it has been a little bit challenging.

12:10 We will study in our TM and NMO and also AFM an atypical study visit goes like this so we do some sensory test in with heat or just for sensitivity to heat cold vibration. What else. Light touch and other things and we do this at the dermatome level. You guys know what a dermatome is? Now some of you. So, a dermatome is area on your skin that is connected to your spinal cord level. So, for example someone with a C7 injury would do all the tests in on their middle fingers because that's the area on the skin that's connected to the C7 level. So that's what a dermatome is. On the imaging side. We do the conventional clinical scans in addition to our advanced imaging. And also, we scan everybody twice because we want to make sure our techniques are reliable.
This is all done in 45 minutes, 45 minutes and then another 45 minutes for the second or the second session. And we're looking at C1 all the way to T12 the thoracic scan takes longer to image because it's no longer. On the imaging side. We are testing out these three techniques diffusion tensor imaging which you know are experts at by now. OK. I won't quiz you but I'm assuming you all know what a tensor is now. Then we were doing magnetization transfer imaging as well. And then myelin water fraction. I will not go into detail about these last two. And those are images from one control subject one patient with TM that colored the map is what DTI looks like. I just added this two days ago actually. And the reason why I added it was just to show you the distribution of how our patients at Children's Hospital in Boston are the acute phase and so on the X-axis we have ages on the Y-axis is number of patients and we see this clustering in a right one around 12 and one or six months.

And the reason why I added this was to show the limitation in our project and how we're only targeting ages 7 to 21. Nobody is looking at the babies right. So, I feel like it would be great to study this a younger population as well. We also have high female prevalence ratio two to one. And this is I think a total of 50 patients. OK. And you know I thought I was the first one to come up here and talk about this at a TMA symposium but I'm not. This was actually discussed back in 2001 when it was not called RNDS I think it was called Transverse Myelitis Symposium. OK.

And diffusion tensor imaging was mentioned in a gathering just like this 16 years ago by this man named Norman Beauchamp. I don't know him personally but he did say in the spinal cord. I think we have a shot of diffusion. He even mentioned transfers, I mean magnetization transfer.

Right. And as a technique that has potential in spinal cord imaging. So here I am 16 years later. Right.

And he had 10,000 views and zero thumbs down so I'm assuming all 10,000 people agreed with what he said. That's fantastic, right guys. So, I went on and I did a little more research to see if his predictions were right. This is the list of publications DTI spinal cord since the beginning of time. OK. So here. This is when he made his prediction 2001. OK. And then there was some. Something happened and then boom an explosion of publications. Why do you why do you think that happened. Any guesses. I wasn't born at the end something else. No no guesses yes. What is it. No. No. Nope nope this is when clinical research started.

Before that it was all just theory. You know what a tensor is what these techniques are. But this is when all of that started. You know people start
publishing applications. How does this relate to the clinic? This is in other words this is one the Ph.D. I’m an M.D. start hanging out together. You. That's true too. Yes. So OK so I'm going to end with this. Remember there's so DTI in brain we said for 5000 publications the spinal cord three hundred. Any guesses DTI spinal cord and pediatrics.

17:09 Who says less than 100? OK. Who says less than 50? you can’t raise your hand twice.

17:22 No. No. Good. Wow. Well we have scientists in the audience. OK. OK.

17:28 Who says less than 20? 19.

17:36 I'm going to say one more. OK. DTI pediatric transverse myelitis. Who says less than five?

17:47 OK let's say this is the glass half empty side and who says less than 50?

17:57 Who says less than 100? OK. All right. Two.

18:06 Two publications ever. Ok so I mean it's actually good. That means we have a lot to do. We have a lot of avenues to innovate right. We're going to be the first and only way which is you know it's pretty cool. I think it’s pretty cool but it’s a long way right to go from 2 to 5000. I made it in the brain and now it was in the clinic routinely. But I really, I really think I have high hopes for spinal cord imaging. So, OK so this ends it for me. I just want to acknowledge my team our neurologists who are fantastic and very patient with me. My funding sources. And of course, I would like to thank you all for your attention. I think I may have a minute for questions maybe not know.

18:55 If. My e-mail is right there or not anymore. We think.

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