Genetics of Familial Transverse Myelitis

2017 Rare Neuro-Immune Disorders Symposium

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Transcription from presentation available at https://youtu.be/bMkoYOlT_FE

00:02 So for the most part what as we've been learning about transverse myelitis we haven't known any genetic susceptibility. And so it really came as a surprise when Sandy called me and he said I have two sisters. Both of them have transverse myelitis. Do you want to talk to them. And my first thought was there's no genetics involved and transverse myelitis. You know what are the chances. But we did anyway and my first inclination was I bet one of them doesn't have true monophasic transverse myelitis, going to be MS or something like that but now they both had transverse myelitis. So we undertook this study. And again I just want to emphasize which type of transverse myelitis we're talking about here we're talking about the acute type. The one that comes on suddenly that doesn't have an explanation like neuromyelitis optica, it just happens one time and one time only and that causes the lesion and the spinal cord with disability from that attack.

01:06 And as you know this is the very rare type. most types of transverse myelitis occur with multiple sclerosis. But this type that happens once and only once is about one to two per million. So that's how rare we're talking here. And as Dr. Greenberg said that thought there was thought to be a female predominance but maybe in kids it's more equal and we didn't notice a seasonality to it at the time.

01:32 But like I said the genetics underlying any sort of susceptibility in transverse myelitis was completely unknown. We didn't really have enough patient families to make any sort of conclusion about genetics. Until Sandy call and this is the story of the first patient who had her onset at age 15. But this was a while ago. This was she's in her 50s now. So this happened many many years prior. She woke up with weakness sensory loss bladder dysfunction it was in the days before MRI and she had a spinal tap but we couldn't get the results because that hospital had long since been closed they probably threw away the records. But the reason we think that this was transverse myelitis and they recognized it as such is because she got a course of steroids and she seemed to improve. It took her a while to get out of a wheelchair but now she uses an assist device and can walk Here's her MRI that was done.

02:33 I don't know maybe 30 years after the fact and the lesion is still there. You can hardly make out this little white vertical line here within the gray spinal cord. So it's pretty small. I point to it with this arrow here if you take a cross section of the spinal cord and look down the spinal cord is here in gray and the lesions are

those two white dots that's all that's left that's the scar. 30 years after after an attack.

03:03 That was the first case then. The reason this was brought to our attention is because her sister had a very similar presentation except it was 35 years later at age 50.

03:14 Her onset was also acute. She had some weakness although not as severe some sensory some bowel bladder issues and her MRI is a little bit more subtle I'm not sure if you can make it out but her lesion was right here pointed to by the arrow. And again pointed to the cross section here by the arrow was a little bit smaller and she got treated pretty quickly and then responded pretty well to steroids. And both these sisters did not have a relapsing disease because they've gone at least five years or in the case of the first sister 35 years. With no what no additional attacks. So we know that this was the monophasic idiopathic transverse myelitis variety and we took these numbers we won it one to two per million in one family having two sisters. We took that to our geneticist at Johns Hopkins and we said what are the chances right.

04:12 So they agreed with us and they said hey let's look for a genetic basis. Here are some of the technical details for what what the folks at Johns Hopkins did in collaboration with Baylor College of Medicine. What this involves is sequencing every base pair in the genome there 3.1 billion base pairs 80 G's and C's that comprise your genome and they sequenced every single one of them in the two sisters. And there were three healthy siblings. They have three one sister and two brothers I believe. And none of them none of the three siblings had transverse myelitis as yet. So we sequenced as many as we could and then we looked for differences. What did the two sisters have that the other three siblings did not have and what I'm showing you here is called chromatograms.

05:01 This is a zoom in a snapshot of one gene and you can see here here all the 80 G's and C's. They're represented by these peaks here the higher the peak the more reliable call and they're color coded.

05:14 So I can't tell what color this is but a Green is an "A". And what it's supposed to be is a "C" and literally out of 3.1 billion letters. There's only one difference here. The two sisters hadn't an "A" all of her all of the other siblings had a "C" There was one brother who had a mix he could see there two peaks there. The computer called an "A" but you could see there's two peaks and that's because he was a carrier. So he had one gene from the mom and one gene from the dad and one of them was an "A" and one of them was a "C" that the two sisters got the two A's. And the rest of the world has two C's.

06:00 Now what's really interesting is when you look throughout all of the populations in the world that have been sequenced and there are at least a quarter of a million now and all of their DNA is in these searchable databases and you could look through and see what what are the chances that this could be present in the world somewhere else in people who don't have transverse myelitis.

06:21 And the answer is zero. Not another single human being that's ever been sequenced who has two A's right there like our two sisters have not a single human being. Then you look in other animals and you say OK in this same gene what are the chances that the result of that would be mutated. And there not a single animal in the animal kingdom that has this mutations. Wow this is really really really rare. And it might be clinically meaningful to not have this mutation here because no other animal has that. But then we thought OK maybe this explains just these two sisters right. What are the chances that other people with transverse myelitis would have this mutation when no one else in the world has ever had it. So that's the question we asked of our patients who came to our patient day, Transverse Myelitis Patient at Johns Hopkins.

07:17 And we happened to get 86 samples total with transverse myelitis, 25 with neuromyelitis optica, 25 with multiple sclerosis. These are control groups who also get transverse myelitis as part of their disease. But it's not the type we're talking about which is the monophasic type. We also had a few healthy controls which is really unnecessary because we already have a quarter of a million in databases. But but still. And we did find another woman who came to our patient day who had this story age 51 woke up with sensory loss weakness and pain around her her chest her MRI was done and it showed a lesion pretty similar to our two sisters here. You could see the whiteness within the gray. You could see most of her spinal cord at this level was white. That's the lesion. So a little bit more obvious of an MRI.

08:14 And she too had the exact same extremely rare genetic mutation that the two sisters had and the sister this patient happened to come with her sister from Canada. And we also sequence that sister and she is a carrier for that mutation. Just like one of the brothers was. So now we have two separate families we have one family I didn't mention the two sisters are Polish origin. This patient here was Scotch-Irish. So two separate family trees. All three patients have this monophasic transverse myelitis has in one case it's familial where there's two patients and the other case. No no family history. But she also tested positive.

08:55 Here's the pedigree because see the first family I wish we had the parents to sequence to see if they were carriers. But here are the two sisters who were both affected. Oh a missing one of the family members I apologize. Here's the one of the brothers who's a carrier. There's another brother here who's healthy and a not a carrier. And the sister here I'm not showing who's also not a carrier.

And then this other family here with one sister who has transverse myelitis and her healthy carrier sister. It suggests that this is passed down from from the parents. The fact that you have multiple siblings. Who have the disease with both who have what's called the recessive presentation that is both genes are mutated and healthy family members with only one gene that's mutated suggesting it's coming from the parents. So what's this gene that that's involved in transverse myelitis? it's it's a gene called.

09:51 Vacuolar Protein Sorting 37A. And I first saw this as like in the, VPS37A. What is that? Had to look it up. It's not really known to neurologists this is not a gene associated with any immunological process at all. And what it does is this is a cell here in green. And all these purple dots here are proteins on the surface of the cell and VPS37A just helps bring those proteins into the cell and recycles them decides if the protein should go back out onto the surface of the cell or get chewed up in and broken down into its components. That's what VPS37A does and nobody's really thought of this process being involved in transverse myelitis. VPS37A turns out is only one of over 30 proteins that's involved in this protein recycling process.

10:49 So there are a lot of other proteins here that are involved in neurological diseases. There is one can't really see the slide so well but there's one within this ESCRT. One system that's involved in Alzheimer's disease. There's one that's involved in hereditary spastic paraplegia which is another spinal cord disease but none of those are immunological. This is the first one this transverse myelitis mutation is the first one that we've found that's associated with an immunological process. Here's what it looks like in cells. This happens to be brain tumor cells and you could see in green here this is that VPS37A protein just doing its job. It's not mutated here it's just within a cancer cell recycling proteins. This is what it normally does. It's also present in the gut it's present in almost every cell in your body including the spinal cord.

11:46 But why. Why would it be doing something in the spinal cord to disrupt function there and not anywhere else in the body. We don't know the answer to that. But as I mentioned there's lots of other diseases now that are being associated with protein recycling genes and it gives us a little idea about how this might be involved. To give you a sense of. What we're thinking here I listed three infections that involve the nervous system. One is called Herpes Simplex Encephalitis. West Nile Virus and another really rare Necrotizing Encephalopathy. And these infections occur more commonly in people and kids who have these genetic mutations. These are all different genes and they all have mutations in them.

12:35 And so these people are more susceptible to an infection in the nervous system than people who don't have the mutations and the same might be true for

people who have this mutation in VPS37A perhaps it takes this mutation plus the context of an infection and then together they may contribute to the phenotype of transverse myelitis. So this is why I've been begging for you DNA across the hall. I want to see if we could put together a mechanism for how VPS37A is involved in transverse myelitis and it's not just transverse myelitis is that I'm interested in the truth is if if this protein recycling mechanism can be disrupted and cause transverse myelitis perhaps it's involved in other neuro immunological diseases. Or maybe other diseases that are not not just confined to the nervous system. Lupus and myasthenia gravis other diseases where protein recycling interact with the immune system even outside of the neurologic system. Same three kids.

13:44 Happy to take questions at the end. Thank you so much.