Neuropsychiatric Aspects of TM
2013 JHTMC 1st Regional Symposium
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Transcription from presentation available at https://youtu.be/SD98a0Hdsj8

[00:00] Great, thank you all for coming out here. We all know it’s a great commitment to get out here and get going and come here. I did want to start off by giving a special thanks to Carla Michael and Marine and let you know that these guys work incredibly hard and yet at the same time it really is like a family, they not only work really hard they also make it a great atmosphere to work you guys feel a part of this extended family and I will tell you that we had to actually kidnap Marine because she was here last night at nine o’clock preparing for this symposium so a group of us had to kidnap her and get to go out and have some dinners so she worked incredibly hard to make this possible.

[01:16] And I want to just so I don’t forget thank Daniel Becker who has been a remarkable collaborator and I am going to tell three stories and the third story is what he should be besides me to tell because it is one we did together, you probably didn’t know Cody Unser any way she … Oh wait there she is in back, so Cody also could also be up here as well for that part.

[01:45] OK, so with that in mind I am a psychiatrist and the question is what a psychiatrist doing in a place like this, it reminds me of the joke how many psychiatrist does it take to screw in a light bulb. The answer is just one but the light bulb has to want to change.

[02:03] So it has been a privilege to work as a member of the Transverse Myelitis Center, this is just going to go rather quickly to get through the three stories in the time that I have so Janis doesn’t get the hook and start pulling me off stage. But transverse means across affect both sides of the spinal cord, myelitis means inflammation of the spinal cord and as you guys know, I don’t have to tell you this but you know this the spinal cord is basically all the cables that come out of the brain and goes to the body and depending where you get the lesion on the body you get everything below it and it says here wherever you get the lesion it can effect everything below that. Having said that, TM is as tenth as common as we know as Multiple Sclerosis so most of the work that’s been done has looked at Multiple Sclerosis I want to use Multiple Sclerosis as the kissing cousin of TM about which we know more although because of the work being done in the TM Center things are definitely caching up.

[03:26] Like with MS, TM is presumably a combination of a certain predisposition that people have that have perhaps an aggressive immune system combined with something that fools the immune system that lead to dysregulation and ultimately combine with some environmental thing so you could imagine the combination just as an example somebody who has a viral infection that is sort of hiding, a wolf in sheep’s clothing and it’s looking like the myelin which is wrapping around the neurons and then the immune system gets fooled into attacking that virus but now it also will attack the myelin and then something happens that lead to a breakdown of the blood brain barrier could be a simple as a whiplash or something like that and then you could imagine you could be off to the races when your system got going.

[04:24] So that just a quick overview and it’s important to know that one of the stories that I am going to tell is that traditionally TM is been thought to be strictly below the neck kind of thing and I am a above the neck kind of guy so I am going to try to explain how we get more and more evidence to say the brain
is actually involved too, the diagnostic criteria for TM includes seeing when you actually put a needle down here in your lumbar region seeing that there are white blood cells even if the lesion is higher up here (he points to his neck) you can see the blood cells down here (he points to his lower back) the cerebral spinal fluid is bathing the brain and spinal cord so it is not so crazy to imagine that because the spinal fluid is full of these cells that there might be brain involvement. But when we first started this that wasn’t known.

[05:19] I would like to talk briefly about this study, this study was out of San Francisco and they phoned up people with Multiple Sclerosis ten years after the diagnoses and they asked how has the MS affected your life. And the interesting thing about it is that although it’s true one in five people and gave responses to say that it had created a strain in their relationship depending on other people or working together as a family unit in adversity in life under life under altered circumstances can be very trying, 30% of the people said that they were demoralized but what I think was most interesting about this study was that 60% of the people gave responses that researchers had to lump into this category that they said “benefit finding” that means that these people 10 years out from the diagnoses where saying that in some way shape or form the diagnoses of this neurological autoimmunological disease had actually benefited them in some way and I know what you are thinking, ‘California before medical marijuana’.

[06:25] So let me just show you what kinds of things that they said, “My friends and family have been more helpful; I am closer to my family; I have the opportunity to see individuals”. Men who have to stay home more than they used to, taking care of their family getting to know their kids in a new way. People who have reset their priorities learn to be more compassionate, respectful of others, appreciate the independence and the like.

[06:55] So I just think that the important thing is not to say that you should feel great about being touched in some way shape or form by this transverse myelitis, no one would wish any of these diseases on anybody but it not inevitable that it should alter one’s course and one’s life and one’s goals necessarily in a limited way. So, I would just like to point that out so when we are going to get into the issue of depression it’s not inevitable, in fact if there is depression it sorts of, there smoke there and there is a fire going on and you put out.

[07:35] So to give you a quick overview this just shows us that unfortunately and mea culpa this is a problem with psychiatry specifically with our society in general that not only have we not been winning the battle against depression but this shows us that over the past decade there has been a 30% increase in the suicide rate in this country, we now have reached epidemic proportions, so if you don’t know about this because it has been in the news, you should know that as a society the rates of suicide are astronomically high in the military, more people by far dying at their own hands than from any active combat anywhere in the world. And the other thing that you should know is that last year there were more suicides, death from suicides then there were from automobile accidents.

[08:22] So this is really a time that we really need to sound the alarm and this is something we can’t stop saying, “Well you would be depressed too, it’s not my problem it’s someone else’s problem” this affects all of us. And this just shows also after the down turn it the stock market things got even worse. And I am just driving this home, the last slide, what his shows that after 2007 you saw that increase what has happened is that it’s become the third leading, suicide is the third leading cause of death for our kids 10 to 24 it’s the second leading cause of death for young adults, that has pushed suicide to the top ten list, not something that we wanted to be in the top ten list.
[09:06] So, this is something that we need to address more globally, I will tell you that the work we are doing looking at Transverse Myelitis as well as Neuromyelitis Optica, Michael Levi is doing very exciting work looking at NMO the effects on the brain as well as cognition and depression. These are things that hopefully will translate into a better understanding of these illnesses for the general population.

[09:29] So what is depression what is clinical depression? The most important thing is it is not normal sadness so what I teach the medical students is depression is a syndrome it not just sadness, sadness is to depression what cough is to pneumonia. Meaning during the course of this presentation someone will cough and it’s not because they have pneumonia it’s because they are drinking a sip of water, it’s dry air, maybe it’s they got asthma. There are many reasons that people cough, cough can be an indicator of pneumonia but not every cough is a result of pneumonia sometimes pneumonia presents even without a cough particularly in the very young or very old. You get depression without sadness normally you see irritability, it’s sort of the equivalent symptom and you say “Johnny are you sad?” and he says NO! and he kicks the chair and he storm up and slams his door, right. And so what you really to do is consider the company the cough keeps, is it a productive cough with rapid breathing and temperature and you look at the x-ray and there’s this fuzzy region and you call that pneumonia. So it’s really a symptom cluster.

[10:35] This is the symptom cluster for depression, we remember it as SIG E CAPS Because it means more to a doctor because SIG is what we write on our prescriptions for how to prescribe, CAPS is capsules. But any way the important thing to know is you need to have five of these nine symptoms at least one of them is decreased interest or decreased mood, and is basically that: you have trouble sleeping or you have increased sleeping or early morning awakenings; your get up and go has gotten up and gone; things that give you pleasure no longer do; feelings of guilt or worthless; peoples self-esteem has hit rock bottom; energy and fatigue is very common; mood and remember that’s the sadness the one of nine symptoms you don’t need it to make the diagnoses. Concentration problems, appetite changes, normally it’s food doesn’t taste right and people stop eating or they start comfort eating and they crave carbohydrates. For men, it’s often salty food for women it’s chocolate but obviously there is a big cross over. Doctor Gidouski is saying, “Oh no she eats a lot of chocolate! You’re not depressed I promise you. and the what call psycho motor retardation which means you are not you normal bubbly self and then thoughts of death or dying or wanting to call it quits. This is the equivalent to chess pain in psychiatry, OK, this is an emergency. If you or your loved ones are having those symptoms that needs to be addressed just like if someone was have chess pains that needs to be addressed because that is life threatening.

[12:05] So all you need is to have five of nine or more of those symptoms lasting more than two weeks you’ve bought yourself the diagnoses of depression. (note 1)

[12:12] The more symptoms you have the more likely you are to respond to treatment. Now the important thing to know is that MS is generally considered to be the Michael Phelps of depression meaning its associated with 50% of people following the diagnoses of MS not prior to it but following it will get the diagnoses of clinical depression not just gee you’d be depressed too it’s that symptom cluster of all those things. And you can see though all of those things that many thing cause depression particularly things that effect the brain since that’s where are regulator is for our moods. There is a mood regulator in your brain that essentially like the thermostat in the room if it get stuck it will get quite hot here or cold depending on where it gets stuck and there is a mood regulator in brain and if you
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don’t believe me ask anybody how has ever done cocaine, that’s what stimulates that mood regulator. Cocaine has no withdraw symptoms people just crave it like crazy cause you get next to that mood regulator and hypothyroidism, B-12 deficiency many things that effect the brain can cause depression, MS is the number one traditionally thought of as the number one now we shown that the number of rates in TM are roughly equivalent we can’t tell the difference because it is so common. It could be more it could be less it is in the ballpark.

[12:34] So again compared to the population at any given time one in four patients with MS is depressed that is five times the general population there is also cognizant impairment in MS about 50%, we will get back to that later, but as you can see it’s very common. It is not a matter of personal weakness however. But here the problem if you miss it if someone is have trouble, if their depressed and have these symptoms and their having trouble with sleep they often get put on sedatives like Valium or Ativan or these kind of things the problem with those kinds of medicines is there sort of alcohol in a pill and they affect concentration so it often get written off as memory loss but that make memory worse, the other problem is that also worsen fatigue so people get put on stimulants as a result of the fatigue and the higher the stimulants the harder the people have sleeping so then you have to increase the sedatives and then you see how you could get into trouble treating symptom by symptom as a posed to getting the underlying cause. And the other thing is that if you have a little bit of pain it’s bad and if you have depression and a little bit of pain its really bad, It basically magnifies the suffering of anything, including pain. So a lot of people take marijuana for the pain but then that’s going to impair there concentration, etcetera, etcetera. If you miss the diagnoses and you start treating symptom by symptom you will actually start doing more harm than good most of the time.

[15:00] So again I am just going to summarize a lot of the literature and tell you that we now know and there extensive evidence that MS depression is caused not because of people not being strong enough or weak it’s nothing like that in fact what I always worry about are the people that are the strongest hiding their depression and going along just fine but actually their depression is getting worse and worse until it finally grabs them by the collar because their now not getting up and not going to work or they are having panic attacks or something that brings them to attention.

[15:32] So we really know that it’s periods of inflammation that makes the difference that’s when people get depressed when that happens. And it’s important to say that depression is important for a number of reasons among them it’s the primary determine factor in one’s quality of life. It’s more important if you have cognitive impairment, it’s more important than if you are in a wheel chair or not, it is the number one correlate and I can prove that to you just by showing you in a minute that it has a very high rate of suicide associated with it and obviously if you are willing to kill yourself you give up everything else because this is the number one issue that you are dealing with. It’s also the number one quality of life for the caregiver if it’s not for you if you won’t get treated for yourself do it for your loved ones because that’s also going to have a big effect.

[16:21] I don’t have time to get into this in any detail, but if there is one message to get out to the caregiver in the room the people who have tied their wagons to the people whose bodies have TM it’s just to let you know that when you are riding in an airplane and the oxygen masks drop down who do you put it on first yourself or your loved ones. Right and for those of you who hesitated just so you know you have about 30 seconds before the air is sucked out of the airplane and if you are struggling with your loved ones your kids for instance and their screaming and you are screaming to get on that then
they’re going to pass out and you are going to pass out and no one’s going to make it. If on the other hand, you put your oxygen mask on first you can struggle with them if that’s what you want or you just can count up to thirty and then they’re going to be resting comfortable there beside you to put the mask on, it just depends, the important thing is to let you know it very important that you make sure that you are getting enough oxygen. So, that means of course you have to go out with friends you have to go out to the movies, don’t feel guilty if you leave your loved one at home and you go to recharge your engines you are doing that for your loved one.

[17:29] So again this is to drive home the point 30% of those with MS will have suicidal ideation and 10% of people with MS will actually attempt suicide. So, it’s a big problem, this is the good news, (He points to a cartoon of a Mother talking to her daughter) “Of course your daddy loves you he’s on Prozac he loves everybody.” So it didn’t have to be the case that the kind of depression coming from the immune system getting activated would respond to the same medication that we use for depression in the general population from genetic reasons or the like. But it turns out that they do, so that is good news because treatment is possible.

[18:08] Now the other part of the treatment that’s important to know, if you take blood from patients who have MS and you measure how aggressive and angry those white blood cells are the immune system is when you activate it and people who are depressed it’s twice as aggressive, you treat their depression and the depression comes down, the activation of the immune system comes down to normal level. And that lead this important study that was published a while ago to say: “That the treatment of depression may provide disease modifying therapeutic strategy as well as symptomatic treatment.” What they mean by disease modifying is in treating the depression is actually treating the MS itself.

[18:52] And we have further evidence of that this is a study that came out, white bars show what happens when you put people who are not depressed with Multiple Sclerosis on Fluoxetine, SSRI, Prozac compared with those who get put on a placebo this is increasing the number of lesions over the course of 24 weeks who were put on a placebo and if they were put on an SSRI they didn’t have activation. And this is statistically significant for those of you who like statistics this was a statistically significant finding. And to just give an idea the number of patients with no enhancing lesions that didn’t increase was 63% and that was more than twice as many as the 23% on placebo who did not have enhancing lesions. So it made a really big difference to be on the treatment. So now we know on that there’s this complicated triad which is depression, MS causes depression, depression worsens the MS, and inflammation seems to be involved in both, if you are depressed you have higher inflammation, which also worsens the MS and you can go round and round and round here if you don’t make an intervention.

[20:17] So again why did I tell you all this here at the Transverse Myelitis symposium? Because this shows you what the suicide rate was from the first 500 patients seen in the Transverse Myelitis center we are a long way from that but we were tracking to see what was going on and there are huge error bars on this but out of the first 500, five individuals had committed suicide while waiting to get into the TM Center but we hear about this on Facebook on the TM website all the time, there was someone in South America who committed suicide recently with Transverse Myelitis. But these huge error bars this is TM, this is the rate of suicide in MS this is rate of suicide in general depression we know that TM is at least as high and we know the depression rates are at least as equivalent to MS. So, it’s important but the good news is that with treatment, first of all you could be put back to your old self in terms of those
symptoms the SIG E CAPS symptoms, it’s very hard to get some of the symptoms better which is why there is this symposium. Depression is one of the set of symptoms that can be completely treated back to your old level of mood, energy etc. that’s being caused by the depression.

So let me just switch gears and tell you that it used to be considered that only 30 years ago that only 3% of patients with MS had any memory problems you know that none of you have ever experienced this but we are talking about going into the next room and wondering what you came in there for and when you used to be able to have just have everything in your memory just go to the phone and dial it, now reading what the phone number is and by the time you get to the phone what all those digits are, those are the kinds of things that we are talking about. Usually we are not talking about really dramatic, can’t remember where you live, those are the kinds of things we are talking about the more mild to moderate kinds of memory problems. It used to be 3% of MS, we now know but were not looking we now know it is closer to 50% and most of the people who have it of that 50% it is mild to moderate.

So what we did was, and this was work done with Christian Ron when we went to CC camp, Camp for Courageous Kids and we just basically brought a tablet and she went around and she had kids, kids like that adorable child right there, Mackenzie did this. So where they had this asterisks pop up and when it pops up they had to hit the screen and they got data back and compared it from the kids with TM to their siblings and there was a highly statistical difference between, in this case controls were their siblings, their response rate was much higher the number of response rates per minute than those kids with Transverse Myelitis and if you look at the reaction time how long it took them to respond to the correct responses there was statistically significantly highly significant differences in the kids with TM. Now it doesn’t mean that they couldn’t do it, it just means they needed more time more practicing and so the important thing to know is that people with TM, 50% of people that do have an effect really just need to know that it just means that now it great if you can keep everybody’s phone number in your head now you just have to (he points to a palm pilot) this is my brain by the way, it happens to sit on my waist, all my phone numbers, I wouldn’t remember my daughters cell phone number if I didn’t have it right here so it just means you have to rely on other technologies and it may take a few more times to learn.

So just switching gears here’s the good news though this is TM, this is MS when you see all these lesions in MS people with TM do not have all those lesions, however what’s interesting is they have nothing to do with cognitive impairment and if you look at these lesions and try to correlate them with cognitive impairment in MS they don’t correlate or very, very poorly correlate and the reason why that is, is because the people with TM still don’t have the brain involved but still get depression, still get cognitive impairment and so we know it’s not these,

So the question is what can you do if you can’t rely on these lesions and the answer is you can actually look at the chemistry of the brain so this shows these peaks are obtained from an MRI scanner that was tuned not from water which was from, this was showing you water, instead it was tuned to look at chemicals in the brain and this is showing you the hippocampus and this is involved in learning and memory and this is involved with people with Alzheimer disease for instants and we looked at this little peak here which was very predictive how people did on their paper and pencils testing could be predictive correlative coefficients of say point 9 where 1 is a perfect correlation. How their levels of this
particular neuropeptide in the brain called NAAG, N-Acetylaspartylglutamic, there is not going to be a quiz on this later, was highly predictive on how people would do.

[25:36] So there is a drug that can increase the level of NAAG in the brain, it’s not available for human use so instead Christian Ron went to the animal model of MS, but by the way the animal in MS model is the same as the animal model in TM in that most of the lesions occur in the spine, it’s called EAE, Experimental Autoimmune Encephalomyelitis, almost all the lesions are happening in the spine and yet they still have cognitive impairment these mice and you can see those animals that got placebo were running all over and could find their way to this hole on day one, same thing with those on day one who got this drug TAP. However, those animals on placebo by day four were still running all over the place a little bit, and those animals that got the drug went right for it pretty much.

[26:25] So you can see the path efficiency went from point 3 to one point three is path efficiency point three to point seven-five that’s an over 200 percent increase, I know it looks sort of funny this way so let me show it to you this way which is to say right here it’s this forgetting from one day to the next this is what the problem is so they go through four practice runs the next day you come in, the animals that were getting placebo forgot, the animals in blue got the drug didn’t forget, and the black shows you the animals that didn’t have EAE where healthy mice without any autoimmune problems and you can see that it get all the way back up, this got the animals with EAE the animal form of MS got them,

[27:10] Oh wow so here we are, I have three minutes, so I’m looking at that clock, that’s when I started, so you can see it got them all back to where they were. And now the exciting thing is not just what we learned in TM effects all of medicine and now were looking at Alzheimer’s disease cause Alzheimer’s disease is the same thing low levels of this protein in the brain.

[27:33] Really this quite healing waters is done with Daniel Becker based on this totally insane idea that Cody Unser had that maybe scuba had an effect on people, rehabilitation when she went scuba diving she notices these zingers you can ask her she is in back of the room you can corner her later and you can ask her why she came up with this crazy idea. And what you can see here is that Daniel and I went with Cody and Daniel did the neurological examines and it showed that all the paralyzed war veterans who have been paralyzed for an average of fifteen years had deceased Spasticity after doing ten scuba dives all the patients had some level of increased sensation up to 20% that they hadn’t had in 15 years and half of them got some motor function back.

[28:28] That’s unbelievable that not expected and you can ask Daniel how surprised he was because he started paging me of the hook, Adam, Adam, because when we got back he looked at the data and started calling me up. So just real quick just to let you know we now know that there is this particular effect of the nitrogen that happens when you scuba dive that leads to a dramatic increase in serotonin, it turn out that all of walking, and you can talk to Daniel about this, that chicken with their heads cut of will walk because their walking is really programmed into your spine in the central pattern generator that why you can walk and chew gum and you don’t think about it. And it turns out that what we believe is going on is that the scuba leads to nitrogen accumulation in the tissues and in the brain so there’s a significant increase in serotonin in the brain that activates the central pattern generator and that’s what beings to reactivate the spine. It’s very exciting and the reason we haven’t followed this up is that we are waiting to get more funds. We’d love to be able to do this with more patients with TM, it’s very exciting.
[29:25] This is what happens when you take an epidermal stimulator and you do it three times a week for seven months, remember this is one week and we saw these effects. If you do a stimulator where you just leave a stimulator in general release of neurotransmitters from electricity, they took someone who was completely paralyzed by a motor vehicle accident and he was able to stand up and bear weight and walk after seven months with this stimulator and we think you could do that if you could go scuba diving for three times a week for seven months or maybe if it’s the serotonin that’s the key the next thing is to actually test that out.

[29:28] So it’s a very exciting time because first of all I’m done, that’s exciting and the second reason is because we now have evidence that there are other ways to reactivate what exists in other people spines not acutely 15 years after injury there are ways of reactivating the pathways that exist pathways to be repeated anything you do in science has to be repeated to make sure that it’s not a fluke and it’s all those things. It’s very exciting because it suggests the idea that what exists right now in people’s spines even before you get stem cells or anything else from outside may be able to activate the existing circuitry. I don’t think and I don’t think Daniel that this is the answer in of its self but if you combine this with exercise and eventually stem cells and other treatments that come on line it’s a very exciting time I think the fact that we are going to reactivate the spinal cord is just down the road.

[30:58] So the take home messages are the brain is involved in TM, depression happens it’s treatable, if you worry about it in yourself our your loved one just have them seen by a mental health professional, have them screened to see if that’s what’s going on. The second thing is that cognitive impairment does look like it happens, so if you have kids where we have the data, they just need a little more time and we are happy to write and say: “Your kid need a little more time on the standardized test and etc.” we now have data to support that. Also, out of UT Southwestern they also found some of these findings as well and published them and the last thing is the scuba diving, if you stay tuned and there is something in your packet about what we did. So now Maureen is being good because she just wants to grab me and throw me off but I am only 2 minutes late so thanks very much for your time.

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1 This is from the 2004 symposium – Depression and Cognitive Dysfunction - https://youtu.be/3YRo-cpXtqY?t=24m21s On the chart the nine symptoms are: You have to have five or more of these symptoms for greater than two weeks and one of them has to be deceased interest in pleasure not enjoying things as much as you used to. A low mood most of the day for the past two weeks. And then sleep is either increased or decreased the same as eating or comfort eating as some people call it or loss of appetite food doesn’t taste the same as it used to, there are physiological changes in the body, people just don’t want to eat cause it just doesn’t taste the same and there is also the feeling of being worthless, fatigue, low energy and concentration. This psychomotor retardation just means as we all know you just look at someone and they are just walking through molasses. And then thoughts of Suicidal ideation or thoughts of death. If you have five of nine of those you got the diagnoses of depression.

1 Sleep lack or too much. 2 Interest or pleasure changes. 3 Guilt or worthlessness. 4 Energy or fatigue. 5 Mood 6 Concentration 7 Appetite up or down or weight loss or gain. 8 Psychomotor retardation or agitation. 9 Suicidal ideation or thought of death.