59| Neuropsych Bite: Limbic Encephalitis – With Dr. Joel Kamper

November 15, 2020

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Speakers: Joel Kamper, John Bellone, Ryan Van Patten

Intro Music 00:00

John Bellone 00:17

Welcome, everyone, to Navigating Neuropsychology: A voyage into the depths of the brain and behavior, brought to you by INS. I'm John Bellone...

Ryan Van Patten 00:26

..and I'm Ryan Van Patten. Today we have the last Neuropsych Bite in our series exploring rare neuropsychological conditions in adults with Dr. Joel Kamper, a board certified neuropsychologist at the James Haley VA in Tampa, Florida. In this episode, we talked to Joel about limbic encephalitis. Similar to Balint's syndrome, moyamoya, and CJD, you're not likely to encounter this condition very often. But it's important to be aware of the pathophysiology and the clinical symptoms in the event that you do see a patient who has it.

John Bellone 01:01

Although this is our last Neuropsych Bite with Joel, we plan to release more Bites in the near future. Specifically, we're currently working on a mini-series of Bites on rare pediatric conditions, so stay tuned for those. As usual we want to give a brief reminder that select NavNeuro episodes are available for CE credits through INS. If you need CE's, check out navneuro.com/INS for more information. And, with that, we give you our Bite with Dr. Joel Kamper.

Transition Music 01:32

John Bellone 01:41

Okay, so, limbic encephalitis or LE refers to inflammation in the limbic system. Joel, how common is this condition? What are the common causes and symptoms?

Joel Kamper 01:51

It is not common. And, yes, the name kind of says it all, right? Limbic encephalitis - it is inflammation in the limbic system. Typically, it's going to be caused by - well, classically, it's paraneoplastic syndrome. So it's associated with cancer in the body somewhere, and we can talk more about that in a minute. It can also be due to infection. I think I've seen HSV...

John Bellone 02:15

The herpes simplex virus.

Joel Kamper 02:17

There's a couple different causes of it and it has a telltale presentation on testing, which we can also talk about. But it is rare. I'm trying to actually remember now what the base rates are. But low, they are very low. [laughs]

Ryan Van Patten 02:35
Is there something specific about the limbic system that makes it more prone to encephalitis than anywhere else in the brain?

Joel Kamper 02:43
That's an excellent question. I'm not 100% sure. I know, typically, the antibodies that are associated with it - so, it's NMDA; it's Hu, which is an anti-neuronal antibody; it's AMPA; and there are a couple others - I think those antibodies are more found in the limbic system and that's probably why. It's my guess. We think about herpes in the limbic system when we think about people who are densely amnestic because herpes likes the mesial temporal lobes. It's not like that. I think it has more to do with the autoimmune condition.

Ryan Van Patten 03:19
Yeah, that's a perfect segue. If we think about LE as an umbrella term, we can divide it into two primary types or causes. There's the infectious LE and then autoimmune limbic encephalitis. So first, can you talk about infectious LE or HSV? What does this look like?

Joel Kamper 03:40
Well, I would, if you don't mind, reclassify that as paraneoplastic or autoimmune. The autoimmune and the infectious types kind of go together. The herpes virus will trigger the autoimmune encephalitis, but it's not like the herpes virus is infecting the limbic system itself and causing that. But it's almost - you guys have heard of PANDAS, the pediatric condition that's a little controversial? Or like PML, multifocal leukoencephalopathy? A lot of folks, you know, with the JC virus, who are immunocompromised? So it's something that's caused by a virus, but then the body's response is to go into hyperdrive, there's an autoimmune reaction, and that's what actually causes the damage. It's the virus that precipitates it, but it's not the direct cause. It's sort of the instigator.

John Bellone 04:31
Gotcha. It's like a downstream consequence of it.

Joel Kamper 04:33
Yep. So, for autoimmune encephalitis, the classic patient is a 30-something year old woman. That actually is also true for the paraneoplastic syndrome. But the autoimmune type is most often related to NMDA. You may have heard of

anti-NMDA encephalitis. The classifications differ, but a lot of people will say that anti-NMDA receptor encephalitis is a type of limbic encephalitis, where the body's immune system is attacking NMDA receptors throughout the brain, but predominantly in the limbic system. As far as the clinical features, people will have headache, fever, kind of like a viral illness. Like, "I had the flu a little bit". They often don't recognize it until retrospect. Then they'll develop what looks like psychosis - hallucinations, agitation, delusional disorders that can look like schizophrenia or like a primary psychotic disorder. But they're also going to have insomnia, memory deficits, seizures - that's a big telltale that you're not just looking at a psychiatric presentation - and some motor movements, some dyskinesias. The dyskinesias can look similar to what we see in a lot of folks with schizophrenia but those symptoms are often due to the medications, they're not due to the actual syndrome itself. These symptoms will all kind of come on at once.

John Bellone 06:06

Seems like the common underlying factor is the inflammation though, right? There's different types, but ultimately, it's the inflammation that causes these symptoms. That "-itis", right? It means inflammation, so that's an easy way to think about it.

Joel Kamper 06:18

Yes. Correct. That is an excellent way to think about it. Encephalitis is inflammation of the brain; meningitis, inflammation of the meninges. Anything "-itis" is "inflammation of the...". Right. Absolutely.

John Bellone 06:33

And the treatment for LE obviously depends on whether it's caused by an autoimmune process or a paraneoplastic process. What are some of the common therapies for each type?

Joel Kamper 06:42

So, let's start with the autoimmune. We've been talking about that for a bit. They'll often use immune suppressors. So rituximab is one, which is often used for different sorts of cancers actually. But it's an immune suppressor on B-cells, which is the type of immune cell. These are the cells that are attacking the limbic system, the NMDA receptors if we're talking about anti-NMDA encephalitis. So, it's suppressing the immune system. Oftentimes, in these patients, especially if there's that strong psychiatric flair, someone's going to have put them on an antipsychotic that's not going to have done anything. The book "Brain on Fire", which was in the popular press a couple years ago, was about a woman who had this. You get put

on, you know, risperidone or something. And it does not do a whole lot other than snow you a bit. You need a drug to suppress the immune system to reduce the flare up, and then it should clear up.

John Bellone 07:43
And then the paraneoplastic intervention?

Joel Kamper 07:46
Sure. So let's talk about paraneoplastic a bit more broadly. I was not familiar with what paraneoplastic syndrome even was until a fair way through my training, and I'm not sure that everyone does. A paraneoplastic condition is something indirectly caused by cancer. So if you think of a met - metastases or mass effect that a tumor puts on something - that is not a paraneoplastic, that would be a direct effect. It would be something like, there are tumors that can cause hormones to go haywire and people can get deliriums because of weird hormonal imbalances. That would be a secondary effect, that is a paraneoplastic condition. So, in the case of limbic encephalitis, it's a classic paraneoplastic condition. Typically, it's related to germ cell tumors, which is the type of cell. Testicular tumors are a common type of germ cell tumor, or an ovarian teratoma is another type. Those are the classic ones. The ovarian teratoma is the textbook one. But you can also get it with small cell lung cancer, which is the most common cause of any type of paraneoplastic condition. You can get it with lymphoma. You can really get it with a lot of things, the textbooks won't necessarily say that. If this was on a test, you shouldn't necessarily say that, but this field is so ill-defined that, you know, I've seen tables of what antibodies can cause this and it's dozens, and there's one or two case studies for each one. [laughs] So, we really don't know. But those are the most common. I don't know exactly what causes it, other than the immune system recognizes there's something wrong, tries to attack the cancer, screws up, ends up attacking the body - in this case, the limbic system - and you get that limbic encephalitis that we talked about.

John Bellone 09:44
I'm glad you defined the paraneoplastic syndrome and to further help listeners, it's para neoplasms. A "neoplasm" is cancer and "para" meaning due to the cancer, but not a direct cause. I like your definition.

Joel Kamper 09:59
Thank you. Yeah, it's interesting. In these conditions, the paraneoplastic syndrome is often seen before the cancer is diagnosed. In some cases when you have positive antibody findings, you will presume it's due to a cancer but no cancer is

ever found. Like there was something emerging in the body, but not before the immune system went into overdrive. It's really kind of freaky. But, in a classic case, where there's, let's say, an ovarian teratoma, if you take the ovarian teratoma out and you do treatment for the cancer, it should go away.

Ryan Van Patten 10:33

So you've provided a really helpful overview of the biology of limbic encephalitis, Joel, we haven't talked as much about the behavioral and cognitive sequela. I can imagine, and guess, you know, the amygdala and hippocampus is what we may be seeing here, but is there any more nuance to add?

Joel Kamper 10:51

Not a whole lot. You're gonna have the psychiatric sort of presentation. You're going to have some Alzheimer's-looking memory problems because of the limbic involvement with the medial temporal areas. Sleep problems, agitation, seizures. All the patients I've seen who've had this were seen in our inpatient psychiatric unit, for obvious reasons, because of the symptom presentation. That's the classic presentation.

Ryan Van Patten 11:21

Okay. So that's a perfect transition. Tell us about a few of your cases.

Joel Kamper 11:25

Sure. I will talk to you about two cases, one that had it and one that I thought had it and didn't. It's good to use that as a learning experience. I was all excited thinking I had found this case. [laughs] So, both were actually quite similar.

I'll tell you about the one who had it first. It was a late-60s Latina who came into our inpatient psychiatric unit with this new onset psychiatric syndrome. You guys probably know, but the listeners may not - a good rule of thumb for anyone who's over the age of, let's say, 50, certainly 60, if it's a new onset psychiatric syndrome, assume it's neurologic until proven otherwise. People don't really get schizophrenia at age 70.

John Bellone 12:16

There are rare cases, but yeah.

Joel Kamper 12:18
There are rare cases, yes.

John Bellone 12:19
But you shouldn't assume that it's psychiatric necessarily.

Joel Kamper 12:22

Right. You should assume it's neurologic until proven otherwise. If you do a full neurologic workup and nothing pops, then maybe you can think this is one of those one in a million really, really late onset schizophrenia cases. But, anyway, this lady's case. So, she comes in and she's very, very agitated. She's very suspicious, paranoid, delusional, and hallucinating. She's very religious, so it took on a bit of a religious flair, and it was difficult at first for the staff in our inpatient psychiatric unit to kind of parse apart, "Okay, is she just very religious or is it more than that?" You know, talking about seeing demons in the room and things like that. But it got a little worse. They put her on some antipsychotics and that helped a bit, not a lot, but a bit. But she was agitated. She did not have seizures and that is one of the very common things that's seen. She did not have that, but she was quite agitated. She had sleep problems. And they were thinking, "Well, yeah, if you're hallucinating and it's freaking you out, you're not gonna sleep well." But the antipsychotics they had her on just didn't do a whole lot, and they had tried a couple, so they called us. So we come down there...

John Bellone 13:29
They called in the big guns. [laughs]

Joel Kamper 13:31

Yeah, well. I have a couple of psychiatrists that I have a very good relationship with and they know to call and chat before they put in a consult for service. You know, three quarters of the cases that they think they should send us end up being, "Well, no, he's not wearing his CPAP. I can't make him wear his CPAP."

Ryan Van Patten 13:49
[laughs]

Joel Kamper 13:50
"He's got some cognitive problems associated with that. He should wear his CPAP."

Ryan Van Patten 13:53
Quick work.

Joel Kamper 13:54
Yeah. So I go down there, work her up. And it was weird. She was very, very, very forgetful. We did what I like to call the “RBANS-special”, which is an RBANS with Trails and a couple other executive things, and then our homemade neurobehavior test that we like to use here in Tampa. So we did that. She's pretty amnestic, surprisingly. Pretty dysexecutive. Some fluctuations in attention that we associated with the acute psychiatric symptoms, but she's not able to focus. But it was kind of weird. So I'm thinking, "What gives you late-onset psychosis and executive dysfunction and dense memory problems?" I can't think of too much. We wanted to rule out nonconvulsive status epilepticus, which is a not super uncommon thing where patients can have status epilepticus, constant seizures, but they don't look like they're seizing. They're not having a tonic clonic seizure or a GTC. We've seen a couple of weird psychiatric cases like that. So they threw on EEG and, yeah, it's dysfunctional, it looks like it's more temporal, but it's not status. Okay, well, that's weird. So they do another MRI. She didn't have too much of the classic hyperintensities in the limbic areas, but that's what you'd expect to see. So then what do you want to do? Well, you need to get an LP, a spinal tap. You need to take a look and see if there's antibodies. And there were. I think, in her case, there were

AMPA, which is anti-AMPA, often a cause of limbic encephalitis and typically related to cancer. She then had a full body CT PET scan to look for any active neoplastic activity. Didn't find any. But the CSF tests confirmed that it was a type of limbic encephalitis, and the syndrome fit. So that's what it was presumed to be. They gave her some steroids and some other immune suppressors and she improved. Although she came back to see us about a year later, she didn't get followed up on to continue those treatments and basically it's back. So we're recommending the same workup again, sans the CSF because we already know the findings. She didn't actually go to oncology last time, they just did the scan. So we think a more thorough oncologic workup is probably necessary to see what is going on because it's back, which is interesting.

The other patient I had looked broadly similar. A late 60s woman with new onset psychiatric symptoms, densely amnestic. We thought she was hallucinating, and she was a little bit, not too badly. They did the workups and it was all negative. What we ended up coming to, conclusion-wise, was that she had Alzheimer's disease, towards the moderate stage. Visual hallucinations are not uncommon in Alzheimer's disease that's progressed a bit. And it was just that she was amnestic because it was Alzheimer's disease. She had medial hippocampal sclerosis on

imaging, but there were no hyperintensities. It was just like you'd expect to see with Alzheimer's disease. And she had a family history of Alzheimer's disease when we followed up. So, initially, I thought it was limbic encephalitis. It was a very similar clinical profile, but the workup was all negative. The EEG was negative for something focal. And then we got the family history and got the imaging back and it's like, "Okay, this is, you know, let's call it a horse. Not a zebra." [laughs]

John Bellone 17:43
Right. Not a zebra. It sounds like the CSF, the lumbar puncture, was, in both cases, really important. Because in one you found the antibodies, and in the other one you didn't. It's pretty clear it also helps the differential.

Joel Kamper 17:57
Correct. Yeah, and there can be false negatives and false positives and things like that.

John Bellone 18:01
That's a good point.

Joel Kamper 18:01
But, like anything else, there's the possible probable. When you get a positive antibody, and the syndrome looks like it, and the history looks like it, I mean you're not going to get a whole lot cleaner than that in real life.

John Bellone 18:17
Yeah. Awesome. Well, thanks, Joel. Appreciate it.

Joel Kamper 18:20
Absolutely.

Transition Music 18:21

John Bellone 18:25
Well, that does it for our conversation with Joel. Be on the lookout for future Neuropsych Bites on rare pediatric disorders. As always, thanks for listening and join us next time as we continue to navigate the brain and behavior.

Exit Music 18:39

John Bellone 19:02

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Ryan Van Patten 19:14

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