Expert Interviews

National STD Curriculum Podcast

Neurosyphilis: Symptoms, CSF Testing, and Treatment

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Dr. Khalil Ghanem, a Johns Hopkins University Professor of Medicine and a syphilis expert, discusses neurosyphilis manifestations, CSF evaluations, and neurosyphilis treatment in an interview with the National STD Curriculum Podcast Editor Dr. Meena Ramchandani.

Topics:

- Syphilis
- neurosyphilis
- Bicillin
- CSF
- HIV

Khalil G. Ghanem, MD, PhD
Professor of Medicine
Division of Infectious Diseases
Johns Hopkins University School of Medicine
Principal Investigator, STD/HIV Prevention
Training Center at Johns Hopkins

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Meena S. Ramchandani, MD, MPH
Associate Professor of Medicine
Division of Allergy and Infectious Diseases
University of Washington

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Transcript

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In this episode:

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introduction**[00:00] Introduction**

Hello everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STD [sexually transmitted disease] literature review for health care professionals who are interested in remaining up-to-date on the diagnosis, management, and prevention of STDs.

For this episode, we welcome Dr. Khalil Ghanem. Dr. Ghanem is a Professor of Medicine in the Division of Infectious Diseases at Johns Hopkins University. He's an expert in the field of HIV and STIs. In this interview, we are going to focus on one of the more serious complications that can occur with syphilis, which is neurosyphilis. Hello, Khalil, and welcome.

Dr. Ghanem
Hi, Meena. I'm so happy to be here. Thanks so much for inviting me.

Dr. Ramchandani
Thank you for coming. We're very appreciative of you being here today.

changes-2021-cdc-sti-treatment-guidelines**[00:47] Changes in 2021 CDC STI Treatment Guidelines**

Dr. Ramchandani
So let's start by having you highlight some of the key changes for the management of neurosyphilis in the 2021 CDC STI Treatment Guidelines.

Dr. Ghanem
Sure. So the first major change is that most people treated for neurosyphilis will no longer need a follow-up CSF [cerebrospinal fluid] examination at six months, as long as they experience both clinical and serological responses. The exception to that are persons with HIV who are *not* on antiretroviral therapy, and those persons would still need a follow-up CSF examination six months later. So, that was one of the big changes related to neurosyphilis.

Dr. Ramchandani
Thank you. That's a fantastic overview.

neurosyphilis-manifestations**[01:33] Neurosyphilis Manifestations**

Dr. Ramchandani
So now, let's dive into some issues related to neurosyphilis. Can you review some of the typical clinical findings that should make a clinician concerned about neurosyphilis?

Dr. Ghanem

Sure. I like to think about it based on the pathophysiology of neurosyphilis. I know it sounds insanely complicated, but it's really not. It's actually quite simple. Remember, neurosyphilis can occur during any stage of the infection, meaning of the syphilis infection, either early or late.

Early neurosyphilis is a meningovascular form of neurosyphilis, and what does that mean? It means that it can affect the meninges and/or it can affect the CNS [central nervous system] vasculature. And so, what do you anticipate would happen with patients? Of course, they would probably present with meningitis symptoms, so for example, headaches, photophobia, or the light bothering their eyes, neck stiffness sometimes, and sometimes they can also present with cranial nerve abnormalities. And that's because syphilitic meningitis is usually a basilar form of meningitis, so it affects the base of the brain where all the cranial nerves are, so it's really important to do a good cranial nerve exam if you suspect meningovascular syphilis.

And then, of course, the vascular part of meningovascular syphilis, you think about the possibility of stroke, and then you can have both motor and sensory deficits as a result of the stroke, and sometimes you can also have seizures that result from a cerebral vascular accident. So that's early neurosyphilis with meningovascular manifestations.

Late neurosyphilis can present also with meningovascular manifestations, just like early neurosyphilis, but late neurosyphilis can also present as a parenchymatous form, which essentially means that the parenchyma, either of the brain or the spinal cord, are affected by this condition. And usually, the parenchymatous presentation of the brain is often referred to as general paresis, and it presents with cognitive dysfunction, for example, problems with concentration or short-term memory loss. Sometimes they can present with personality changes, euphoria, mania, depression, and apathy. And then the parenchymatous forms that affect the spinal cord, that's called tabes dorsalis, and patients can present with weakness and gait abnormalities. Sometimes they can present with bladder abnormalities, severe paresthesias, severe pains going down their back, and that's classic for tabes dorsalis. And when you think about it, almost any neurological presentation could be due to neurosyphilis.

Dr. Ramchandani
Thanks, Khalil. You know, I love hearing you speak, because I always learn so much. You mention headache. What's your take on headache as a manifestation of neurosyphilis? People get headaches all the time, and I find those with secondary syphilis often have a mild headache because they just have systemic symptoms.

Dr. Ghanem
You're absolutely right. The specificity of headache as a symptom for neurosyphilis is actually low, but many, many of us—and I bet you have as well, Meena—you've seen patients with neurosyphilis whose only symptom was a headache, right? I tend to use a litmus test, and I'll tell you what that litmus test is. If a patient complains to me spontaneously of a headache when I ask them, "How are you feeling?" then I tend to take it more seriously. If I have to actually elicit whether they're having a headache or not, then I feel a little bit better. Of course, that's just, you know, a basic litmus test, and you can always be wrong. And I always tell clinicians, "Listen, go with your gut," but I think that litmus test is actually useful. If you have to ask the patient, "Are you having a headache?" after you've asked them, "How are you feeling?" and they don't tell you anything about a headache, I think that's a reasonable litmus test to not take it as seriously as if a patient spontaneously tells you about their headache.

Dr. Ramchandani
That's perfect. That's really helpful in the clinical context when a provider is seeing a patient, and that does happen in our clinic all the time.

csf-evaluation-neurosyphilis**[05:37] CSF Evaluation for Neurosyphilis**

Dr. Ramchandani
So, in a person without HIV and there's a concern for neurosyphilis, do you always need to do a lumbar puncture [LP] to analyze the CSF? And if so, can you walk us through the important tests to order on the CSF

and how to interpret them?

Dr. Ghanem
Of course. So if you suspect neurosyphilis, in my opinion, you should *always* do a lumbar puncture because a normal CSF exam rules out the diagnosis of neurosyphilis, so you don't have to expose the patient to antibiotics unnecessarily, and it will clue you in as well. If it's not neurosyphilis, then you should be looking for something else. And so, it would keep that differential diagnosis alive for clinicians.

And so the tests that should always be obtained on the CSF are, first and foremost, the white cell count, the total white cell count, which is absolutely critical. It is the most sensitive test. It's not specific for neurosyphilis, but it's really sensitive. I can't remember the last time I had a diagnosis of neurosyphilis in a patient that had a normal white cell count. So, the sensitivity of the CSF white cell count is exceedingly high and, in my opinion, is a critical test to obtain. Of course, what you would be looking for with the CSF pleocytosis, or elevated white cell count, is essentially mononuclear cells. In other words, lymphocytes. If you see a predominance of neutrophils, think of another possibility other than neurosyphilis causing these manifestations.

Another test that is very important is the CSF-VDRL [Venereal Disease Research Laboratory] test. People are familiar with the VDRL test and the serum, but the CSF-VDRL test is actually an important test to make the diagnosis of neurosyphilis, but keep in mind that it's only about 50% sensitive. So, in other words, about 50% of patients who actually have neurosyphilis will have a nonreactive CSF-VDRL, *but* it is certainly the most specific test. In other words, if you have somebody that has a reactive CSF-VDRL, they have neurosyphilis without a doubt, except if there is gross blood contamination of the CSF. And what that means is, if when you look at the CSF, when you obtain it, you see a red tinge to it, then the specificity of that test goes down, so you'll have to interpret that test carefully. But if the CSF is relatively clear, then a reactive CSF-VDRL essentially makes the diagnosis of neurosyphilis.

And then, of course, there's the protein. It's sort of the unloved cousin of the CSF, mainly because I don't know what it really means. You know? It certainly has absolutely, I think, very little specificity, and the sensitivity can be pretty good, but the specificity is so low that I don't know what to do with a protein that's elevated with no other abnormalities. The CDC criteria suggest that an elevated protein is a reasonable criterion to use if making a diagnosis of neurosyphilis. I tend to be a little bit less optimistic. And so, in somebody who has a mildly elevated protein and the absence of any other symptoms, I usually tend to ignore it. I do not make a diagnosis based on a mildly elevated protein in the absence of pleocytosis or a CSF-VDRL.

Now the last test that I know you're going to ask me about later, and I'm going to do it now so that we don't forget, and that is, and I get a lot of questions about it, is, "Should I get a CSF treponemal antibody test, like the FTA-ABS [fluorescent treponemal antibody absorption]?" And the CSF treponemal antibody test may be obtained in limited circumstances, and the reason why in limited circumstances is because the specificity of that test is actually not very good, but it has a very high sensitivity.

So, in other words, you can rule out, in some instances, the diagnosis of neurosyphilis if the CSF FTA-ABS is nonreactive, but you should not make a diagnosis of neurosyphilis with a reactive CSF FTA-ABS in the absence of any other abnormalities. So, it has a high sensitivity, you can rule out the diagnosis, but the specificity is not very good, so you shouldn't make the diagnosis based on a reactive test.

Dr. Ramchandani
Thank you. That's great.

csf-evaluation-neurosyphilis-persons-hiv**[10:07] CSF Evaluation for Neurosyphilis in Persons with HIV**

Dr. Ramchandani
How would this be different if the person had HIV?

Dr. Ghanem
So that's another great question, and I think there are only slight differences for the diagnosis of neurosyphilis, right? So the only difference there is the degree of pleocytosis. In persons with HIV, who are not on antiretroviral therapy, it has been shown that by using a higher white blood cell cutoff than in somebody who doesn't have HIV, you may increase the specificity without affecting much the sensitivity.

So, in other words, in somebody who is HIV negative, a cutoff usually is a five white cells and above, and that would give you significant pleocytosis whereby you can make a diagnosis of neurosyphilis. On the other hand, in somebody living with HIV who's not on antiretroviral therapy, a higher cutoff, either ten and, in some cases, 20, has been used to make the diagnosis of pleocytosis. And so usually I use 10, but many people use somewhere between 10 to 20. That's the major difference in terms of diagnosis. The CSF-VDRL is not changed. The CSF protein is not changed.

Now, of course, what you're asking me now, even though you're not asking it, but yet I'm still going to answer it because I think it's one of the most common questions that we get, and that is, really, you know, who should get a CSF evaluation amongst people living with HIV? I mean, should you do it routinely? And I think it's important to answer that question because it is still somewhat of a controversial question. In my opinion, there isn't a right answer, but this is what normally I do when I'm dealing with a person who doesn't have neurological signs or symptoms, who has HIV, and who has syphilis.

So people who have neurological signs or symptoms should always get a lumbar puncture, whether they have HIV or not. Persons who have tertiary syphilis, meaning cardiovascular syphilis or gummata syphilis—we rarely see that—but if you see somebody who has that, you should definitely do a lumbar puncture because the data suggests that about 30% of those patients will have underlying asymptomatic neurosyphilis, and that will change the way you manage them, right? Tertiary syphilis, gummatous, and cardiovascular, you treat with three doses of benzathine penicillin G, but if they have underlying neurosyphilis, you have to give IV penicillin. So, anyone that has tertiary syphilis, cardiovascular, and gummatous, they should undergo a lumbar puncture.

And then somebody whose titers don't do what they're supposed to do after you treat them and they deny reinfection, you should consider a lumbar puncture, and so those are mainly the individuals that should have a lumbar puncture.

Now, what about somebody who's asymptomatic, who is living with HIV? Should they routinely get a lumbar puncture? And the answer is nobody really knows. I don't usually do that. Now, there have been many studies to suggest that if the RPR [rapid plasma reagin] titer in those individuals is greater than or equal to 1:32, or if their CD4 count is less than 350, their risk for neurosyphilis increases. Of course, the majority are not going to have neurosyphilis, but the risk increases.

And so, some people have used these criteria to decide whether to perform a lumbar puncture or not in somebody who's asymptomatic. I usually do not perform a lumbar puncture routinely in persons with HIV who are asymptomatic, even if their CD4 count is low or their RPR titers are high, unless I feel I will not be able to follow up with them, or they will have a hard time following up with me.

If I feel that follow-up is an issue, I will usually get an LP, but otherwise, if I don't feel that it's an issue, I usually just follow them expectantly and ask them to contact me should they develop any concerning symptoms, and I usually go through what those concerning symptoms are. So I know you didn't ask that question. I know it's a long-winded answer, but there you have it.

Dr. Ramchandani
That's a fantastic answer! And I love that you're answering questions that are in my mind, so I appreciate it.

preferred-treatment-approach**[14:32] Preferred Treatment Approach**

Dr. Ramchandani
So let's say you have a patient and you've made the diagnosis of neurosyphilis. Can you review the preferred treatment approach for neurosyphilis in these patients?

Dr. Ghanem
Absolutely. Penicillin, penicillin, penicillin. So, IV penicillin is really the preferred treatment of choice. Certainly, IM penicillin can be used as an alternate, and that's perfectly fine, but it's much more complicated to do because you're probably going to need outpatient follow-up for that 10- to 14-day course. And so if you have that, if you have that available, you can certainly use IM penicillin, but IV penicillin is usually the way to go, and the treatment duration is 10 to 14 days. Should it be ten days? Should it be 14 days? Nobody knows. It really depends on the center and on the individual. I think somewhere between 10 to 14 days is probably reasonable, but whenever you can, you should always try and use penicillin. We have the most data on penicillin, and so really, it is the drug of choice to treat neurosyphilis.

give-bicillin-or-not-after-10-day-course**[15:31] Give Bicillin or Not After 10-day course?**

Dr. Ramchandani
Now I'm going to throw in another question just because I'm curious. So let's say you had a patient with late latent disease, and you give them the 10-days of course for neurosyphilis with IV penicillin, do you typically give a dose of Bicillin at the end?

Dr. Ghanem
Meena, you ask me the question that I think I get asked the most frequently. So if you were going to ask me, "What is the question you get asked most frequently about neurosyphilis, ocular syphilis, and otic syphilis?" I would say, "Should we give additional doses of benzathine penicillin G when we finish the 10-day course of IV penicillin?" And in fact, because I get it so often, I'm in the process of writing a manuscript. But that's really an important question, and the answer to that, my answer to that, is that I don't do it. I don't use additional doses of benzathine penicillin G at the end of a 10- to 14-day course of penicillin, mainly because we don't have any data to suggest that it actually makes a difference.

Now, the problem is we just don't have any data, right? There's a difference between not having, you know, data to suggest that it makes a difference and having *no* data, and the answer here is we have no data. What's fascinating about this recommendation is that it has figured in the guidelines, either the public health guidelines starting in 1959 or the CDC treatment guidelines starting in 1982, in some way or another. And the reason why is because experts, it's not based on any data, but there are some experts who have said, "Listen, in the setting of late latent syphilis, the duration of treatment should be at least 21 days, at least 21 days, of treponemicidal concentrations of penicillin." And if you're treating somebody with late syphilis and they have neurosyphilis, and you're only giving them 10 or 14 days of IV penicillin, they're not achieving those 21 days.

And so, that's where it's coming from, so it's not an unreasonable thing to do. I do feel, though, that if you're going to use it, then one additional dose of benzathine penicillin on the last day will get you to 21 days. You don't need to do three additional doses.

So, the answer to this fabulous question is, if you're going to do it, do it with one additional dose on the last day of IV penicillin, and that's going to give you what you need for 21 days, but you do not have to do it. And in fact, I don't do it. And so I think if you feel strongly and it would make you sleep better at night, then, by all means, give that one extra dose, but otherwise sleep just fine. You don't have to worry about it.

Dr. Ramchandani
That's super helpful. Thank you. Yeah, it hasn't been our practice either, and so we get this question asked a lot, and so it's helpful to hear your perspective on what you do.

alternate-treatment-options**[18:22] Alternate Treatment Options**

Dr. Ramchandani
I'd love to turn to asking you about the use of ceftriaxone or high-dose doxycycline for the treatment of neurosyphilis. Have you ever used it? What cases might you consider using either of those regimens?

Dr. Ghanem
So let's start with ceftriaxone. That's the easier one. I think that we have a lot more data on penicillin. So whenever I can use penicillin, I will definitely use penicillin over ceftriaxone, but there are some circumstances where it really is impossible to use penicillin. One example would be somebody that's being transferred to an acute care facility, and the acute care facility is just unable to provide the penicillin dosing at the necessary frequency. And so, in those cases, I don't have a problem using ceftriaxone. I think we have enough observational data that, if you absolutely cannot use penicillin, I don't think it's unreasonable to use ceftriaxone. And ceftriaxone, the dosing is one to two grams, and it's given essentially for 10 to 14 days as well, and I think that's a reasonable approach if you absolutely cannot use penicillin.

Doxycycline is a different story, and here we're talking about high-dose doxycycline, so essentially, 200 milligrams of doxycycline twice a day orally that is used for 28 days. That is a recommendation that shows up as an alternate recommendation in the UK guidelines, but it's based on very, very limited data.

Recently there was a case series of 16 patients that was published that showed that it works pretty well, but I would be very careful here. What I would tell clinicians is doxycycline should not be offered as an option to patients. It should *not* be offered because the data are so limited, we still don't know what we're doing. Now, we're trying to push for a study to look at doxycycline, but until that study is done, it should not be routinely offered to any patient.

Now, have I used it? I have in a couple of instances. Only when a patient who has neurosyphilis, ocular syphilis, or otic syphilis and they are leaving against medical advice and they will not consider IV penicillin or ceftriaxone. In those instances, I've written a prescription for doxycycline, and I've given it to them, and I've said, "Listen, this is not recommended, but it's hopefully better than nothing. And so I urge you to stay, but if you're going to walk out, take this prescription with you." That's the only situation I think where doxycycline should be offered to patients, but otherwise, I do not think it should be used.

Dr. Ramchandani
Thank you, Khalil. That is so helpful.

managing-treatment-disruption**[21:09] Managing Treatment Disruption**

Dr. Ramchandani
One other question that came up from actually one of our clinicians in our sexual health clinic is, let's say you have a patient who has a disruption in penicillin treatment for neurosyphilis. They missed two days of treatment—whether it's IV penicillin or procaine penicillin with probenecid, would you restart the treatment, finish out the 10- to 14-day course, or would you actually extend the duration of treatment accounting for the days that they had missed?

Dr. Ghanem
So Meena, I don't know what the right answer is. I'll tell you what I do. So, if the lapse is more than 24 hours, the option that I use is I restart treatment over again. That's the option that I use. I have tried to find data on that, and there are no data that exist on that, that I've been able to find.

I have heard other people who actually extend the treatment course by that period of time, but I think to me, it makes a little bit less sense because that 24-hour period, that greater period of time, more than 24 hours, theoretically allows the organism to replicate, and theoretically might bring you back to the starting point. And so I've always looked at it that way, and I've always restarted the regimen.

I do think that it is not unreasonable, if it's only a short period of time, maybe 48 hours, maybe up to 72

hours, to extend the course of therapy. I think that's perfectly reasonable because I don't know of any data that would guide you in that situation. I think for a longer break in duration where they did not get it, I feel strongly that you should probably restart over again. So between one and three days, I think it may not be unreasonable to prolong the course, but beyond that, I think you should probably restart. I don't know how you feel about it.

Dr. Ramchandani
Yeah, that's really helpful. So err on the side of restarting, but sometimes it can be a case-by-case basis, depending on the patient and their follow-through.

Dr. Ghanem
I think that's exactly right. That's how my approach has been.

Dr. Ramchandani
Dr. Ghanem, thank you for joining us today. It's been an absolute pleasure to speak with you on these important topics. I've learned so much.

Dr. Ghanem
Thank you for being so thorough. It's been a real pleasure.

credits**[23:31] Credits**

This podcast is brought to you by the National STD Curriculum, the University of Washington STD Prevention Training Center, and is funded by the Centers for Disease Control and Prevention.

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