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Case Discussions

National HIV Curriculum Podcast

Neurosyphilis: Evaluation and Management

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National HIV Curriculum Podcast Editors Dr. Jehan Budak and Dr. Aley Kalapila discuss their approach to diagnosing and treating neurosyphilis in a person with HIV, including clinical manifestations, diagnostics, treatment, and therapeutic monitoring.

Topics:

- OIs and HIV
- Neurosyphilis
- penicillin allergy
- ocular syphilis
- ART

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Transcript

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intro--case**[00:00] Intro & Case**

Hello, everyone. I'm Dr. Jehan Budak from the University of Washington in Seattle, and welcome to the National HIV Curriculum Podcast. This podcast is intended for health care professionals who are interested in learning more about the diagnosis, management, and prevention of HIV.

I'm back with my colleague, Aley Kalapila, an ID [infectious diseases] physician at Emory University in Atlanta. Hi, Aley.

Dr. Kalapila

Hi, Jehan. Hi, everyone. Looking forward to this episode.

Dr. Budak

So, let's get started on this case, which is of a 49-year-old man with HIV who was previously on ART [antiretroviral therapy], but had been out of care for the past year. He came to clinic to restart ART, and what actually prompted him to come in was a three- to four-month history of intermittent headaches, mostly focused at the left temporal region and at the back of his head. He was experiencing blurry vision and seeing black spots over the past few months, but denied any photo or phonophobia. No over-the-counter interventions have helped. And on further neurologic history, he denied any syncopal episodes, seizures, or any focal muscle weakness or focal neurologic symptoms.

His review of systems, aside from the headache and blurry vision with floaters, was negative. On past medical history, he has HIV and has a history of bacterial sexually transmitted infections for which he has received treatment in the past. For some social history, he's from Atlanta, he has sex with men, and was last sexually active two weeks prior. He does not smoke or use drugs, and rarely drinks alcohol. And then on physical exam, he was afebrile and had normal vital signs and an unremarkable exam, including a completely normal and thorough neurologic exam. And I'll share with you that his CD4 count was 370 and his HIV viral load (or RNA) was 29,000. So Aley, what are you thinking with all of that?

differential-diagnosis**[01:45] Differential Diagnosis**

Dr. Kalapila

So, his CD4 is well above 200. So my concern for opportunistic infections in this case, things like cryptococcal meningitis, are much lower. So, for him, my differential diagnosis would include etiologies of subacute headache that would affect hosts that are more immunocompetent rather than severely immunocompromised. And same for the visual symptoms as well. So, the main infection that I think would explain both his headache as well as his visual symptoms, especially given his HIV as well as the risk factors that you just mentioned, would be syphilis.

Dr. Budak

And what would you want to do next?

Dr. Kalapila

Now, I think it's reasonable to get a CBC [complete blood count] as well as a comprehensive metabolic panel (CMP), and I would also get syphilis testing as well. And based on those serum syphilis test results, I might decide to pursue some head imaging and a lumbar puncture (LP) as well, given his headache. Now, because of the subacute changes in the vision, I do want to consult ophthalmology as well. And this patient is someone that can be managed in the ambulatory setting, but in order to expedite diagnostics and consultations, an inpatient admission could be helpful here.

Now, in this specific case scenario, because of certain social barriers, including transportation, we decided to admit this patient for additional workup, also because our concern for syphilis was so high, and also because we wanted an expedited dilated fundoscopic exam.

Dr. Budak

Totally makes sense. So, since he's admitted, all these things that you're wanting are happening simultaneously, but for the purposes of the episode, I'll systematically go through the data. So, let's say labs. He had a normal CBC and a normal CMP. His serum RPR [rapid plasma reagin] was 1:256, and the last one we have from a year ago was 1:2. I should mention that he's been appropriately treated for syphilis in the past. So, with that information, what are you thinking?

Dr. Kalapila

So, to me, that is a definitively positive RPR, and given that, I think neurosyphilis and ocular syphilis have now moved to the very top of my differential.

Dr. Budak

Now, Aley, you said “definitively positive.” As we know, many individuals, especially those with HIV, can have a persistently positive RPR, even despite appropriate treatment, and this is referred to as a serofast state, where the RPR can be low-level positive, such as 1:1, 1:2, or even higher, though once I see titers greater than 1:8 or 1:16, I tend to feel less comfortable calling it serofast, despite having some scenarios where individuals are serofast at very high titers.

And I used to think being serofast was a bad thing, but evidently, it's just plasma cells secreting antibodies. Technically, we’re all serofast with other infections, so being serofast is actually the norm, where our plasma cells continue to secrete antibodies. It's just that we don't usually track those antibodies, whereas in syphilis, we actually do. So again, it's not a bad thing, but it does make it difficult to figure out if it's a new infection or if the person is serofast, and requires some math, where a fourfold increase in titer would signify a new infection. So, the fact that your patient who was likely serofast and an RPR of 1:2 in the past now has an RPR of 1:256, which is much greater than a fourfold increase, signifies a new infection, and is, as you've been saying, definitively positive. So, enough about serofast. Sorry I digressed.

lumbar-puncture**[05:11] Lumbar Puncture?**

Dr. Budak

Do you want to do an LP (lumbar puncture)?

Dr. Kalapila

That was a great explanation, and absolutely, yes, I do want to do an LP. Now, aside from calling the ophthalmologist as mentioned, we're going to do this LP if the patient has a headache. So, the first thing before I do that LP is I'm going to get a noncontrast head CT, and provided that is normal, we can proceed

with the lumbar puncture. I would want all of the usual studies on the CSF (or the cerebrospinal fluid), including a cell count and differential protein and glucose, and in addition to that, I would send off a CSF VDRL [Venereal Disease Research Laboratory]. Now, if there are other infectious considerations on our differential, then we can send off tests for those specific infectious pathogens as well from the CSF, but for the purposes of this discussion today, I just want to focus on neurosyphilis testing.

Dr. Budak

I agree with you that the CSF VDRL, along with a CSF cell count with diff (or differential) protein and glucose are the tests I would want the most. It's important to not anchor, to obtain as much CSF as is safely possible, and ask the lab to store it or hold onto it should we decide later that extra tests are needed. So, let me now share some of his results. His noncontrast head CT was negative and the LP was performed. His CSF cell count had two RBCs (or red blood cells), 25 white blood cells (or WBCs), and the differential on the CSF WBC was notable for 14% neutrophils and 38% lymphocytes. His glucose was 57, protein was 86. The admitting team also sent off a multiplex PCR [polymerase chain reaction], which was negative for several common viral and bacterial pathogens, and the CSF VDRL is pending. His ophthalmology (or ophtho) exam was notable for panuveitis bilaterally, and so with all that data, what are you thinking now, Aley?

Dr. Kalapila

Well, panuveitis are eye findings that are classically associated with ocular syphilis, so given that eye exam, given the elevated CSF white blood cell count and the elevated CSF protein in the context of a positive serological or a serum RPR, I'm confidently making a presumptive diagnosis of neurosyphilis in addition to ocular syphilis as well, and I would initiate treatment for both.

Dr. Budak

Great. So as an aside, let me talk a little bit about ocular syphilis.

ocular-syphilis**[07:30] Ocular Syphilis**

Dr. Budak

Ocular syphilis can occur on its own or in combination with otosyphilis or neurosyphilis. Ocular syphilis, otosyphilis, and neurosyphilis can occur at any stage of syphilis, and symptoms of ocular syphilis can include visual disturbances, or floaters, tearing, pain, or photophobia, and can occur unilaterally or bilaterally. It can involve almost any part of the eyeball, but posterior uveitis and panuveitis, the latter of which this patient had, are the most common exam findings. When an ophthalmologist who has experience in diagnosing ocular syphilis examines the patient and comments on these findings, there's no need for a vitreal sample. The serum syphilis studies with these findings are sufficient. And ocular syphilis on its own, without any neurologic findings, does not warrant a lumbar puncture, and that is because up to 40% of people with ocular syphilis will have a normal LP. I know this patient doesn't have any auditory symptoms, but I should also mention otosyphilis, which can *also* occur at any stage of syphilis, and otosyphilis typically presents with sensor or neural hearing loss, or tinnitus, or vertigo.

Dr. Kalapila

Oh yeah. I had another patient who actually came to me stating that for a week prior to presentation, he had worsening hearing, to the point that he actually could not hear his fire alarm, so definitely have had cases of otosyphilis.

Dr. Budak

And I have had patients present mostly with tinnitus as their predominant manifestation of otosyphilis, but

again, we can see hearing loss, tinnitus, vertigo, et cetera. Similar to ocular syphilis, otosyphilis can be unilateral or bilateral, and also can occur in isolation or in conjunction with other symptoms associated with neurosyphilis. And in the case of otosyphilis, you may need to get an audiology or ENT [ear, nose, and throat/otolaryngologist] evaluation, but this should not delay treatment if your pretest probability is high. And as previously mentioned, individuals with isolated otic or ocular symptoms without other neuro symptoms do not need an LP, as up to 90% of individuals with otosyphilis will have a normal LP. So Aley, back to this case, what if he didn't have ocular symptoms, if he just had that headache and didn't have the visual disturbance and the blurry vision? Would you have thought that he had neurosyphilis?

Dr. Kalapila

Definitely yes. So, even if he didn't have the ocular symptoms, given the headache, a definitively positive RPR, and the CSF findings, I would think for sure that this is neurosyphilis. Now, you know, as you mentioned earlier, neurosyphilis, much like ocular and otic syphilis, can occur at any stage, and the symptoms, really, for neurosyphilis can be variable. You can have a headache, which is without any altered mental status, so I sort of think of that more on the aseptic meningitis kind of a syndrome. You can have cranial nerve dysfunction. You could have symptoms of like a true stroke or acute or chronic changes in mental status. You could see dizziness, or even a loss of vibratory sense. So, there's a myriad of neurological manifestations that can be associated with symptoms of neurosyphilis.

Now, the CSF findings that we would be looking for would be an elevated CSF white blood cell count, which we often refer to as a pleocytosis, and/or you could see an elevated CSF protein, and you might also have a positive CSF VDRL, but the presence of the CSF VDRL is helpful, but the absence is not.

Dr. Budak

So, I think that's a great segue to discuss neurosyphilis diagnostics.

neurosyphilis-diagnostics**[10:51] Neurosyphilis Diagnostics**

Dr. Budak

Let's start with the CSF white blood cell count. Both the HHS [Department of Health and Human Services] opportunistic infections and CDC STI [sexually transmitted infection] guidelines mention that in people with HIV, the CSF WBC can be greater than five at baseline, so using a higher cutoff, such as greater than 20 white blood cells, may improve the specificity of your neurosyphilis diagnosis. But, that the association of CSF WBC and plasma HIV RNA have not been well characterized. Next is the CSF protein, which may or may not be elevated, and in my experience, the glucose is often normal in neurosyphilis.

Dr. Kalapila

So, the tests in the CSF that I primarily rely on are really indirect markers of inflammation. We're talking about the CSF white blood cell count and the CSF protein. Now, for those two specific markers, for this patient, the CSF white blood cell count and CSF protein were both elevated, and so we can take those positive test results in the context of the patient's also positive serum RPR as well as his neurological symptoms as well.

Dr. Budak

Now, Aley, you also mentioned the CSF VDRL, which should be sent when neurosyphilis is considered. CSF VDRL is very specific, provided there's no blood in the CSF, but it lacks sensitivity. Furthermore, depending on one's institution, the test result may take several days to come back.

Dr. Kalapila

Yes. You know, I agree with that. I often make my decision whether a patient has neurosyphilis or not before our CSF VDRL has resulted, so it's helpful. Actually, for me, it takes almost a week for me to get it back at my specific institution, so while having a positive CSF VDRL is helpful to rule in neurosyphilis, oftentimes, treatment decisions may need to be made before that test result is actually available to us.

Dr. Budak

And what about the CSF FTA [fluorescent treponemal antibodies] antibodies test?

Dr. Kalapila

So, for me personally, I will tell you that I really almost never order this test, because it is actually very difficult for me to obtain this at my health care facility. It usually is a send-out test, and so even if I do get it, it's going to take like weeks for the test result to come back. And, so by the time the result is actually available, I've already made the decision to treat or not treat. Now, the CDC STI guidelines do state that the CSF FTA antibody is actually less specific than the CSF VDRL, but it is highly sensitive, with a high negative predictive value. So, with a negative CSF FTA antibody test result, neurosyphilis is highly unlikely. But from a practical perspective, if you have access to it, I think it's reasonable a test to order, especially if you have other diagnostics that have really been unrevealing.

Dr. Budak

Personally, I only send it if I'm on the fence, and as you mentioned, the CDC STI guidelines say that when CSF VDRL is negative but there are clinical signs of neurosyphilis, that you might consider sending off the CSF FTA antibodies. And it's also important to note that for both the CSF VDRL and the FTA antibodies, the CSF should be non-bloody. Otherwise, it will pick up these values from the serum and can be falsely positive.

Dr. Kalapila

Agree. I think the issue that both of us have in common is that these treponemal test results from the CSF often are not available to us, or if available, take a while to actually get a result back on. So, as I mentioned, we're often several days into treatment by the time they actually do come back.

Dr. Budak

And in fact, the CDC STI guidelines state, and I wrote this down because this is so important, that, quote, "Laboratory testing is helpful in supporting the diagnosis of neurosyphilis. However, no single test can be used to diagnose neurosyphilis in all instances," end quote.

treatment**[14:30] Treatment**

Dr. Budak

So back to the case. Several days into treatment, his CSF VDRL titer came back positive with a titer of 1:4, confirming your presumptive diagnosis of neurosyphilis, so what neurosyphilis treatment was he receiving, and did you do something different because he had ocular syphilis as well?

Dr. Kalapila

So, conveniently, you know the treatment for neurosyphilis and/or ocular syphilis and/or otic syphilis is exactly the same, right? So, this is like 10 to 14 days of intravenous (or IV) penicillin G. The antibiotic is usually given as a continuous infusion, although you can use Q4 (every 4)-hour dosing as well, and so this is when I really kind of rely on our very talented and very necessary essential clinical pharmacists. Now, I'm not going to get into the weeds with the dosing, but if you really want to know more details, you can actually look

them up in the HHS opportunistic infections guidelines or in the CDC STI guidelines as well. But the important thing here is that there isn't any additional therapy that's indicated beyond the antibiotics for the management of neurosyphilis or ocular syphilis or otic syphilis. All you have to do is give the penicillin G.

penicillin-allergy**[15:35] Penicillin Allergy**

Dr. Budak

So, what if the patient had a penicillin allergy?

Dr. Kalapila

You know, that's a great question, Jehan. I think it is first of all going to be super important to determine if the patient actually has a true penicillin allergy or not. Mostly because oftentimes, it can be something that was historic, that they were told that they had, but they don't necessarily have that reaction, or the reaction that they describe is not necessarily a true allergy, even though the patient tells you that it's an allergy. So, I think the first thing is to do a little bit of thorough history-taking to determine if the patient actually has a true allergy to penicillin. Now if they do, then you know an alternative option in the CDC STI guidelines is ceftriaxone. Now, ceftriaxone can have cross-reactivity with penicillin, so if you absolutely cannot use penicillin or ceftriaxone, then the other option that you would need to consider in this specific case would be to use penicillin desensitization. Now, this is usually when I really engage with a specialist such as an allergist or a clinical pharmacist to help me determine if the patient has a true allergy, but then also if they do, what are my treatment options for this patient.

Dr. Budak

So, it sounds like if there was a true penicillin allergy and the patient was, let's say, pregnant, sounds like desensitization may need to be the way to go.

Dr. Kalapila

Pregnancy, when you need to treat for syphilis, is definitely a situation where you absolutely need to desensitize. There are no known alternatives to penicillin that have been shown to prevent fetal infection with syphilis, and as you and I both know, our rates of congenital syphilis in this country have been rising over the last several years.

Dr. Budak

Great points, Aley.

monitoring**[17:22] Monitoring**

Dr. Budak

So, let's get back to the case. The patient is on IV penicillin. Any monitoring that should be done during therapy?

Dr. Kalapila

Yes. You know, whenever we put someone on long-term IV antimicrobials, you absolutely need to do sort of toxicity monitoring. And so, in this particular case, I would get a baseline and at least a once-weekly CBC and a CMP to evaluate for any cytopenias or issues with the kidneys.

Dr. Budak

Okay, so he's on penicillin, he's getting the once-weekly CBC and CMP, and he is improving. So, what about any monitoring after that treatment would be complete?

Dr. Kalapila

Well, you know, based on the current guidelines for people treated with neurosyphilis, if the patient has a good clinical and serologic response with the RPR, then a follow-up LP and CSF evaluation is actually no longer necessary as per the 2021 CDC STI guidelines. Now, in this particular case, because the patient is sexually active, I would go back to regular STI screening, including a serum RPR every couple of months, but I wouldn't really repeat the LP based on his history of neurosyphilis, given that he actually has improved. Now, of course, this patient also had ocular syphilis as well, and so ophthalmology may want to follow a patient if someone has symptoms consistent with ocular syphilis, and similarly, if someone had otic syphilis, an ENT or audiology may want to continue to follow up with the patient and do routine and regular evaluations to ensure that their visual and hearing symptoms were getting better.

penicillin-dosing**[18:54] Penicillin Dosing**

Dr. Budak

And then one more question that often comes up in practice, especially after you're done with therapy and we're kind of talking about the wrap-up of his treatment. Do you give any doses of benzathine penicillin intramuscularly immediately after neurosyphilis treatment?

Dr. Kalapila

This is a very controversial topic, and it stems from the fact that the duration of therapy for neurosyphilis is shorter than the duration that's used for late latent syphilis. Now, there's no data, really, as to what exactly to do in this specific scenario, but there are some experts that would recommend administering additional benzathine penicillin intramuscular doses in order to complete a full duration of antibiotics for late latent syphilis. So, in practice, what this would mean is that you would administer benzathine penicillin injections once per week for one to three weeks after completion of IV penicillin G infusion.

Dr. Budak

Yeah, there's a lot of variability in clinical practice for this. I've seen some people not give any additional doses of benzathine penicillin, I've seen others give just one dose, and I've seen others give the full three doses weekly.

So, to wrap up, can you give us an update on how the patient's doing?

Dr. Kalapila

Yes. You know, so as you had mentioned earlier, his headache was improving. He did really well on his IV penicillin, and by the end of treatment, he had full resolution of his headache. He did not actually have complete resolution of his eye symptoms, but ophtho is continuing to monitor him. And with regard to his antiretroviral therapy, he was restarted on his antiretroviral therapy while he was admitted as an inpatient, because this is definitely a situation where we would not want to delay initiation of ART.

Dr. Budak

Great. Glad to hear that he did so well.

summary**[20:34] Summary**

Dr. Budak

So, to summarize some key points, neurosyphilis or otic syphilis or ocular syphilis can occur at any stage of syphilis, and can occur either in isolation or in combination with one another. Isolated ocular or otic syphilis symptoms do not warrant CSF analysis, but CSF analysis should be done for an individual with concern for neurosyphilis. Classic CSF findings in neurosyphilis include a pleocytosis and an elevated protein, and the CSF VDRL is specific, but not sensitive, and a negative test should not exclude a diagnosis if a compatible clinical syndrome is present along with a positive serum RPR. Treatment of ocular, otic, or neurosyphilis is IV penicillin for 10 to 14 days, and monitoring after treatment should include clinical and serologic testing for syphilis, but routine repeat LPs with CSF testing is not needed for follow-up. And then last, antiretroviral therapy can be started immediately, and should not be delayed regardless of neuro, oto, or ocular syphilis.

So, with that, thank you, Aley, and we'll chat more next time.

Dr. Kalapila

Thanks, Jehan. Bye, everyone.

credits**[21:39] Credits**

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