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Case Discussions

National HIV Curriculum Podcast

Evaluation of a Headache in Advanced HIV

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National HIV Curriculum Podcast Editors Dr. Jehan Budak and Dr. Aley Kalapila discuss an approach to working up a headache in a patient with a CD4 count less than a 100.

Topics:

- Headache
- OIs and HIV
- syphilis
- meningitis
- HIV

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Transcript

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introduction**[00:00] Introduction**

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 with my colleague Aley Kalapila, an ID physician at Emory University in Atlanta. Hi, Aley.

Dr. Kalapila

Hi, Jehan, and everyone listening. I am excited to be here and to do this. This is our inaugural National HIV Curriculum podcast, and Jehan and I are going to be going through the diagnosis, management, and treatment of different opportunistic infections.

case-intro**[00:40] Case Intro**

Dr. Budak

And in this episode specifically, we will be discussing a case that Aley saw of a person with HIV with headache. And we all know that headache is a very common symptom in pretty much anyone. And the differential diagnosis in persons with HIV can vary drastically based on their CD4 count. So our goal today is to discuss and approach the evaluation of a person with HIV and headache, and we will actually discuss treatment and management during a later episode. So with that, let's dive into this case.

So, it's a 28-year-old man, newly diagnosed with HIV, with a CD4 cell count of four, who comes to clinic with one episode of emesis and two weeks of throbbing headache, photophobia, blurry vision, and nausea. He's from Atlanta, endorses no recent travel, has sex with men only, has a longstanding partner, and was last sexually active one week ago. His exam is unremarkable, vital signs are normal, and he has a nonfocal neuro exam.

Aley, can you take me through what's going through your mind regarding possible diagnoses when this man walks through the clinic door?

Dr. Kalapila

Absolutely. So, I think the first thing that I focus on in this case was his CD4 count, which is very, very low. So immediately I'm thinking that almost every opportunistic infection is fair game here, right? Because this is a very immunocompromised host. Now, more generally, this is a patient who is sitting in front of me in clinic, he seems afebrile, he's mentating appropriately, he's able to answer questions. He's not complaining of any neck stiffness or meningismus. So this actually does lead me away from things like bacterial meningitis caused by strep pneumo or *Neisseria meningitidis*, where we would expect someone to have a much more acute presentation where they look a lot sicker. Because typically those patients do tend to present with fever, headache, altered mental status, nuchal rigidity, and photophobia for instance.

Other pathogens that I often think about when I go through my neuro infection workup are HSV [herpes

simplex virus]. So, basically HSV would cause a meningoencephalitis. Again, this patient is not really showing signs of encephalitis. He doesn't really have altered mental status, he doesn't have seizures, there's no focal deficits, so, that too would be a little bit lower on my differential. So, of course, with him, he's got blurry vision, he's vomiting, he's been nauseous, and this has been going on for a few weeks, so we're thinking a little bit more subacute. And, of course, the big things that I would worry about with these symptoms is that he has elevated intracranial pressure (ICP). And of course then when I think about elevated ICP in a patient with advanced HIV and a CD4 count less than 100, the big thing that I would think about would be cryptococcal meningitis.

Now, obviously to round out the differential, I need to think about other things that could cause maybe subacute presentation. So syphilis would be one. Toxoplasmosis maybe. And then of course a brain mass. So again, someone with advanced HIV, you would think about primary CNS [central nervous system] lymphoma or even a brain abscess. But again, headache, blurry vision, nausea, vomiting, subacute presentation, CD4 count less than 100: always, always, always think about cryptococcal meningitis. And of course, because of these symptoms that he's having, because of that CD4 count, he absolutely needs urgent brain imaging and a lumbar puncture as well.

Dr. Budak

Right. So, you mentioned urgent brain imaging, and I think it's just important to reiterate that having a CT head before getting an LP [lumbar puncture] is critical because the differential is broad. And then we also need to rule out an intracranial pathology that can cause an elevated intracranial pressure, which could then place the patient at risk for brain herniation. So, thank you for bringing that part up.

need-opening-pressure**[04:12] Need for Opening Pressure**

Dr. Budak

So, this patient was then admitted from clinic and this is not the patient to send home. This is definitely the patient to admit. And it sounds like on the inpatient service he gets a CT head, which is unremarkable, and an LP is done. When you have somebody with a CD4 count less than 100 who needs an LP, what's an absolutely can't miss point that we should convey?

Dr. Kalapila

Yeah. So, the absolutely can't miss point that I want to emphasize here is the opening pressure (OP). You absolutely must get that opening pressure. And the reason is that the opening pressure is actually a surrogate measure of an intracranial pressure. Now, in order to obtain an accurate opening pressure, and this was something that I learned the first time I did an LP in residency, is that you need to actually have your needle entry point at the same level as the midline of the spine, which should also be at the same level as the head of the patient. So, I'll tell you that I used to like doing LPs with patients sitting up, you can't do that when you want to measure an opening pressure because it'll artificially elevate the opening pressure. Also, even if you remotely try to tilt the head of the bed or put the patient's head on a pillow, all of those can actually artificially increase the opening pressure. So the patient should be lying completely flat in a lateral decubitus position in order for you to get an accurate opening pressure measurement.

Dr. Budak

This just happened to me on service, where I was called to the bedside to help someone regarding how to take and how to obtain an opening pressure, including putting the manometer together onto the 3-way stopcock, watching the CSF [cerebrospinal fluid] rise, and then waiting for it to stop rising, and that is the point in which we measured the opening pressure.

four-buckets-approach**[5:49] Four Buckets Approach**

Dr. Budak

So, back to this case, his opening pressure was 33 centimeters water, and as a reminder, a normal opening pressure is between 7 and 18. So, this means that this patient's OP was markedly elevated. What other CSF or basic lab studies is your team sending at this time?

Dr. Kalapila

So, after obtaining that opening pressure, you've gotten your CSF. So, I would send out for a typical studies first, right? So, your cell count, your differential, protein, and glucose. And then, there's a lot of things going through my mind at this point in time and there's a lot of pathogens that I would be thinking about that would be causing his presentation. So, to be systematic about it, and this is how I work through it when I'm working with my learners, when I'm on service, I like to organize my differential diagnosis by looking at bacterial, viral, fungal, and protozoal etiologies that could be driving his presentation. Because when I think about it in that way, then it systematically helps me determine what tests I should order.

Dr. Budak

I love that you're organizing this by bucket. Bacterial, viral, fungal, protozoal. Do you mind taking us through each of the studies you're sending for each of these buckets?

bacterial-testing**[07:00] Bacterial Testing**

Dr. Kalapila

Yeah. So let's start off with bacterial because I think that that's the easiest. So, I'd mentioned earlier that he was afebrile, no meningismus, he's mentating normally. So, like we said before, my suspicion for typical bacterial etiologies is going to be a lot lower here. I don't think this guy has pneumococcal meningitis or meningococcemia. But, sending off a bacterial culture of the CSF is pretty easy. And even fungal etiologies, like what we were thinking about here, fungal organisms like crypto will actually grow on bacterial culture. So, I think it's very reasonable to send off a CSF bacterial culture.

Dr. Budak

And earlier you mentioned that syphilis was also on your differential, so I'm guessing that you're going to send off a CSF-VDRL [CSF – venereal disease research laboratory test], which will probably be a podcast in and of itself.

Dr. Kalapila

Yeah. Syphilis is in the bacterial bucket. It is something to always consider. It can certainly present with kind of subacute neurological symptoms, and it is something that I think a lot of people sometimes might ignore, you know, and this is something that I always, again, talk about when I'm on service. Syphilis is a great imitator. Neurosyphilis can present at any stage of syphilis, and this patient certainly could be at risk for syphilis acquisition, and so his CSF needs to be tested for neurosyphilis by sending off a CSF-VDRL.

Dr. Budak

And Aley, I think that there's another big bacteria that's in your bacterial bucket. Can you chat about that?

Dr. Kalapila

Yeah. So mycobacterial etiologies, of course, I always have to think about now. Again, this patient he's not from an area where TB is endemic. He didn't endorse any travel to a TB-endemic region, but it is always

something that I keep at the back of my mind. Because we do know that for patients who have a history of being exposed to TB in the past when you have HIV infection, and particularly when your CD4 count is low, you can reactivate that TB and you can get TB meningitis. And TB meningitis can also have a subacute presentation. So, I'm not obviously going to get into too much detail here about TB meningitis, but if that is on your differential, then you would want to send off your CSF for an AFP [acid-fast bacilli] culture and also an MTB [*Mycobacterium tuberculosis*] PCR as well.

viral-testing**[09:10] Viral Testing**

Dr. Budak

And then your next bucket was viral.

Dr. Kalapila

Right. So, let's talk about viral etiologies here. So at our hospital right now, we can do a BioFire, which is actually a multiplex PCR platform, and it looks for a broad range of bacterial, viral, and even fungal pathogens as well. In my mind, I think about the BioFire as being most useful for bacterial and viral etiologies. So its official term is BioFire FilmArray Meningitis/Encephalitis panel PCR test. So lots of words here. It will test for all of our herpes viruses. It can test for common bacteria like pneumococcus that could cause a meningitis picture. And it can actually also test for cryptococcus. But I think the point that I want to make here is that BioFire is for fungal pathogens and particularly for crypto. It can have false-negatives, especially when the organism burden is low. So a negative BioFire doesn't rule out cryptococcal meningitis if that's on your differential.

Dr. Budak

And we don't have the CSF BioFire here. So could you talk about what studies people should send if they don't have access to that test?

Dr. Kalapila

So, actually when this patient had initially presented, this is a few years now, we didn't have BioFire available. So if you didn't have that BioFire available, probably the most common things that you would want to be sending off would be for your herpes viruses. Now, again, and so, of course, HSV PCR I think would be the most common one that you would want to send off. And we sent that off. It's an easy enough test to send off. Again, my suspicion for HSV meningoencephalitis was exceedingly low for this patient. Other herpes viruses that could cause problems in profoundly immunocompromised hosts. So you would think about things like VZV [varicella-zoster virus] or CMV [cryptococcal meningitis]. But again, this patient did not have a classic presentation that I would associate for say CMV encephalitis or VZV encephalitis, and so I didn't send off for those specific herpes virus PCRs.

fungal--protozoal-testing**[11:08] Fungal & Protozoal Testing**

Dr. Budak

And then the next bucket that you had mentioned was fungal.

Dr. Kalapila

Yeah, so as you know, we talked about suspicion for cryptococcal meningitis was very, very high. So, I actually asked for an India ink, which we still do at the hospital system that I work at. And then pertinent to crypto, the other studies that I had sent off were a cryptococcal antigen off the CSF, which we also commonly call a CrAg. And then we also send off a CSF fungal culture as well.

And then, finally, in the last bucket of organisms is the protozoal causes. So, for a patient with HIV and a CD4 count less than 100, the big thing that would cause neurological manifestations for someone with that CD4 count would be toxoplasmosis, so this, of course, is if someone has a prior history of being exposed to toxo. You would determine that by testing for a serum toxo IgG. Now if that was positive, it means that the patient has been exposed to toxo before, and when the CD4 count drops to below 100, that toxo (the cysts) can actually reactivate and it can cause encephalitis, which typically can manifest with seizures, fever, altered mental status, et cetera. So, if toxoplasmosis is on your differential, then you would want to send off a CSF toxo PCR as well.

Dr. Budak

Right. So that's everything you send from the CSF.

serum-studies**[12:28] Serum Studies**

Dr. Budak

What about serum studies? What should people be sending?

Dr. Kalapila

So, this patient was new to the clinic, right, so I would send off all the typical labs that you would want to do for someone with newly diagnosed HIV. But specific to this presentation I always start with a CBC and a comprehensive metabolic panel, because it does help me to know if the patient has cytopenias, if he has any baseline renal or hepatic dysfunction, because inevitably much of the medications, be it antibacterial, antiviral, antifungal that we're going to throw at this patient almost overwhelmingly will likely affect one of these large organ systems. And then of course, let's talk about other serological infectious disease workups. So, we just talked about toxo. So yes, I do want to send off a serum toxo IgG. We talked about syphilis. So I'm either going to send off a syphilis IgG or an RPR, and of course that can vary based on the syphilis-testing algorithm at your specific hospital system. And then we talked about crypto, so I would want to send off a serum cryptococcal antigen or the serum CrAg.

interpreting-results**[13:30] Interpreting Results**

Dr. Budak

And, in addition to diagnostics, speaking of other things that you all did, you also asked for an ophtho consult. And my guess is that's because this person had advanced HIV and photophobia and blurry vision. And so, luckily, their exam was pretty unremarkable. It showed nonspecific cotton wool spots. A retinal scan did not have any retinitis, and there was no concern for papilledema. And then you started getting some results. CSF showed 17 white blood cells, 85% of which were lymphocytes, zero RBCs, which was a very nice tap. A glucose of 39 and a protein of 111. What do you make of that?

Dr. Kalapila

So, we already know that the patient had an elevated opening pressure, which is very suggestive, right, of a high intracranial pressure, and now you have that CSF white blood cell count. So both of those results combined, to me, it's very concerning for cryptococcal meningitis. So, there's one very important point that I do want to emphasize here, which is that the CSF findings for people with cryptococcal meningitis can actually be quite variable. So, about 40% of patients with crypto can have normal CSF profile, so this means that their white blood cell count in their CSF is pretty low. If they do have cells in their CSF, it'll be predominantly lymphocytes. You may see a higher white blood cell CSF count or CSF white blood cell count, sorry, if they're on antiretroviral therapy. The CSF glucose level may be low or normal, and the CSF protein level can sometimes be elevated.

Dr. Budak

I'm so glad you mentioned that the CSF findings are super variable or can be variable. And for somebody with a CD4 cell count of four, I'm actually surprised that his CSF white blood cell count was as high as it is at 17, because oftentimes we see single digit CSF white blood cells in cryptococcal meningitis, especially when someone's T-cell count is as low as his.

Dr. Kalapila

Yeah. You're absolutely right. And I was, to be frank, quite surprised with that white blood cell count in the CSF as well. And this is definitely a teaching point that I have to make over and over again whenever I'm on service to my learners. Because I can't tell you the number of times when an LP result becomes available and crypto is on the differential and people see a very bland CSF, either no cells or low CSF white blood cell count, and my trainees are like, \"Yay, he doesn't have crypto.\" And I'm like, \"No, no, no, no, no! This is actually the patient that you should be the *most* worried about because this is what we usually see for cryptococcal meningitis." And it is actually not a good prognostic sign because this is exactly the type of patient that when you get started on an antiretroviral therapy, especially if you're not treating them adequately with antifungals beforehand. These are the patients that are going to reconstitute and they will reconstitute quite badly and they can have a pretty profound crypto IRIS [immune reconstitution inflammatory syndrome] that can result in pretty significant morbidity and mortality. So yeah, very, very important point to make.

Dr. Budak

And then this person's serum and CSF CrAg come back at greater than 1:512. What do you make of these results?

Dr. Kalapila

Yeah. So this pretty much confirmed what we had been discussing right from the very get go, which is that based on the clinical presentation, his CSF findings, his opening pressure, and now of course we have a serum and CSF CrAg that are both floridly positive. This confirms what we suspected all along, which is that this person does indeed have cryptococcal meningitis.

india-ink--crag**[16:56] India Ink & CrAg**

Dr. Budak

And can you talk a little bit more about the CrAg and then also the India ink, which you mentioned?

Dr. Kalapila

Yeah. So we get the CrAg and the India ink after we get the cell count, protein, glucose. So, the India ink is actually a stain. It's a suspension of carbon black particles. And the suspension can't really penetrate the capsule of the *Cryptococcus* so it looks like the organism has like a clear halo around it. We use it at our hospital system, but not many health systems may have it. And the sensitivity is only about 80% so it is actually a lot less sensitive than the cryptococcal antigen of the CrAg. And if a patient has a low organism burden, then the sensitivity is actually lower. And then of course after your cell count and the India ink stain that, if it was done, then the CrAg is the next test to come in. So this is a lateral flow assay (LFA) and it is a point of care test. And what it does is that it actually is responsible for detecting the polysaccharide capsule of the cryptococcal organism by using anti-cryptococcal antibodies against the capsule of the *Cryptococcus neoformans*. And the sensitivity and specificity of this test is over 90%.

Dr. Budak

And I think a really interesting point about the CrAg is worth mentioning that rarely if the burden of disease is really high, that you can get a false-negative result with the CrAg LFA and that's because high cryptococcal antigen loads can interfere with the antigen antibody complex, producing false-negative results. And many of us may think of this as a prozone similar to what we see in syphilis, but it's actually a postzone here. So, there's an umbrella term called the high-dose hook effect that refers to both prozone and postzone. And prozone is actually regards antibody excess, whereas postzone is about an antigen excess, and so, since a false-negative CrAg is a result of high concentrations of capsular antigen, postzone is a more appropriate term if you see this in *Cryptococcus*. So, if you have a high clinical suspicion and see a negative CSF CrAg, then you should ask the lab to dilute the sample and repeat the assay. But, that was not necessary in this patient's case.

Dr. Kalapila

Yeah, so you know, he had the positive serum cryptococcal antigen, he had the positive CrAg so to me that confirmed his diagnosis. But not surprisingly, a few days later, his CSF fungal cultures also ended up growing *Cryptococcus*. So, of course, this is the gold standard to diagnose cryptococcal meningitis. But, you know, cultures can take a few days to come back and you really do not want to be delaying antifungal therapy, particularly because of serum and the CSF CrAg results will come back much, much faster.

teaching-points**[19:32] Teaching Points**

Dr. Budak

Now that we've talked to the initial evaluation of a person with HIV with a low CD4 count and a headache, to wrap up, just wanted to highlight some teaching points. That first, cryptococcal disease is an opportunistic fungal infection that can actually cause high morbidity and mortality in people with HIV with severe immunocompromise. And typically we'll see this in someone who's got a CD4 count less than 100. That patients with cryptococcal meningitis typically present with subacute to chronic progressively worsening headache, like in this case. And depending on the duration, may also have symptoms of an elevated ICP or intracranial pressure. That *everyone* with suspected cryptococcal meningitis and/or a positive serum cryptococcal antigen should undergo an LP, and opening pressure should be obtained. And, as we saw in this patient's case, a high OP is extremely common in crypto meningitis and is actually thought to be due to the cryptococcal yeast cells gumming up any sort of potential outflow of CSF or any resorption of CSF, and so this is kind of why the fluid backs up, builds up and can lead to the symptoms we saw in this patient. As Aley pointed out, to not be falsely reassured by a low CSF white blood cell count when cryptococcal meningitis is on the differential, and that the diagnosis is typically made with a CSF CrAg and by growing *Cryptococcus* yeast in CSF culture.

closing**[20:56] Closing**

So, in the second part of this episode, we will pick right back up to discuss treatment and other management considerations in a person with HIV and cryptococcal meningitis. And Aley, thank you so much for sharing your expertise with us and being our discussant today.

Dr. Kalapila

Thank you. I'm looking forward to part two.

credits **[21:15] Credits**

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