Case Discussions

National HIV Curriculum Podcast

Toxoplasma Encephalitis: Management

May 7, 2024

Season 1, Episode 9

National HIV Curriculum Podcast Editors Dr. Jehan Budak and Dr. Aley Kalapila discuss the diagnosis and treatment of toxoplasma encephalitis, potential side effects, and when to start or restart HIV antiretroviral therapy.

Topics:

- OIs and HIV
- toxo encephalitis
- trim-sulfa

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Disclosures
Disclosures for Jehan Z. Budak, MD
None

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Disclosures
Disclosures for Aley G. Kalapila, MD, PhD
None

Transcript

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In this episode:

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

Dr. Kalapila

Hi, Jehan. Hi, everyone listening. Looking forward to picking up where we left off.

Dr. Budak

And, in our last podcast, we had discussed the evaluation of a patient with advanced HIV who had been off ART [antiretroviral therapy] for a few years, whose last recorded CD4 count was 90, who presented with a subacute headache, nausea, and focal cerebellar symptoms, ring-enhancing lesions on head imaging and herniation, and a positive toxo IgG [toxoplasma immunoglobulin G], and so was felt to have a presumptive diagnosis of toxo encephalitis. And, whereas last time we focused on diagnosis, in this episode, we are going to talk a little bit more about the management of toxo encephalitis. And, as a reminder for our listeners, *Toxoplasma gondii* is a protozoal parasite that humans can be exposed to via accidental ingestion, and once ingested, those latent cysts can form primarily in the brain, heart, and skeletal muscle, and some other places too. But in patients who are immunocompromised, and specifically in persons with HIV whose CD4 drops below 100, who are not on appropriate prophylaxis, the cysts can reactivate and cause disease, which typically, in this patient population, presents as encephalitis. So, enough background. Let’s move forward.

why-presumptive-diagnosis**[01:36] Why Presumptive Diagnosis?**

Dr. Budak

Listeners may have noticed I had said that this patient had a *presumptive* diagnosis of toxo encephalitis. Aley, can you speak to that word choice of mine?

Dr. Kalapila

Yes. So, our treatment is empiric or presumptive, exactly like you said. So, if you’ve noticed, we don’t actually have a confirmed microbiologic diagnosis. We have indirect signs. So, the indirect signs that this patient has toxo is that he has a positive serum toxo IgG. We have imaging findings showing ring-enhancing lesions, and we have a clinical presentation and symptoms that is also congruent with toxo encephalitis. We don’t typically do a definitive diagnosis for toxo because the gold standard for this is to actually visualize the organism on path [pathology] so that would mean a brain biopsy, which is incredibly invasive. So, because of that, the Opportunistic Infection (OI) Guidelines do recommend that we initiate presumptive treatment based on clinical manifestations, which this patient had; positive serum toxo IgG, which this patient had; and also suggestive imaging finding, also which this patient had, in a person with HIV with a CD4 count less than 100, which was this patient.

acute-presumptive-therapy**[02:47] Acute Presumptive Therapy**

Dr. Budak

And can you take us through the presumptive treatment that we should be starting?

Dr. Kalapila

Yeah, definitely. So, the treatment is actually divided up into two stages. There's an initial acute phase of treatment, and then there's actually a chronic maintenance phase. Now, the initial acute preferred treatment regimen consists of three drugs, so you have pyrimethamine, sulfadiazine, and leucovorin (lots of words). So the leucovorin is actually a folate analog that we have to give along with the pyrimethamine to prevent any sort of severe hematologic toxicities. So, the drugs that are really kind of doing the heavy lifting in the acute treatment of toxo is pyrimethamine and sulfadiazine. Now, the biggest problem with this specific regimen at the moment is that pyrimethamine is extremely expensive in the U.S. There is a company that acquired the marketing rights to this drug, and after they got the rights, they majorly hiked up the price. So, I'll tell you that when we first saw this specific patient that we're discussing in this case, we were able to get pyrimethamine in the hospital. Today, the same patient, we would not be able to get pyrimethamine in our hospital system, primarily because of the price. And, the OI Guidelines do speak to this. They acknowledge that it is difficult for certain facilities to maybe get access to pyrimethamine, and so they give you an option of using high-dose trimethoprim-sulfamethoxazole, which I'll sort of abbreviate as trim-sulfa. You have to dose the trim-sulfa based on weight, and so you can actually use trim-sulfa if you can't get pyrimethamine right away or there's a delay in getting pyrimethamine.

Dr. Budak

And for those of you wondering if trimethoprim-sulfamethoxazole is as good as pyrimethamine-containing regimens, there is a paper I'm going to talk about. So, there was a nice meta-analysis in *Clinical Infectious Diseases* from 2023 from Connor Prosty and colleagues that looked into this. So, in the meta-analysis, they looked at six randomized control trials and 26 observational studies of approximately 2000 persons with HIV who received toxo encephalitis treatment, and they found that trim-sulfa appeared to be as effective as pyrimethamine-containing regimens and had less toxicity. So, although many of us were already using trim-sulfa as an alternative, it was reassuring to have some data about those practices.

And, going back to this patient, Aley, you mentioned that because it was a couple years ago, you were able to start pyrimethamine, sulfadiazine, and leucovorin. Can you take us through kind of what happened?

Dr. Kalapila

Yeah, so as I said, we were able to obtain pyrimethamine, sulfadiazine, leucovorin, and that's what he got, and we initiated the acute treatment with this. I monitored him for about two weeks until we had follow-up imaging. Now, because our treatment is empiric, it's ideal to have a repeat MRI brain in two weeks to see if there's a clinical response. And if it's toxo, then 90% of our patients will have a good clinical response by then. Now, depending on the extent of the brain lesions, for instance, in this case he had extensive lesions on MRI, you may not see full resolution, but that's okay. The radiologist will still say that there's at least regression or improvement in the lesions compared to your imaging findings at the start of your diagnosis of toxo.

Dr. Budak

And in your practice, do you keep the patient hospitalized for those initial two weeks of the acute treatment?

Dr. Kalapila

I tend to. I mean, again, I would say that there is no one size fits all approach, and I think you really have to decide what is best based on your patient's circumstances. Oftentimes, the patients that we take care of have

many social barriers that might make adherence to medications difficult, it's a lot of pills for people to take. And, we know that the neurological consequences of untreated or undertreated toxoplasmosis can be devastating. So, in this specific case, just to err on the side of caution, I kept him in the hospital for those first two weeks of the acute treatment phase.

Dr. Budak

If you could remember back when you were taking care of this patient, did you and your team consider steroids for him based on the mass effect and herniation?

Dr. Kalapila

Yeah, that's a great question. So, I'll tell you without getting too much in the weeds, but in this specific case, our patient had numerous other comorbidities that actually precluded the use of steroids. But the OI Guidelines also speak to this. They do state that you can use adjunctive steroids, corticosteroids in toxo encephalitis to treat mass effect associated with focal lesions or edema. But they also say in an ideal world, you want to discontinue it as soon as possible because in the long run the steroids can actually make immune reconstitution challenging.

radiographic-results**[07:23] Radiographic Results**

Dr. Budak

So, in this case, the patient remained in the hospital while receiving his therapy, did not get steroids because he had other things going on that precluded its use, and after two weeks, you did an MRI, which showed marked improvement. The ring-enhancing lesions were still present, but smaller, but the midline shift and cerebellar tonsillar herniation had mostly resolved. But, Aley, what would you have done if there was no radiographic improvement at that 2-week point or the patient continued to decline, despite your initiation of empiric toxo treatment?

Dr. Kalapila

Yes, this is definitely something that I've dealt with. I know you have too. So, as we said, about 90% of people with toxo encephalitis have clinical improvement after 14 days. Now, if there was no improvement, then I would be very concerned because what this means is that there's a diagnosis that I'm missing. So, we went through the initial work up. We went through this broad differential and because this patient has advanced HIV, low CD4 count, there's a lot of other organisms that can cause these mass lesions. And so now, at this point, I would want a more definitive diagnosis and so this is where I would get neurosurgery involved to do that brain biopsy to see what the pathology is because the bottom line is that I'm not going to be able to empirically add an antibiotic to treat all of the other organisms that I'm considering on my differential diagnosis for mass lesions in a patient with advanced HIV.

Dr. Budak

Okay. So luckily, that was not the scenario in this patient. He actually did have improvement on his MRI after two weeks of treatment, so what did you all do for him next?

Dr. Kalapila

So, with that improved MRI, in my mind, we had now unofficially confirmed his diagnosis of toxo encephalitis. So, now we can continue with the acute treatment, and the recommended duration for acute treatment is at for at least six weeks, and this is the recommendation in the OI Guidelines. So, around the 5- to 6-week mark, I would actually repeat imaging again, so I would repeat an MRI to determine if I should prolong his acute therapy for more than six weeks. Now, you may want to consider doing a longer course if there's extensive

clinical or radiologic disease, and you don't have a great response by the 6-weeks point. So, you want a minimal six weeks of therapy for acute treatment but you can prolong it longer based on clinical and radiographic resolution.

resolution-vs-improvement**[09:41] Resolution vs Improvement**

Dr. Budak

And there was actually a paper in 2023 that came out that you and I have talked about that kind of gets at this very issue. It was in *Open Forum Infectious Diseases*, by Benjamin Coleman and colleagues and it was a retrospective study looking at 24 people with HIV with toxo encephalitis. And in that study, though the vast majority of them had substantial improvement in their MRIs, only four had complete resolution, and that was lower than I had expected. So, to your point, Aley, and based on this paper, it's actually somewhat rare to get full resolution of lesions and really what one is looking for is improvement, not resolution.

Dr. Kalapila

So, for our listeners, that's a really key point that you may not get full resolution of lesions but you want to see marked improvement compared to the imaging that you obtained at the time of your initial diagnosis.

chronic-maintenance-therapy**[10:24] Chronic Maintenance Therapy**

Dr. Budak

And once your patient has demonstrated an appropriate clinical and radiologic response, what do you do next?

Dr. Kalapila

So, once you complete your acute therapy, then you move onto the second phase of toxo treatment, and so that is your chronic maintenance therapy. The preferred maintenance therapy regimen that we would use is typically pyrimethamine, sulfadiazine, and leucovorin, again, but you're going to use these drugs at a lower dose compared to what you used for acute treatment. But, as we mentioned previously, if pyrimethamine is not available or easily accessible, then you could use trim-sulfa instead, again, at a lower dose compared to what you used previously for acute treatment.

Dr. Budak

And, Aley, I don't know about you, but I'm typically using trim-sulfa at this point, even if I've used pyrimethamine, sulfadiazine, and leucovorin up front.

Dr. Kalapila

Yes, absolutely, and a lot of that is because of the duration, right, of chronic maintenance therapy. Because we want to continue chronic maintenance therapy until the patient no longer has signs and symptoms of toxo encephalitis, until they have a sustained increase in CD4 count to greater than 200 for at least six months or more on combination antiretroviral therapy. So, at this point, you are having to use chronic maintenance therapy for a minimum of six months and sometimes longer, often longer, and, because of the price of pyrimethamine, more often than not most of us would actually flip to using trim-sulfa at this point for chronic maintenance therapy. Now, the other point to kind of mention about chronic maintenance therapy is that some experts would recommend full resolution of brain lesions, but, as you and I both discussed and also in this paper that we talked about, this may not actually always be feasible.

starting-art**[12:10] Starting ART**

Dr. Budak

And then kind of shifting gears a little bit, when would you start, or in this patient's case, re-initiate ART?

Dr. Kalapila

Another great question. Not a lot of great data about the optimal time to initiate antiretroviral therapy in a patient with toxo encephalitis, but OI Guidelines typically recommend 2 to 3 weeks post-acute treatment initiation.

Dr. Budak

You and I both tend to err, I know, on the shorter end of this, as toxo IRIS [immune reconstitution inflammatory syndrome] is rare, but we can always modify based on imaging, and this is a patient in whom I think waiting the two weeks before starting ART makes sense, because that brain herniation on imaging at baseline was *so* profound. Aley, when did you end up starting him on ART?

Dr. Kalapila

Yeah, like you said, based on that brain imaging alone, I waited for two weeks, and it might have been two, two-and-a-half weeks by the time we kind of got his care coordination and got him safely discharged out of the hospital and linked to outpatient HIV care, so I would say between the 2- to 3-week mark is when we initiated antiretroviral therapy.

sulfa-issues**[13:12] Sulfa Issues**

Dr. Budak

And so, moving on, another common clinical scenario with toxo treatment is either that the patient has a sulfa-allergy precluding the use of sulfadiazine or trim-sulfa or they have experienced a sulfa-toxicity. Are there alternative medications you can use for toxo encephalitis treatment if you get into trouble with one of these?

Dr. Kalapila

Yes, the guidelines definitely have some clear recommendations on this. So, for both acute and chronic treatment, if you cannot use sulfa drugs then you have an option to use pyrimethamine, leucovorin, and clindamycin or you can use atovaquone on its own or you can use atovaquone combined with pyrimethamine and leucovorin. I'm not going to get into sort of the nitty gritty of like dosing and frequency because it's rather involved. I will say that if our listeners were to go to the Opportunistic (OI) Guidelines section on toxo, or our National HIV Curriculum (OI treatment module), you'll see some nice tables there that actually get into the details of dosing of these specific drugs.

side-effects**[14:10] Side Effects**

Dr. Budak

And then, talking about the toxicity, you actually got me thinking about side effects. To kind of wrap up this podcast, can you take us through some of the common medication side effects we see with these treatments?

Dr. Kalapila

Yeah, so pyrimethamine—not a side effect, but it is very expensive. Side effects-wise, it can cause nausea and vomiting. It can cause a bone marrow suppression if you're not going to give it with leucovorin. Sulfadiazine can cause a rash. It can cause also leukopenias and it can also cause crystalluria, as well.

Dr. Budak

Oftentimes I feel like in the initial two weeks, most commonly I am dealing with cytopenias when I start someone on a pyrimethamine-containing regimen, and then even if I have somebody on a sulfa, the trim-sulfa regimen. What about side effects from that and some other options?

Dr. Kalapila

Yes, so just like you said, so with trim-sulfa you can see leukopenia, and the most common cytopenia I see is neutropenia. Trim-sulfa's a sulfa drug: you can get a mild rash. On the more severe spectrum, granted this is rare, you can see Stevens-Johnson syndrome, but that's rare. You can definitely see renal dysfunction with trim-sulfa, hyperkalemia. You can see hepatitis or transaminitis, as well. Now, atovaquone, in my clinical experience, doesn't have a ton of common side effects. Probably the most common thing or the thing that patients complain about it when I prescribe atovaquone is that it tastes really bad.

Dr. Budak

I've heard that too.

summary**[15:30] Summary**

Dr. Budak

Okay, well, let's wrap up with a summary of some key points, I scribbled some of these down, that I think we really should make sure that everyone takes away from this.

1. So, first I would say that the treatment of toxo encephalitis is divided up into two stages, an acute phase and a chronic maintenance phase, which consists of the same medications, just at lower doses.

2. That the preferred treatment Aley took us through is pyrimethamine with sulfadiazine and leucovorin, but the cost of pyrimethamine often makes this regimen less feasible, in which case trimethoprim-sulfamethoxazole should be used, which is I think what a lot of us end up using.

3. That if within 14 days of acute treatment initiation, there is no clinical and radiologic improvement, then brain biopsy should be considered to ensure that toxo encephalitis is the correct diagnosis. But, if on the other hand, there is improvement after 14 days of treatment, then the acute treatment phase can be continued for at least six weeks, and then the patient can switch to the chronic maintenance phase and take that until they've had immune reconstitution once, presumably, you've started that ART.

4. And then, probably the last thing to reiterate is that ART can be initiated within 2 to 3 weeks of toxo encephalitis diagnosis.

So, with that, I just want to say thank you, Aley, for taking us through that and I look forward to our next OI podcast.

Dr. Aley

Thanks, Jehan. See you soon.

credits**[16:57] Credits**

Transcripts and references for this podcast can be found on our website, the National HIV Curriculum at www.hiv.uw.edu. The production of this National HIV Curriculum podcast was supported by Grant U10HA32104 from the Health Resources and Services Administration of the U.S. Department of Health and

Human Services. Its contents are solely the responsibility of the University of Washington IDEA program and do not necessarily represent the official views of HRSA or HHS.