

## **Neurologic & Ophthalmologic Complications**

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George Siberry: Hi. My name is George Siberry, and today I'm going to speak to you about neurologic and ophthalmologic complications of pediatric HIV infection. The objectives of this talk are to review the range of neurologic and ophthalmologic complications in HIV infection in children, and to contrast the neuro-ophthalmologic complications seen in HIV infected children to those seen in adults.

The spectrum of central nervous system disorders associated with pediatric HIV infection range from opportunistic infections of the central nervous system, neoplasms, cerebral vascular disease, including stroke; and HIV encephalopathy.

Opportunistic infections occur in HIV infected children in the central nervous system, but they occur much less frequently than they do in adults. This is primarily because most of the opportunistic infections of the central nervous system that occur in adults are a reactivation of long-standing, latent disease in the adults. For similar reasons, when these infections do occur in the pediatric age range, they tend to occur in older children and adolescents.

Typically, these opportunistic infections occur only in those children and adolescents with severe and, often, long-standing immunosuppression. One special feature of pediatrics is the possibility of these same opportunistic infections causing congenital infections. In fact, toxoplasmosis, cytomegalovirus, and syphilis are all infections that can occur in the neonate transmitted from the mother, whether the neonate has HIV infection or not.

We'll start with cytomegalovirus as an example of an opportunistic viral infection in the central nervous system. Again, congenital cytomegalovirus in HIV infected newborns, in HIV exposed newborns, and in newborns born to entirely healthy mothers. So, this is something that can be seen, generally, in newborns.

Related specifically to HIV infected children, CMV can also cause a subacute, or chronic, encephalitis or ventriculitis. In fact, it can also cause a more acute type adult pattern version of this encephalitis, presenting with rapid onset illness consisting of headache, fever and delirium, as well as in some cases, cranial nerve defects. In all these cases, examination of the cerebral spinal fluid typically shows a neutrophilic pleocytosis and, if available, PCR for cytomegalovirus DNA from the CSF is generally positive.

Another manifestation of CMV the infection of the central nervous system is an acute ascending reticular myelitis. Presentation of this illness is generally one of paraparesis, areflexia of the lower extremities, and voiding dysfunction. Examination of the cerebral spinal fluid in these cases also reveals neutrophilic

pleocytosis and, if available, a positive CMV PCR, both of which contribute to making the diagnosis of CVM ascending reticular myelitis.

It can also produce a pattern of acute or subacute neuritis. In all these manifestations, the treatment, in most cases, is ganciclovir. In cases of intolerance of ganciclovir, or, occasionally, of CMV resistance, alternative agents such as foscarnet and cidofovir are used.

These manifestations, other than congenital CMV, are restricted to those patients with severe immunosuppression, and therefore, institution of effective HRT can be very useful in both recovering from the illness as well as preventing the illness from occurring.

Other opportunistic viral infections of the central nervous system include herpes simplex virus; this virus, of course, can cause encephalitis in healthy children as well as in HIV infected children. Its presentation may be acute, but it also may be one of a more insidious onset. Treatment for this infection is with acyclovir. Typical presentation involves headache, fever, seizure and, sometimes, cranial nerve defects.

Varicella-zoster virus can cause, also, a similar pattern of acute or subacute encephalitis. The treatment for these VZV infections of the central nervous system is also acyclovir. Presentation includes fever, headache, altered behavior, seizures, and focal deficits. In this case, it is often preceded by or accompanied by a zoster eruption, although this is not always the case. Examination of cerebral spinal fluid will often, but not always, show a pleocytosis that's mild and mononuclear. The protein in the CSF maybe elevated and, where available, a VZV PCR that's positive helps to confirm the etiology of this manifestation.

JC virus is responsible for causing progressive multifocal leukoencephalopathy, or PML. This clinical entity is seen in adults with HIV infection, but is only rarely seen in children with advanced HIV infection. Its presentation is one of progressive neurocognitive decline, generally without headache and without fever.

MRI is the most useful modality to identify the typical white matter changes; sometimes these changes can be seen on CT, but often they are not apparent. Examination of the cerebral spinal fluid in cases of PML generally reveals normal indices, however, PCR for the JC virus that is positive helps to confirm the diagnosis. Treatment of this illness in children, as for adults, most often is with HAART, and effective immune reconstitution can often help improve symptoms and manifestations of PML. Some small case series have looked at the use of an antiviral agent, Cidofovir, but it's not clear how effective this is as a treatment for PML.

Other opportunistic infections of the central nervous system include toxoplasma encephalitis. This parasite can be transmitted from the mother as a congenital

infection, or it can reactivate after latency and cause a later onset disease. The congenital form of toxoplasmosis is seen in both HIV infected and entirely healthy infants. The later onset disease is really that only seen in those with severe immunosuppression. As mentioned, this is much more common in adults than it is in children.

The exposures that put someone at risk for infection from toxoplasma include eating undercooked meat, exposure to cats, and the cat litter boxes; and exposure to water that has been contaminated by this parasite. Presentation is typically subacute, and manifests with headache, fever, altered mental status, and neurologic deficits. Imaging typically shows intracranial mass lesions, usually multiple lesions, and these are ring-enhancing. There may be some edema as well, but not as much as may be seen in lymphoma, as we'll discuss shortly.

The treatment for toxoplasma encephalitis is pyrimethamine and sulfadiazine, together with leucovorin rescue. In lower resource settings, cotrimoxazole with apparent good clinical effect for treatment of this infection as well.

Other infections that may complicate HIV infection include acute bacterial meningitis. This has not been a particularly common feature in HIV infected children, but when it does occur, it's most commonly due to the usual childhood bacterial meningitis pathogens such as pneumococcus, H. influenza, and meningococcus.

Mycobacterium tuberculosis is discussed in another lecture, and is a very important cause of CNS infections in HIV infected children, particularly in areas where tuberculosis is endemic.

Other opportunistic pathogens may also cause CNS infections, including nontuberculous mycobacteria, listeria, nocardia, and cryptococcus. Taken altogether, these are all exceedingly rare in HIV infected children. Even cryptococcus, which is a common cause of meningitis in immunocompromised adults with AIDS, is a relatively uncommon cause of infection in children.

Another problem that can manifest in the central nervous system of children with HIV infection is neoplasms. By far, the most common neoplasm seen in the central nervous system is primary CNS lymphoma; in fact, it's the most common cause of CNS mass lesions in children with AIDS. Presentation is typically one of headaches, focal neurologic deficits, and seizures, and usually there is no fever.

Examination of the CSF, if undertaken, will sometimes reveal an increase in mononuclear cells, an increase in protein, and where available, an EBV PCR on the CSF that's positive is a very useful way to confirm that this is a primary CNS lymphoma.

Imaging of this disorder typically shows single or multiple enhancing lesions with prominent edema and mass effect. It can be difficult sometimes to distinguish

primary CNS lymphoma from toxoplasmosis, but the more prominent edema and mass effect, particularly if there is a single lesion, may be a clue that this is more likely a lymphoma. Sometimes, it requires an empiric therapy for toxo, see if there's a response; and if no response, or if there's other diagnostic uncertainty, you can biopsy to help distinguish these two disorders.

Cerebrovascular disease manifesting as a stroke is the most common cause of focal neurologic deficits in children with AIDS. Stroke, overall, is exceedingly uncommon in the pediatric population on the whole, however, HIV infection in children is a potent risk factor for stroke. These strokes may be hemorrhagic in children with bleeding disorders, may be embolic, and may also be vasculitic, related to complicating opportunistic infections that cause vasculitis or other more primary causes of vasculitis.

In addition, children with longstanding advanced immunosuppression may have a vasculopathy that's quite typical for children with AIDS, and involves stenosis and aneurysmal dilatation in the circle of Willis. Again, this is seen primarily in those with advanced or longstanding immunosuppression.

It is thought to contribute, as a previous position, to stroke, in these children. And it may be as a primary result of HIV infection, or it may be secondary to a vasculitis, secondary to another infection, such as varicella-zoster virus infection. Even with effective HAART, this vasculopathy may not reverse, and it is thought that is because the damaged vessels are not able to completely reverse.

HIV encephalopathy is very common in children, particularly in the pre-HAART era. Infants and young children were those who were at highest risk of this primary HIV disorder of the brain. And in particular, those children with intra uterine infection at a time when the brain was undergoing major development were thought to be the ones at highest risk of developing consequences of HIV affects of the brain. In fact, early in the epidemic in the United States, HIV encephalopathy was one of the common presenting signs of HIV infection leading to that diagnosis.

The typical triad is one of delays in motor and language milestones, as well as acquired microcephaly and pyramidal tract deficits. These pyramidal tract deficits look like primary cerebral palsy and may have a spastic diplegia, they may be quadriplegic, or other pattern or manifestation.

The typical patterns of HIV encephalopathy are three. First, a subacute progressive pattern, in which milestones that had been acquired are then lost; a plateau pattern, in which children who were developing at a certain pace arrested their development or began then acquiring milestones at a much slower pace; and finally, a static pattern, which represents fixed deficits, like the insults to the brain, but without ongoing injury or progression of illness.

The most important treatment for HIV encephalopathy is effective highly active antiretroviral therapy. Early on, it was noted that children who received zidovudine were able to have a halt in the progression of their HIV encephalopathy, and in many cases, a reversal of the manifestations of their HIV encephalopathy. For this reason, many experts believe that it's important to include zidovudine in a HAART regimen for a young infant or child who is manifesting signs of HIV encephalopathy.

In addition, others feel that choosing antiretroviral agents that are known to have better CNS penetration as part of the regimen is an important aspect guiding the choice of antiretrovirals in children affected by this disorder.

Defining HIV encephalopathy, it is quite clear that these children, as they get older, are subject to increased risk of learning and behavioral problems. And this applies to both children who manifested with HIV encephalopathy at younger ages as well as those who didn't manifest evidence of HIV encephalopathy.

Briefly, ophthalmologic disorders are important, and where resources allow, annual exams can be particularly important at detecting silent and progressive lesions of the retina. CMV retinitis is much less common in children than in adults, but it is the most common ophthalmologic opportunistic infection, nonetheless, in children with AIDS.

In addition, CMV retinitis may be a part of congenital cytomegalovirus infection, and in this case, is not thought to be HIV-related. The main risk factor for CMV retinitis is severe and often long-standing immunosuppression.

The pace at which damage to the retina can occur can be quite variable, but it should be known that the pace may be rapid, and the effects and presence of the retinitis due to CMV may be quite silent up until the point when they start to cause visual loss. Retinal detachment and blindness are both important and severe consequences of CMV retinitis. Treatment of CMV retinitis is both of systemic therapy and intraocularly injected therapy with anti-cytomegalovirus agents.

Toxoplasmosis is also an important cause of retinochoroiditis. Again, in pediatrics, it's more common to see this as part of a congenital toxoplasma syndrome, but it can be seen in older children who have HIV-related reactivation, CNS toxoplasmosis with associated retinitis. Important complications of this infection are retinal detachment, severe uveitis, and blindness. Treatment is with the same systemic agents against toxoplasma, as already discussed.

Finally, there's an HIV retinopathy that involves progressive outer retinal necrosis, and in this process, there can be completely painless but rapid vision loss. This appears to be due to varicella-zoster virus or herpes simplex virus. This again, is most commonly seen in children with more advanced HIV-related immunosuppression.

In summary, central nervous system opportunistic infections are much less common in children than in adults. Children presenting with focal neurologic deficits, one should consider stroke and CNS lymphoma as the most common causes, and then toxoplasmosis and cryptococcosis as less common causes in children. HIV encephalopathy is a common problem, particularly in untreated and younger children, and this is best treated with effective HAART that often will include zidovudine.

Ocular manifestations include cytomegalovirus, most commonly, and toxoplasmosis. Treatment for these disorders includes reversal of immunosuppression and direct treatment of the infection itself.

Thank you very much.