Does syphilis affect HIV in the brain?

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Outbreaks of sexually transmitted infections (STIs) are occurring in Canada and other high-income countries. STIs can cause inflammation, sores, ulcers or lesions on or inside delicate ano-genital tissues. In addition to the specific damage that each STI causes, the inflammation and sores caused by STIs can provide a portal for HIV and other germs to be transmitted.

Researchers have noted several similarities between syphilis and HIV, including the following:

- Co-infection with syphilis and HIV is relatively common because both microbes are sexually transmitted.
- The germs that cause syphilis (called treponemes or spirochetes) can invade and replicate inside the brain and spinal cord (the central nervous system, or CNS) shortly after they invade the body. HIV also enters the CNS shortly after infection and replicates inside cells of the immune system that are in the CNS.

Syphilis is particularly problematic because it can damage such organs as the heart, kidney, liver, eyes and brain. There are reports of increased rates of syphilis among some men who have sex with men, some of whom are also HIV-positive.

Researchers at the University of California at San Diego, a centre for excellence in neuroAIDS research, are concerned about the impact of both HIV and syphilis on the brain. This concern arises in part because HIV infection is generally associated with an increased risk for neurocognitive impairment. A large study has found that such impairment can persist despite the use of potent anti-HIV therapy, commonly called ART or HAART.

If treponemes invade the CNS, there is the possibility that they might increase inflammation. This, in turn, can increase the production of HIV and its proteins, which are toxic for brain cells. Ultimately, if such effects persist, there is the possibility that they could slowly degrade the brain, amplifying the possibility of neurocognitive decline.

The San Diego team has found that HIV-positive people with neurosyphilis had higher levels of HIV replication in the brain than other HIV-positive people without neurosyphilis. The possible reasons for these findings and their implications are explored in this report.

**Study details**

Researchers collected extensive health data from 225 HIV-positive participants who were being monitored as part of a larger long-term study. All participants received extensive neurological, psychiatric and medical assessments.

With regard to syphilis, participants’ blood samples were first screened for antibodies suggestive of having syphilis, and positive results were confirmed with other tests. Similar testing was done on cerebrospinal fluid (CSF), in which the brain and spinal cord float.

The basic profile of participants was as follows:

- age – 40 years
- 1% females, 99% males
- current CD4+ count – 357 cells
- nadir (lowest-ever) CD4+ count – 191 cells
In summary, study volunteers were mostly men around the age of 40 with a history of immune deficiency.

**Results**

Based on the reports from laboratory testing, researchers divided participants into three groups as follows:

- 23 people with neurosyphilis
- 42 people with systemic syphilis who did not have neurosyphilis
- 160 people who tested negative for syphilis

Participants who tested positive for syphilis were asked for permission to contact their family doctor so that treatment for syphilis could be coordinated.

**Syphilis before neurosyphilis**

Most participants who had neurosyphilis reported that they had been diagnosed with and treated for syphilis in the past. According to the research team, this previous treatment for syphilis had been “appropriate”; however, details about specific treatment were not published.

**Viral load in the blood and CSF**

CSF viral load was greatest in people classified as having neurosyphilis, followed by people classified as having systemic syphilis, followed by people classified as not having syphilis.

Researchers did analyses of the anti-HIV regimens that all three groups of participants took but found that there were no significant differences between the regimens and their ability to penetrate the brain. Further analysis that took many factors into account—a multivariate analysis—found that the effects of neurosyphilis and syphilis on viral load in the CSF were not affected by viral load in the blood.

**Putting together the puzzle**

Based on the data gathered, the research team suggests that syphilis co-infection may increase viral load in the CSF. However, researchers were intrigued by their findings because none of the participants classified as having neurosyphilis appeared to have signs/symptoms suggestive of active neurosyphilis and their prior treatment for syphilis was considered “appropriate.”

Moreover, routine laboratory tests used to assess the severity of neurosyphilis did not suggest rampant infection in the CNS.

The researchers note that both treponemes and HIV affect sentinel cells of the immune system called macrophages. These cells alert the immune system to the presence of invading germs. Macrophages can do so because that is one of their major roles. Activated macrophages release chemical messengers called cytokines that help activate and inflame the local immune system in the CNS so that it can better identify and control invading germs.

The San Diego team suggests that the immune system in the CNS of some HIV-positive people who have had syphilis or neurosyphilis appears to become permanently activated. This activation has an inadvertent effect of making immune system cells susceptible to HIV infection. As these cells become infected with HIV, they are transformed into miniature virus factories, spewing out more copies of HIV, raising viral load and releasing proteins that are toxic to brain cells.

The researchers also note that ongoing immune activation (triggered by syphilis) in the brains of HIV-positive people could “predispose them to a higher frequency of neurocognitive impairment.” Although neurocognitive impairment was not assessed in the present study, a previous study also conducted at the University of California at San Diego in the mid-1990s assessed and compared neurocognitive impairment in 453 HIV-positive and 219 HIV-negative volunteers who had a history of syphilis or gonorrhea. Researchers found that participants who were HIV positive and who had a history of syphilis or gonorrhea tended to have neurocognitive deficits compared to HIV-negative
people with syphilis or gonorrhea. This difference occurred regardless of education level and anti-HIV drugs and was present even though participants had modest CD4+ cell counts (460 cells).

Other studies in the present era have found that systemic syphilis can reduce the CD4+ counts of HIV-positive people. However, once syphilis is treated, CD4+ counts return to their pre-syphilis levels.

Taken together, the two neurology studies done at the University of California at San Diego raise the possibility that even after syphilis has been treated appropriately it may adversely affect the immune system in subtle ways—such as causing immune activation in the CNS.

Immune activation is not a trivial problem; it appears to play a role in many of the complications that are appearing in HIV-positive people, even those whose infections are under control with ART.

The present study was retrospective in design. Such studies can inadvertently cause biased interpretation of data. The San Diego team took pains to reduce the possibility of inadvertent bias, however, this problem cannot entirely be ruled out. Based on the results of the present study, the San Diego team suggests that future studies are necessary to assess whether co-infection with HIV and syphilis is indeed linked to greater rates of neurocognitive impairment. Hopefully such studies will include high-tech tests such as PCR and other assessments for treponemes in the brain.

Acknowledgement

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—Sean R. Hosein

REFERENCES:


Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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