Treatment of neurosyphilis in HIV-infected patients.

A systematic review.

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Background and objective: The aim of this systematic review is to provide answers to the question if HIV status has effect on the treatment of neurosyphilis and whether therapy for HIV-infected patients with neurosyphilis has to differ from non-HIV-infected.

Methods: We performed a literature search on PubMed on January 11th 2010. We selected articles by reading abstracts and full articles. We only included clinical trials, epidemiologic studies and case series.

Results: 5 studies met our inclusion criteria. The decline of laboratory measures, as VDRL, CSF-VDRL and CSF-WBC, were statistically significant slower in patients infected with HIV compared with those not infected with HIV (VDRL p=0.006, CSF-VDRL p=0.02 and CSF-WBC p=0.03) Both the ceftriaxone treatment regime and the penicillin treatment regime produced comparative numbers of patients who responded to therapy, on condition that the same treatment dosage was used.

Conclusions: The results indicate that HIV-infected patients have a slower decline in CSF-values. There is no difference between the effect of penicillin and ceftriaxone treatment among the HIV-infected patients.

Keywords - Neurophilis/therapy, HIV-infections, ceftriaxone, penicillin G

Introduction
After a large decrease in the number of cases of syphilis in the past decades, the incidence of syphilis is rising again. At the end of the nineties, a new epidemic of syphilis has been documented in Western-Europe and the United States. Although the number of patients seems to be decreasing again, this disease is still an important infectious disease that is sexually transmitted. Many patients with newly diagnosed syphilis are also HIV-infected. These patients have a higher risk to develop neurosyphilis, an inflammation of the central nerve system. Several case reports have shown that a concurrent infection with HIV compared with the natural course of neurosyphilis. This might mean that patients with HIV respond different on treatment for neurosyphilis. Though, it is not known whether patients with neurosyphilis and concurrent HIV infection really respond different to treatment compared to patients without concurrent HIV-infection. But if they do, what is the best treatment for HIV-infected patients?

The purpose of this systematic review is to describe what is already known about treatment of neurosyphilis in HIV-infected patients. Do they respond different and if they do, what is the best treatment option?

Methods

Literature search
On the 11th of January 2010 we did a computerized search to identify all relevant studies published in English language in the PubMed database. We used the combination of Medical Subject Headings (MeSH) terms “HIV infections” and “Neurophilis/therapy” to perform this search.

Inclusion criteria
We only included articles that were available in free full text for the Erasmus Medical Centre. We manually searched the available articles and based on the abstracts, we included all clinical trials,
epidemiologic studies and case series. Also based on the abstracts, we excluded studies about ocular syphilis.

Exclusion criteria
From the full text of the remaining articles, we independently assessed eligibility. In the end, we also excluded 1) studies about therapy that was not specifically used to treat neurosyphilis and 2) studies with patients who were not diagnosed with neurosyphilis at the start of treatment.

Results
Normalisation of cerebrospinal fluids

Study properties
Two studies of Marra CM et al.(6,7) study this phenomenon in a clinical trial that compares HIV-infected with non-HIV infected patients. Both studies define neurosyphilis as a reactive Veneral Disease Research Laboratory test (VDRL) in cerebrospinal fluid (CSF), except that the 2004 study also considers a CSF-white blood cell count, WBC: white blood cell count, RPR: rapid plasma regain; MHA-TP: microhemagglutination assay

Decline in laboratory measures
The 1996 study of Marra CM et al.(6) concludes that the decline in most of the laboratory measures was slower in patients infected with HIV compared with those not infected with HIV. Despite the fact that the number of patients is very small, these differences were significant for decline in serum VDRL (P=0.006), CSF-VDRL (P=0.02) and CSF WBC count (P=0.03). The decline in CSF protein was not significantly slower in HIV-infected patients. The stage of syphilis or history of syphilis did not influence this outcome.

A remarkable difference is that in the study of Marra et al. from 2004 (7), the researchers found that only the CSF-VDRL was less likely to normalize in HIV-infected subjects. Normalization of the other parameters was not significantly different.

Influence of clinical state of HIV-infection on the decline in laboratory measures
The Marra et al. 1996 (6) study makes the contention that clearance of Treponema microorganisms from the central nervous system (CNS) may be impaired by concomitant HIV-infection. To support the hypothesis that an intact immune response is -beside antibiotics- needed for cure, the writers cite some articles (8,11,12,13) who have studied this delayed decline in syphilis patients.

The 2004 study concludes that among HIV-infected subjects, those with peripheral blood CD4+ T cell counts of >200 cells/µl were more likely to normalize CSF-VDRL activity than those with peripheral blood CD4+ T cell counts of <200 cells/µl. The writers discuss that these results suggest that HIV-induced immune impairment contributes to the slower normalization seen in HIV-infected persons. They do not know whether decreased likelihood of normalization during the observation period is equivalent to treatment failure, but they think the difference in treatment response in HIV-infected patients is concerning. In their opinion, future research should address this question.

However, the Dowell ME (8) et al. study concludes that there is no correlation among the CD4 cell count, the clinical state of HIV-infection and the outcome of treatment after 6 months of follow-up. Unfortunately, they do not show any data to prove this contention.

The best treatment option for neurosyphilis in HIV-infected individuals
Five articles studied the treatment options for neurosyphilis in HIV infected patients. Marra CM et al. 1996 (6) and 2004 (7) mention, without giving any data, that specific neurosyphilis treatment options were ceftriaxone and penicillin. The used treatment options for neurosyphilis in HIV-infected patients. The used treatment options were ceftriaxone and penicillin.

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**Table 1 - Included studies; IM: intramuscular, IV: intravenous, MU: million units, PPG: procaine penicillin G, APG: aqueous penicillin G, VDRL: Veneral Disease Research Laboratory test, CSF: cerebrospinal fluid, WBC: white blood cell count, RPR: rapid plasma regain; MHA-TP: microhemagglutination assay**

<table>
<thead>
<tr>
<th>Location of study population</th>
<th>Number of patients with neurosyphilis</th>
<th>Intervention (number of patients)</th>
<th>Serum and CSF measures</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dowell ME et al. (1992)</td>
<td>Clinic, USA 9 (9 HIV)</td>
<td>- Ceftriaxone 1-2 g IV or IM for 10-14 consecutive days (7) or; - Benzathine penicillin, 3 times 2.4 MU (2)</td>
<td>VPR, VDRL, MHA-TP</td>
<td>&gt; 6 months</td>
</tr>
<tr>
<td>Gordon SM et al. (1994)</td>
<td>Clinic, USA 11 (11 HIV)</td>
<td>in doses administered every 4 hours, WBC, CSF protein</td>
<td></td>
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</tr>
<tr>
<td>Marra CM et al. (1996)</td>
<td>Clinic, USA 22 (13 HIV)</td>
<td>- 2.4 MU IV APG daily + 500 mg probenecid 4 times a day, 10-14 days (?)</td>
<td>Serum VDRL, CRP, CSF protein</td>
<td>HIV- : 115 days</td>
</tr>
<tr>
<td>Gordon SM et al. (2000)</td>
<td>Clinic, USA 36 (36 HIV)</td>
<td>- Ceftriaxone 2g IV once daily for 10 days (18) or; - Penicillin G 0.4 MU IV every 4 hours for</td>
<td>Serum VDRL, CRP, CSF protein</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Marra CM et al. (2003)</td>
<td>Clinics, USA 59 (46 HIV)</td>
<td>- 18-24 MU IV APG potassium a day, divided into 6 doses (34)</td>
<td>Serum VPR, CSF-WBC, CSF protein</td>
<td>12 months</td>
</tr>
<tr>
<td>Marra CM et al. (2004)</td>
<td>- Ceftriaxone 2g IV (?)</td>
<td>- 18-24 MU IV APG potassium a day, divided into 6 doses (34)</td>
<td>Serum CSF-WBC, CSF protein</td>
<td>12 months</td>
</tr>
</tbody>
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Review
Laboratory measures
In all three studies a serum rapid plasma regain test (RPR), a Veneral Disease Research Laboratory test (VDRL) and a micro-hemagglutination assay (MHA-TP) or fluorescent treponemal antibody-absorption (FTA-ABS) test were done. In all three studies, a patient with a reactive CSF VDRL-test was defined as having neurosyphilis. Gordon SM et al. (9) combines this test with the clinical symptoms of patients.

The study from Dowell ME et al. (8) also regards CSF as abnormal if it contains ≥ 6 white blood cells (WBCs)/µl, or ≥ 46 counts of >200 cells/µl (p=0.02), might support the contention of the 1996 (6) study, which says that clearance of CNS organisms may be impaired by concomitant HIV-infection.

Although the Dowell ME et al. (8) study concludes otherwise, they do not show any data to prove this statement, which makes this study less strong evidence.

Taking this into account, we conclude that HIV-infected patients have a slower decline in CSF-values. In patients with peripheral blood CD4+ T cell counts of ≤200 cells/µl this decline is even slower than in patients with higher CD4cell counts. Based on these findings, we can make the assumption that the treatment of neurosyphilis in HIV-infected persons should be different, for example more intensive, than in patients without HIV, but there is in these articles not enough evidence to conclude this.

According to the results of the studies that compared different treatment options, we cannot conclude that there is a significant difference between the results of treatment with ceftriaxone or treatment with penicillin. In the same dosage both treatments have a comparative result. Though, based on the study of Marra CM et al. 2000 (10) it seems that ceftriaxone gives a significant more quickly decline in serum RPR titers than penicillin does.

Discussion
The studies included in this systematic review all had a very small study population. The Marra CM et al. study from 1996 (6) studied 22 patients; the study of Dowell ME et al. (8) only studied 7 cases of neurosyphilis and the Gordon SM et al. (9) study only 11.

The authors note that this limits their ability to detect differences between these populations. The fact that we could not find any differences between different treatment regimes could have been a result from the small study populations. Small differences between treatment options only appear in large study populations.

Because of this, we think that it is necessary to study the effect of different treatment regimes in larger study populations.

There is only one study (7) that proves with data that the HIV-status of a patient influences the treatment of neurosyphilis. The normalization of the CSF is slower in patients with active HIV. As we have said in the conclusion, we can only make an assumption that HIV-status influences neurosyphilis treatment, but we think that one study is not enough evidence to prove this.

Beside that, a slower normalization of the CSF does not have to mean that after a longer follow-up, treatment also had failed. It could be that it takes more time in HIV-patients to reach a normal CSF, but that success of treatment is as much in HIV-infected as in non-HIV infected patients after a longer time.

The studies of Marra CM et al. 1996 (6) and 2004 (7) mention that there is no difference in normalization of the CSF between the various treatment regimes. Unfortunately, they do not show any data to support this statement. This makes their statement less reliable and useful for our review.

Another point of discussion is the fact that there is a difference between the studies in the inclusion criteria of patients, based on the laboratory measures. There is still discussion about the cut-off of WBCcounts A result of this discussion is that the studies consider the CSF of patients as abnormal at different cut-off values. The study from Dowell ME et al. (8) regards CSF as abnormal if it contains ≥ 6 WBCs/µl, while the study from Marra CM et al. 2000 (10) defines CSF as abnormal if it contains ≥20 WBC /µL. Using a higher cut-off value means that the patients included in the study are more likely to really have neurosyphilis. Patients in the Dowell ME et al. (8) study with a low WBCs might...
have been considered as patients with neurosyphilis, while they were only having latent syphilis. This could have influenced the results of the study.

Another difference is the inclusion of symptomatic and asymptomatic patients. Dowell ME et al. (8) and Marra CM et al. 2000 (10) selected their patients based on laboratory measures, while in the other Gordon SM et al. (9) patients were selected based on symptomatic manifestations of neurosyphilis. In Dowell ME et al. (8) development of symptomatic manifestations of neurosyphilis is seen as failure of the ceftriaxone treatment. It could be possible that the stage of neurosyphilis could influence the effect of treatment. The selection of treatment was not randomized in all studies. In the study from Dowell ME et al. (8) treatment is selected by individual physicians, while in the study from Marra CM et al. (10) treatment is randomized selected. We assume that the results of the study that used randomized selection to select therapy is more reliable. In the study of Dowell ME et al. (8) treatment of ceftriaxone and penicillin was compared. It is remarkable that the patients treated with penicillin got a lower dosage of treatment. This was not enough to treat neurosyphilis. Therefore in this study it is impossible to compare the penicillin treated patients with the ceftriaxone treated patients.

During the selection of studies, we found an article (14) that reported about the effects of HIV-treatment with HAART on the cure of neurosyphilis. This study was irrelevant for the goal of our systematic review, but we think that it is a very interesting subject, to study the influence of HAART therapy and the interaction with the medication for neurosyphilis therapy.

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The effect of Botulinum Toxin Type A on Painful Bladder Syndrome.

A systematic review of the literature.

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Objective: To systematically review and evaluate the evidence on the treatment of painful bladder syndrome (PBS) with Botulinum Toxin type A (BTA).

Methods: The PubMed database at the National library of Medicine was searched for English-language articles published between 2000 and 2009. We found 11 articles and selected 4 for review. We found only one randomized controlled trial. The other 3 articles were prospective cohort studies.

Results: In all the studies the parameters for pain score (reported by patient self-assessment using a 10-point visual analogue scale VAS), and maximum cystometric bladder capacity changed significantly after BTA treatment. Comparing Botulinum Toxin type A treatment with/to bladder distension treatment also showed a benefit of Botulinum with a p-value of 0.007. We concluded that BTA is effective on alleviating PBS symptoms for at least three to six months. BTA 100 Units appears the optimum dose for effective treatment. Knowledge about the side effects of the treatment is still limited. >>>