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Diagnosis of neurosyphilis with cerebrospinal fluid pcr: a systematic review

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ABSTRACT

Background: Neurosyphilis is difficult to be diagnosed. CSF VDRL is the gold standard, but its sensitivity is low. Cerebrospinal fluid (CSF) PCR for the detection of Treponema pallidum DNA has been evaluated; however, its diagnostic value is still poorly understood.

Methods: Here we performed a systematic review including articles that assessed the diagnostic sensitivity of CSF PCR in patients with syphilis and neurosyphilis. The CSF PCR sensitivity and specificity of different PCR assays was assessed in patients with neurosyphilis with or without HIV coinfection and in patients with syphilis with no central nervous system (CNS) manifestations.

Results: Eighteen studies evaluating 703 patients were included. The PCR sensitivity for neurosyphilis was 73.9% among HIV negative and 37.5% among HIV infected patients, having varied from 62.2% to 100% with different PCR assays. The sensitivity of CSF VDRL CSF was 68% in the same population. The specificity of CSF PCR was 93%. CSFPCR was positive in16.4% of the patients with primary and secondary syphilisand 28.9% of patients with latent syphilis. None of the syphilis cases without neurological manifestations were positive with CSF VDRL.

Conclusion: CSF PCR seems to be at least as sensitive as CSF VDRL, with good specificity. In addition, CSF PCR may potentially reveal early neuroinvasion in patients withsyphilis with no CNS symptoms. Future studies are still needed to assess the potential clinical value of detecting T. pallidum DNA in CSF in syphilis cases prior to the development of CNS symptoms.

Key words: neurosyphilis; syphilis; cerebrospinal fluid; polymerase chain reaction (pcr).

INTRODUCTION

Syphilis is a sexually transmitted disease caused by Treponema pallidum. Besides sexual transmission, this infection can also be transmitted vertically or by blood transfusion[1]. There has been an increase in the number of syphilis cases, particularly among people coinfected with HIV[1].

One of the serious complications of syphilis is neurosyphilis, which occurs in about 3.5% of syphilis cases. Neurological symptoms and syndromes vary according to the time of infection. In the earlier stages, manifestations related to meningovascular syphilis, such as meningitis, stroke, cranial nerve damage, including optic neuritis, and myelopathy, are the most important ones. Late phase manifestations include parenchymal disease such as general paresis, with dementia, ataxia, and pupillary changes (the classic Argyll-Robertson pupil), and tabes dorsalis, with ataxic gait, Romberg's sign, and paraparesis. Early and precise diagnosis and antimicrobial treatment of neurosyphilis are crucial to prevent definitive neurological sequelae[2-5].

CSF evaluation is essential for the neurosyphilis diagnosis. However, there is still no universal consensus on the interpretation of CSF findings in neurosyphilis. The Venereal Disease Research Laboratory (VDRL) assay is the gold standard for the diagnosis of neurosyphilis; however, its CSF sensitivity is low. Treponemic assays, such as fluorescent treponemal antibody-adsorption (FTA-Abs) and particle agglutination assay, are more sensitive but less specific than VDRL[6]. Other neurosyphilis CSF findings, such as pleocytosis, increased CSF protein, and intrathecal IgG synthesis

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tests are not specific. The interpretation of CSF findings and neurosyphilis diagnosis can be even more challenging in HIV-infected patients[7].

CSF polymerase chain reaction (PCR) assays for amplification of conserved regions of Treponema pallidum DNA have been studied. The diagnostic value of such assays and their precise sensitivity and specificity are not well established[8]. The precise ability of PCR to identify neuroinvasion in patients with symptomatic or asymptomatic syphilis without neurological involvement is also not precisely known. The aim if this study was to systematically review the sensitivity and specificity of different CSF PCR assays in different forms of neurosyphilis, in patients with and without HIV infection and in patients with syphilis with no nervous system involvement.

METHODS

We searched PubMed and Medline for references on CSF PCR for the diagnosis of neurosyphilis. The used terms were: ''cerebrospinal fluid'' OR ''CSF'' AND ''neurosyphilis'' OR ''syphilis'' AND ''PCR'' OR ''polymerase chain rection''. We included studies published between 1990 and October 2021, published in English, French, Spanishor Portuguese.

We included papers reporting sample CSF PCR positivity. Review papers, papers not reporting PCR sensitivity, and papers not reporting clinical forms of the disease were not included.

For each selected study we collected the following data: number of patients, number of patients in each form of the disease, number of patients with and without HIV coinfection, number of controls, target PCR region, and percentage of positive and negative CSF VDRL. The considered forms of the disease were: primary and secondary syphilis, meningovascular neurosyphilis, latent syphilis, asymptomatic newborns of mothers with syphilis, congenital neurosyphilis, and treated neurosyphilis.

RESULTS

We retrieved 90 articles and 18 fulfilled the inclusion criteria. These 18 studies included 703 patients. The number of patients in each disease form were: meningovascular neurosyphilis: 135 cases; parenchymal neurosyphilis: 4 cases; primary and secondary syphilis: 131 cases; latent (not specified if early and late): 203 cases; treated neurosyphilis: 61 cases; controls without syphilis: 58 cases; congenital neurosyphilis: 40 cases; asymptomatic newborn of a mother with syphilis: 24 cases.

Four different PCR panel assays were used in the studies, targeting four regions of the DNA of the T. pallidum bacteria: polA gene: 181 patients, bpm gene: 27 patients, 47-kDa gene: 420 patients, and TPMA and 4D genes: 75 patients.

The frequency of positive cases in each clinical form and with each target DNA regions are show in Table 1. In patients with meningovascular neurosyphilis the PCR sensitivity was 67%, being 73.9%in non-HIV infected patients and 37.5% among HIV infected cases. The sensitivity varied according to the PCR assay: TPMA-100%; pol A-82%; BMP-71%, and 47-PCR-62.2%. All tests in HIV infected patients were carried out with 47-kDa assay. CSF PCR detected T. Pallidum DNA in the CSF of patients with syphilis without CNS manifestations in a variable percentage of the cases: latent syphilis (28.9%) and primary and secondary syphilis (16.4%). The sensitivity among congenital neurosyphilis was 48%. The positivity among asymptomatic newborns of infected mothers was 3%[7-23].

The positivity among control patients without syphilis and undergoing lumbar puncture for the investigation of other neurological diseases was 7%, with all cases tested with PCR assay targeting TPMA region. The specificity in HIV negative patients was 96.7% and 89.3% among HIV positive patients. In follow-up CSF analyses in patients previously treated patients the CSF PCR was negative in all the 61 cases[7-23].

CSF VDRL results were reported in 88 patients of this population. CSF VDRL was positive in 68.4% of the patients with meningovascular neurosyphilis. None of the cases with primary, secondary, and latent syphilis in which CSF VDRL was carried out were positive with this test, in contrast with CSF PCR that was positive in 23.9%[7-23].

DISCUSSION

The sensitivity of CSF PCR in cases of meningovascular neurosyphilis was 73.9% in patients without HIV infection. The sensitivity varied with different PCR assays. The lowest sensitivity was achieved with 47-kDa assay, which was the most often used. Considering that the sensitivity of CSF VDRL was 68.4%, these present data suggest that CSF PCR is at least as sensitive as CSF VDRL[2-4]. Also, with some DNA region assays, it seems that CSF PCR may overcome the sensitivity of CSF VDRL. No patients with late parenchymal neurosyphilis had positive PCR; however, the number of patients with late neurosyphilis was too small to draw any conclusion about the sensitivity of CSF PCR in this stage of the disease. The above data suggest that CSF PCR may possibly increase diagnostic sensitivity if performed in conjunction with

TABLE 1 - Number and percentage of positive CSF PCR for T. pallidum in different forms of syphilis with different PCR assays targeting different DNA regions of the bacteria

DNA region	NUMBER OF CASES	PCR POSITIVE N (%)	HIV NEGATIVE N	POSITIVE CASES AMONG HIV NEGATIVE N (%)	HIV POSITIVE N	POSITIVE CASES AMONG HIV POSITIVE N (%)
MENINGOVASCULAR NEUROSYPHILIS						
47-PCR	135	91 (67%)	45	28 (62.2%)	24	9 (37.5%)
BMP			7	5 (71%)	NR	NR
polA			57	47 (82%)	NR	NR
TPMA			2	2 (100%)	NR	NR
TOTAL			111	82 (73.9%)	24	9 (37.5%)
PARENCHIMAL NEUROSYPHILIS						
BMP	4	0	4	0	NR	NR
TREATED NEUROSYPHILIS						
47-PCR	61	0	10	0	51	0
CONTROLS WITHOUT SYPHILIS						
TPMA	58	4 (7%)	30	1 (3.3%)	28	3 (10.7%)
PRIMARY AND SECONDARY SYPHILIS						
47-PCR	131	24 (18.3%)	88	12 (13.4%)	3	3 (100%)
polA			40	9 (23%)	NR	NR
TOTAL			128	21 (16.4%)	3	3 (100%)
LATENT SYPHILIS						
47-PCR	203	61 (30%)	91	27 (29.7%)	13	6 (46.1%)
polA			84	20 (23.8%)	NR	NR
TPMA			15	8 (53.3%)	NR	NR
			190	55 (28.9%)	16	6 (46.1%)
ASYPTOMATIC NEWBORN IF INFECTED MOTHERS						
47-PCR	71	2 (3%)	71	2 (3%)	NR	NR
CONGENITAL NEUROSYPHILIS						
47-PCR	40	19 (47.5%)	24	16 (67%)	NR	NR
BMP			16	3 (19%)	NR	NR
TOTAL			40	19 (47.5%)		

conventional diagnostic methods, but future studies are still needed with different PCR assays since their sensitivity does not seem to be the same. The studies including HIV positive patients suggest that the diagnosis of neurosyphilis is more challenging among these patients even with CSF PCR. However, it should be noted that the number of patients in this group was small and that the more sensitive PCR assays were not used among CSF PCR.

The specificity of CSF PCR also seemed to be satisfactory. However, it must be stated that only one PCR assay was used among control patients, therefore, specificity should be better evaluated with the other available PCR assays. In addition to its diagnostic importance, CSF is also used for therapeutic monitoring in patients treated for neurosyphilis[1,2,4]. In this sense, the data suggest that CSF PCR appears to be potentially useful, since PCR was negative in all treated patients, suggesting that the result may become negative with the course of the treatment. Prospective studies are still needed to assess how to use this information in the clinical management of patients with neurosyphilis. For example, we do not yet know whether, in the event of a persistent CSF PCR positive

result, it could be interpreted as an inadequate treatment result, requiring an eventual replacement of the antimicrobial agent.

The diagnosis of congenital neurosyphilis is also difficult[17]. Among newborns of mothers with syphilis, CSF PCR has shown to be a promising method for contributing to the diagnosis of congenital neurosyphilis. General sensitivity was 47.5% but it increased to 67% with PCR targeting the 47-kDa region. In asymptomatic newborns, PCR was positive in only 3% of cases. Considering the diagnostic difficulties in these cases, the use of CSF PCR together with conventional CSF analysis and antibody detection methods can potentially increase diagnostic sensitivity[17].

CSF PCR also showed to potentially identify possible neuroinvasion in patients with syphilis with no neurological manifestations. The identification of the T. pallidum DNA in the CSF in patients with primary and secondary syphilis as well as latent syphilis may possibly indicate an early neuroinvasion occurring before the onset of neurological symptoms[24]. It is not possible to define whether these cases would progress to symptomatic neurosyphilis, as they were not prospectively evaluated. It is also not yet known whether treatment should be done with drugs and doses to control CNS infection, considering that conventional treatments for non-neurological forms of the disease have little effectiveness against the bacteria inside the CNS[1]. Future prospective studies may contribute to answering these questions. Also, it is important to highlight that CSF VDRL was negative in these cases, suggesting that T. pallidum detection with CSF PCR may occur prior to the intrathecal production of antibodies.

CONCLUSION

In conclusion, CSF PCR for the detection of T. Pallidum DNA is potentially useful not only for increasing the diagnostic sensitivity and specificity for neurosyphilis if used in association of conventional methods, both in adults as in neonates. Also, it can potentially identify a possible neuroinvasion of T. Pallidum in patients with syphilis with no neurological symptoms, earlier than other conventional methods. Although there are still many questions to be answered, the data presented in the present review are sufficient to encourage further studies in this area.

Conflicts of Interest: All authors disclaim any conflicts of interest.

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