False Positive Venereal Disease Research Laboratory in Cerebrospinal Fluid in the Diagnosis of Neurosyphilis – A Case Series

shuwei.zheng@mohh.com.sg

SW Zheng[1,2] , RJH Lin[3], CCL Ngan[4]

[1]Division of Infectious Diseases, Changi General Hospital, Singapore; [2]Department of Infectious Diseases, Singapore General Hospital, Singapore; [3]Institute of Infectious Diseases and Epidemiology, Tan Tock Seng Hospital [4]Department of Pathology, Singapore General Hospital, Singapore

Introduction:

There is no clear consensus on the diagnosis of neurosyphilis. The Venereal Disease Research Laboratory (VDRL) from cerebrospinal fluid (CSF) has traditionally been considered a gold standard for diagnosis of neurosyphilis but is widely known to be insensitive. False positive VDRL-CSF has been described in clinical practice, although the specificity of the test has been quoted to be high. In the literature, there are only a few case reports describing this phenomenon[1-5].

From the experience of the Immunology & Serology Laboratory, Department of Pathology, Singapore General Hospital, it is not uncommon for the VDRL test to be ordered on CSF samples as part of a routine panel of investigations, without a prior established serodiagnosis of syphilis by means of a positive serum treponemal test.

Based on a previous study from the Johns Hopkins Hospital, much of the use of VDRL-CSF test is inappropriate[6]. In our study, we seek to describe the clinical characteristics and possible causes of biological false positives in patients with false positive VDRL-CSF.

Methods:

The Immunology & Serology Laboratory at the Singapore General Hospital is a designated, centralized laboratory processing VDRL-CSF from various centres across the country. Our study involved three acute general hospitals in Singapore, namely Changi General Hospital (CGH), Tan Tock Seng Hospital (TTSH) and Singapore General Hospital (SGH) from January 2013 to December 2015.

Serum treponemal tests done in the three hospital centres included TPPA, LIA IgG, LIA IgM and enzyme linked immunosorbent assay (ELISA) IgG. Serum non-treponemal tests performed included VDRL and rapid plasma regain (RPR).

At our laboratory, a pilot project to test for *Treponema pallidum* particle agglutination (TPPA)-CSF on VDRL-CSF reactive CSF samples was started in 2013 and eventually formalized into the laboratory protocol in 2015. This was because the laboratory had encountered sporadic cases of inadvertent misdiagnoses of neurosyphilis due to biological false positive VDRL-CSF results coupled with incomplete syphilis serological workup.

A false positive VDRL-CSF is defined as a reactive VDRL-CSF with a nonreactive TPPA-CSF and/or LIA-CSF IgG, regardless of whether the serum treponemal tests are positive or negative. A true positive VDRL-CSF is a reactive VDRL-CSF with a concordant reactive TPPA-CSF and/or LIA-CSF IgG, with serum treponemal test positive.

We retrospectively reviewed all patients who received a VDRL-CSF examination from three acute general hospitals in Singapore and review the existing literature.

Results:

From January 2013 to December 2015, the laboratory received 1,926 CSF samples for VDRL-CSF testing, of which 63 (3.3%) were reactive for VDRL-CSF and 1,862 (96.7%) were nonreactive.

- Out of the 63 VDRL-CSF reactive cases, 52 (82.5%) were true positive VDRL-CSF results and 11 (17.5%) were false positive VDRL-CSF results.
- One of the 11 false positive VDRL-CSF is only a probable false positive as we do not have a CSF treponemal test result (case 6).

A summary of the demographic, clinical characteristics and laboratory results of the 11 patients (8 males, 3 females) is shown in Table 1.

- Their mean age was 52.8 years (range 22-76 years). False positive VDRL-CSF titres range from 1:1 to 1:32.
- All cases did not have a definitive laboratory diagnosis of syphilis as evidenced by negative serum treponemal tests, except for patient 9.
- We are unable to confidently exclude syphilis in patient 8 (as the only serum treponemal test done was the LIA IgM, which was negative) but based on our neurosyphilis definition, this patient did not have neurosyphilis.
- In addition, all cases had CSF that were negative for treponemal antibodies (TPPA and/or LIA IgG nonreactive), with the exception of case 6 whose CSF was not tested.
- Patient 9 has laboratory evidence of syphilis (serum ELISA IgG reactive) and was initially diagnosed by his managing clinician as neurosyphilis but did not meet our laboratory criteria for diagnosis. His clinical condition also failed to improve despite standard neurosyphilis treatment. He was eventually started on multiple antipsychotics and diagnosed with vascular dementia.

Table 1. Characteristics of Patients with False Positive VDRL-CSF

No	Age/ Sex	Medical History	Clinical Features	Eventual Diagnosis	Serum TT[a]	Serum NTT[b]	CSF RBC[c]	CSF WBC[d]	CSF Glucose (mmol/L)	CSF Protein (g/L)	CSF VDRL Titres	CSF TT[a]
1	66 M	Chronic kidney disease	Delirium and fever	Leukoencephalopathy	TPPA NR LIA IgG NR	VDRL NR	0	0	4.5	0.54	1:4	TPPA NR, LIA IgG NR
2	74 F	Thyroid cancer Parkinson's disease	Functional decline	Progressive Parkinson's disease	TPPA NR	VDRL NR	5	0	6	0.94	1:1	TPPA NR
3	38 M	Nil	Left upper limb weakness and numbness	Multiple sclerosis	TPPA NR	Not done	0	1	4.4	0.38	1:16	TPPA NR, LIA IgG NR
4	32 M	Acquired Immunodeficiency Syndrome Drug abuse	Delirium and fever	Drug withdrawal	TPPA NR	VDRL NR	0	0	2	0.23	1:32	TPPA NR
5	76 M	Metastatic prostate cancer Chronic kidney disease	Delirium, fever, nuchal rigidity	Meningoencephalitis	TPPA NR	VDRL NR	Not done	Not done	Not done	Not done	1:4	TPPA NR
6	32 M	Rheumatoid arthritis	Bifrontal headache, right sided facial numbness and slurred speech	Lymphocytic meningitis	ELISA IgG NR LIA IgM NR	RPR NR	10	461	2.4	1.77	1:4	Not done
7	65 F	Nil	Bilateral ptosis, diplopia and left sided facial droop	Miller-Fisher syndrome	ELISA IgG NR	Not done	334	6	4.9	1.84	1:2	TPPA NR
8	48 F	Nil	Progressive memory loss and left sided apraxia	Early onset dementia	LIA IgM NR	Not done	<1	1	3.3	0.22	1:1	TPPA NR
9	70 M	Diabetes mellitus	Auditory and visual hallucinations	?Neurosyphilis Vascular dementia	ELISA IgG R	RPR NR	<1	<1	3.9	0.52	1:2	TPPA NR, LIA IgG NR
10	58 M	Diabetes mellitus	Insomnia, REM sleep disturbances, short term memory loss, hand tremors	Parkinsonism with dementia	ELISA IgG NR	RPR NR	1	3	4.4	0.35	1:1	TPPA NR
11	22 M	Drug abuse	Delirium and fever	Drug-induced psychosis	TPPA NR	VDRL NR	0	3	3.7	0.2	1:2	TPPA NR, LIA IgG NR

[a]Treponemal Test, [b]Non-Treponemal Test, [c]Red Blood Cells, [d]White Blood Cells, R: reactive, NR: nonreactive, ELISA: enzyme linked immunoabsorbent assay

Discussion:

A total of 11 false positive VDRL-CSF were identified over three years. False positive VDRL-CSF was confined to the CSF. The reactive VDRL antibodies were not a result of impaired blood brain barrier with diffusion of antibodies from the blood, as 8 out of 11 patients who had serum non-treponemal tests performed, had nonreactive serum VDRL or RPR.

Our study highlights cases of false positive VDRL-CSF, which has not been widely reported in the literature. The first reported case was made by Wuepper et al in 1966 in association with lymphosarcoma[1]. Delaney described a patient with false positive VDRL-CSF and fluorescent treponemal antibody absorption (FTA-ABS)-CSF in the setting of a patient with a spinal cord tumour[2]. Madiedo et al presented a case of a patient with meningeal carcinomatosis secondary to underlying lung adenocarcinoma who had repeatedly nonreactive serum VDRL and FTA[3]. Watkins reported a patient with newly diagnosed HIV and CD4 count 50 cells/μL who presented with visual and neurosensory hearing loss secondary to herpes zoster encephalitis[4]. This patient had a reactive VDRL-CSF, reactive serum RPR at 1:1 but a non-reactive *Treponema pallidum* IgG by immunofluorescent labelled antibody staining from CSF and three different nonreactive serum treponemal tests. Tung et al reported 4 cases of false positive VDRL-CSF out of 494 patients who received this test during a 2-year-period, with all 4 patients reported to have lung adenocarcinoma with suspicion of meningeal involvement[5].

In serum, false positive reactions occurring with non-treponemal tests include acute conditions such as viral infections and pregnancy, as well as chronic conditions such as autoimmune disease, intravenous drug abuse and malignancy. It seems that most cases in the literature with a false positive VDRL-CSF occurred in association with HIV disease or underlying malignancy. Amongst our eleven patients, one had diagnosed advanced HIV disease. Only one patient has known malignancy (thyroid cancer) but she has undergone curative surgical resection several years before with no evidence of recurrence.

Conclusion:

Biological false positive VDRL-CSF may be more common than we think. When investigating for neurosyphilis, a serological diagnosis of syphilis with a positive serum treponemal test should always precede any CSF evaluation. CSF treponemal tests on VDRL-CSF reactive samples may also be necessary to confirm neurosyphilis in serologically treponemal positive patients whose clinical presentation and/or progress with adequate treatment is atypical.

References:

1. Wuepper KD et al. JAMA. 1966;195:868-869.
2. Delaney P. Neurology. 1976 Jun;26(6 PT1):591-3
3. Madiedo G et al. JAMA. 1980 Aug 15;244(7):688-9.
4. Watkins RR et al. Infectious Diseases in Clinical Practice 2008 Nov;16(6):411-413.
5. Tung YJ et al. Abstracts of the 7th International Congress of the Asia Pacific Society of Infection Control.
6. Dans PE. Ann Int Med 1986;104:86-89.

Acknowledgements: We wish to acknowledge and thank the staff of the Immunology & Serology Laboratory, Singapore General Hospital for going the extra mile for patients.