Assessing Utilization of the Venereal Disease Research Laboratory Test in Cerebrospinal Fluid for the Diagnosis of Neurosyphilis: A Cohort Study

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Background

- Inappropriate use of diagnostic tests is an important contributor to healthcare expenditures.[1] Diagnostic stewardship leads to cost-effective care and prevents unnecessary testing.
- Neuosyphilis is a low prevalence disease for which testing has historically been overused.[2] However, no recent study has evaluated current testing practices.
- Although there is no gold standard method for the diagnosis of neurosyphilis, the cerebrospinal fluid Venereal Disease Research Laboratory (CSF-VDRL) test is considered highly specific.[3,4]
- Established guidelines for the diagnosis of neurosyphilis recommend performing serologic testing for anti-Treponema pallidum antibodies before CSF-VDRL testing (Figure 1).[3-5]
- False-positive VDRL results in blood have been associated with older age, pregnancy, malignancy, certain infections (such as HIV), and autoimmune diseases.[6] While blood contamination is known to cause false-positive CSF-VDRL results, other potential causes are not clearly identified.[6,7]
- There have been multiple case reports of false-positive CSFVDRL results in patients with neoplasticmeningitis; however, the frequency of false-positive results secondary to this condition or other causes remains unknown.[7,8]

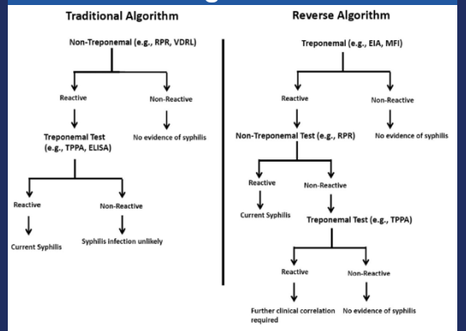
Objectives

1. Quantify the rate of appropriate CSF-VDRL testing for neurosyphilis at our institution
2. Identify the CSF-VDRL false-positivity rate
3. Describe possible cause(s) of false-positive CSF-VDRL reactivity

Methods

- Using an institutional database, we to identified CSF-VDRL tests in patients at any of 3 Mayo Clinic sites.
- Evaluated CSF-VDRL appropriateness in those with negative results from 1/1/2011 – 12/31/2017:[3-5]
  - **Inappropriate Testing:** no prior or negative serologic syphilis testing
  - **Appropriate Testing:** positive serologic syphilis testing prior to CSF-VDRL test
- Records were searched for the terms “syphilis” and “neurosyphilis” to determine how frequently the diagnoses had been considered, and CPT codes were used to determine the number diagnostic lumbar punctures during the same time period.
- Because of the low positivity rate, we expanded our search to 1/1/1994 – 2/28/2018 to identify additional positive CSF-VDRL cases. Medical records of patients with a positive CSF-VDRL were reviewed to determine testing appropriateness and whether the result was consistent with neurosyphilis.
  - **True-positive CSF-VDRL:** concurrent positive syphilis serologic testing in blood
  - **False-positive CSF-VDRL:** negative ancillary syphilis testing with an alternative final diagnosis

Figure 1



Algorithms for detection of syphilis.[13,14] Abbreviations: EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; MFI, multiplex flow immunoassay; RPR, rapid plasma reagin; TPPA, treponema pallidum particle agglutination; VDRL, Venereal Disease Research Laboratory.

Results

- From 1/1/2011 – 12/31/2017, 8,553 unique patients with negative CSF-VDRL results **8,409 (98.3%) had inappropriate CSF-VDRL testing (Figure 2).**
  - “Syphilis” or “neurosyphilis” appeared in notes of 13.8% (1,184/8,553) of these patients
- From 1/1/1994 – 2/28/2018, 33,933 CSF-VDRL tests were performed in 32,626 individual patients: 60 (0.18%) were positive (Figure 3).
  - The positive predictive value of CSF-VDRL testing in our patient population was 71.7%.
  - **All patients with a true-positive CSF-VDRL result had appropriate test utilization**.
  - None of the patients with false-positive CSF-VDRL results had positive treponemal or non-treponemal antibody test results before CSF-VDRL was obtained.
  - Antibiotics were initiated in 4 (26.7%) patients and Infectious Disease was consulted in 10 (66.7%) cases. Confusion over diagnosis led to delay in cancer treatment in at least one patient.
- Of 15 patients with a false-positive CSF-VDRL, **10 (67%) had malignancy affecting the central nervous system.** The remaining 5 (33.3%) had recurrent inflammatory optic neuropathy, multiple sclerosis, Alzheimer’s disease, cerebral venous sinus thrombosis, and transient dizziness (Table).

Figure 2: Appropriateness of CSF-VDRL in patients with negative test results

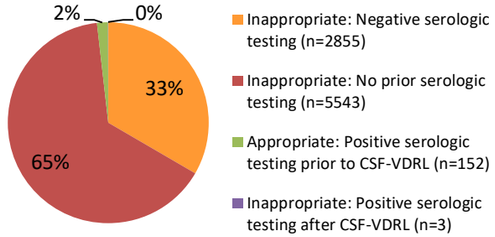


Figure 3: Positive CSF-VDRL Results (n=60)

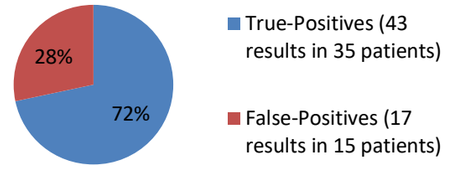


Table: False-Positive CSF-VDRL Patients

Age/ Gender	Clinical Presentation	Final Diagnosis
71/M	Weakness, mental status changes, imbalance	Non-Hodgkin lymphoma-Lymphomatosis
61/M	Spastic quadriparesis, ataxia, bulbar weakness	Meningeal carcinomatosis; metastatic lung adenocarcinoma
79/F	Subacute encephalopathy	Meningeal carcinomatosis; bronchial alveolar carcinoma
60/M	Headache, pachymeningeal enhancement, subdural hematomas	CSF leak; Grade 3 anaplastic astrocytoma
74/M	Multiple cranial neuropathies, leptomeningeal enhancement	Meningeal carcinomatosis; non-small cell lung cancer
14/M	Headaches, pontine lesion, leptomeningeal enhancement	Grade 3 fibrillary astrocytoma with meningeal involvement
59/F	Rapidly progressive cerebellar ataxia; systemic malignancy	Meningeal carcinomatosis; non-small cell lung cancer
16/M	Headache and unresponsive episode, basilar leptomeningeal enhancement	Grade 4 fibrillary astrocytoma with meningeal involvement
61/M	Cauda equina syndrome and root enhancement; known systemic malignancy	Meningeal carcinomatosis; esophageal adenocarcinoma
51/F	Vision loss	Recurrent optic neuropathy
25/M	Progressive left hemiparesis, large enhancing white matter lesions	Tumefactive Multiple Sclerosis
70/F	Headache, mental status changes, hydrocephalus	Meningeal carcinomatosis; lung adenocarcinoma
66/F	Memory decline	Alzheimer’s Disease
82/M	Unresponsive episode	Ischemic strokes/venous sinus thrombosis
52/F	Headache, dizziness and nausea	Transient dizziness and cognitive clouding

Discussion

- Diagnostic stewardship means ordering a test in the right clinical context. Despite calls for reform decades ago,[2] inappropriate CSF-VDRL testing is still common.
- 98% of patients with a negative CSF-VDRL had either no prior syphilis testing or negative serologic results, suggesting that CSF-VDRL ordering represents “box checking” rather than thoughtful testing.
- All patients with a true-positive CSF-VDRL had prior positive serologic syphilis testing, demonstrating the effectiveness of adhering to guidelines to avoid unnecessary testing and minimize false-positives.
- No positive CSF-VDRL without positive blood syphilis results led to neurosyphilis diagnosis, highlighting the importance of pre-test probability in test ordering.
- Neoplastic meningitis was a common cause of false-positive CSF-VDRL results.

Conclusions

- Following diagnostic algorithms for neurosyphilis can prevent unnecessary tests and minimize false-positives.
- Ordering clinicians are encouraged to adhere to published guidelines for test utilization and routinely vet pre-established test order sets.

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