RESEARCH LETTER

Cerebrospinal fluid TPPA titres in the diagnosis of neurosyphilis

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Treponema pallidum can be detected in the cerebrospinal fluid (CSF) in up to 30% of early syphilis infection.[1] The BASHH guidelines[2] recommend a diagnosis of neurosyphilis is based on symptomatology plus CSF white blood cell (WBC) >5 cells/µL, protein >0.45 g/L, a positive CSF Venereal Disease Research Laboratory and a *Treponema pallidum* particle agglutination (TPPA) titre >1:320. Other major guidelines do not recommend CSF TPPA titre assessment.[3] CSF TPPA titres >1:320 are considered to have a high diagnostic yield for neurosyphilis.[4] This test is however not widely available. We assessed the clinical utility of implementing CSF TPPA titre results in the diagnosis of neurosyphilis (clinical utility being the relevance and usefulness of an intervention in patient care).

Data on individuals undergoing CSF examination to investigate possible neurosyphilis before (*period 1*: January 2017 to February 2018, n=26) and after (*period 2*: March 2018 to May 2019, n=23) CSF TPPA titres were routinely available and were assessed and included demographics, HIV status, presenting symptoms and other CSF parameters (table 1). TPPA titre was retrospectively analysed in 16 CSF samples available from *period 1*. '*Clinical neurosyphilis*' was defined as positive syphilis serology, neurological symptoms considered related to neurosyphilis, positive CSF TPPA and receiving treatment for neurosyphilis. '*Laboratory-confirmed neurosyphilis*' (*L-NS*) was defined as the above plus either a positive CSF rapid plasma regain (RPR) or CSF TPPA titre >1:320. χ^2 test was used to calculate p values to compare individuals with and without *L-NS*.

CSF TPPA results were positive in 13 (50%) and 12 (52%) and CSF RPR positive in 4 (15%) and 1 (4%) subjects in *periods 1* and *2*, respectively. In *period 2*, two individuals had a TPPA titre >1:320. The number of individuals with *clinical neurosyphilis* was 11 (42%) and 4 (17%) in *periods 1* and *2*, respectively. In individuals (n=39) with both CSF RPR and TPPA titres available, all with a positive CSF RPR had a CSF TPPA >1:320.

Of 43 individuals in whom a CSF TPPA titre and/or RPR was available, 8 subjects (18%) met the criteria for *L-NS*. No individual with a CSF protein <0.45 g/L met the criteria for *L-NS* (p=0.0001). For those with CSF WBC >5 cells/µL, five met the criteria for *L-NS* and three did not (p=0.0004). There was no significant association between serum RPR of above and below 1:32 and meeting the criteria for L-*NS* (p=0.51).

In our cohort, the numbers of *clinical neurosyphilis* diagnoses fell from 42% to 17% since the introduction in CSF TPPA titre measurements. This was despite similar presenting symptoms and CSF findings preintroduction and postintroduction of

Table 1 Summary of patient characteristics and cerebrospinal fluid results (n=49*)

	Period 1†			Period 2†		
	Total cohort	Clinical neurosyphilis	Non-neurosyphilis	Total cohort	Clinical neurosyphilis	Non-neurosyphilis
Number	**26**	**11**	**15**	**23**	**4**	**19**
Demographics						
Male	24 (92)	11 (100)	13 (86)	22 (95)	4 (100)	18 (94)
MSM	21 (84)	10 (90)	11 (73)	18 (78)	4 (100)	14 (73)
HIV status						
Positive	16 (61)	8 (72)	8 (72)	13 (56)	0	13 (68)
On ART	14	6	8	12	N/A	12
CD4						
≤350 cells/µL	3	2	1	3	N/A	3
>350 cells/µL	13	6	7	10	N/A	10
Presenting symptom‡						
Headache	7 (26)	1 (9)	6 (40)	9 (39)	1 (25)	8 (42)
Dizziness	7 (26)	3 (27)	4 (26)	4 (17)	0	4 (21)
Visual disturbance	7 (26)	3 (27)	4 (26)	4 (17)	1 (25)	3 (15)
Tinnitus	5 (19)	3 (27)	2 (13)	5 (21)	1 (25)	4 (21)
Other	3 (11)	2 (18)	1 (6)	7 (30)	1 (25)	6 (31)
Serum RPR						
≥1:32	18 (89)	9 (81)	9 (60)	16 (69)	4 (100)	12 (63)
CSF						
TPPA +ve	13 (50)	11 (100)	2 (13)	12 (52)	4 (100)	8 (42)
TPPA titre >1:320§	2	2	0	2 (8)	2 (50)	0
RPR +ve	4 (15)	4 (36)	0	1 (4)	1 (25)	0
WBC >5 cells/µL	4 (15)	3 (27)	1 (6)	4 (17)	4 (100)	0
Protein ≥0.45 g/L	13 (50)	9 (81)	4 (22)	8 (34)	4 (100)	4 (50)

All values are number (%).
*The total cohort number 49. Of these, 43 samples were tested for TPPA titre or had a positive RPR (20/26 in *period 1* and 23/23 in *period 2*).
†*Period 1*: January 2017 to February 2018, *period 2*: February 2018 to May 2019.
‡Some patients reported more than one symptom.
§TPPA titre added retrospectively to available samples in *period 1;* no percentage shown for this period as different denominator.
ART, antiretroviral treatment; CSF, cerebrospinal fluid; MSM, men who have sex with men; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination; WBC, white blood cells.

CSF TPPA titre testing in clinical practice. Introduction of this test aided clinical diagnoses and possibly reduced the number of individuals with a diagnosis of neurosyphilis who did not truly have the disease.

The average cost of managing neurosyphilis in a UK healthcare setting is £4700.[5] Addition of CSF TPPA titration does not incur an additional cost compared with assessing a positive/negative CSF TPPA assay, making it a cost-effective measure. Importantly, in individuals with a high index of clinical suspicion for neurosyphilis, if the CSF TPPA titre is ≤1:320, CSF protein and WBC are required to determine the optimal management plan. Our report has limitations, including the small number of participants and a lack of data on long-term clinical outcomes.

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