Lumbar Puncture and Syphilis Outcome

ID: STUDY00001718

16 Dec 2020

Participants were enrolled from September 2013 to March 2018. Study enrollment criteria changed over its course because of slow accrual. The original plan was to enroll PLWH with a new syphilis diagnosis who had serum RPR titer ≥ 1:32 or peripheral blood CD4+ T cells ≤ 350/ul who did not meet CDC criteria for lumbar puncture based on symptoms [5] and to randomize them to LP vs. no LP. Of note, although CDC criteria for lumbar puncture include cognitive dysfunction, we did not consider cognitive complaints as a reason to exclude study participants because cognition was the focus of our study. After the first year only 32 randomized individuals were entered, and the study was opened to persons not infected with HIV and to individuals who declined randomization. The latter 186 individuals were not restricted by serum RPR titer, peripheral blood CD4 or symptoms, with a plan to match eligible individuals to the eligibility criteria for the original study. We systematically collected the reason for not agreeing to randomization in 167 participants. The most common was that the provider recommended LP (n=132). Individuals who were randomized were not allowed to re-enroll in the study with a new episode of syphilis, but those who were not randomized could re-enter and could be randomized or not with a subsequent episode of syphilis.

The first randomized visit for individuals who were ever randomized, and the first nonrandomized visit for those who were never randomized could be included in the analysis if the participant completed the CogState battery. All randomized participants were included in the analysis; 2 individuals were randomized after a previous, nonrandomized syphilis episode, 6 and 8 months later. Of the 186 nonrandomized participants, analysis was restricted to those with serum RPR titer ≥ 1:32 or, for PLWH, peripheral blood CD4+ T cells ≤ 350/ul. All

nonrandomized participants endorsed normal vision, no photophobia or gait abnormality, and normal or at most mild hearing loss based on our previous observation that these symptoms predicted a reactive CSF-VDRL [8]. Ninety-six individuals were included in the entry analysis (Figure 1).

Procedures

Participants underwent a medical history, neurologic examination, blood draw, urine toxicology screen, and lumbar puncture, when indicated. The participant's provider and the participant decided whether neurosyphilis treatment was indicated based on CSF abnormalities alone; neither were aware of cognitive assessment results.

Neuropsychological assessment

The neuropsychological assessment included the Wide Range Achievement Test-third edition (WRAT-3) reading subtest [9] as an assessment of premorbid verbal intelligence, a revised version of the Lawton and Brody instrumental activities of daily living (IADL) scale [10, 11] and the Medication Management Test-Revised (MMT-R) [10, 12], the Beck Depression Inventory (BDI-II) [13], and the CogState battery [14]. The CogState consists of computerized neuropsychological tests and has been used in clinical and research settings, including in PLWH [15-18]. It includes seven tests spanning cognitive domains of psychomotor function, attention, working memory, executive function, and verbal learning. To assess subjective cognitive impairment, we used question 19 on the IADL (difficulties due to primary cognitive problems or

to cognitive and physical problems) and question 19 on the BDI-II (difficulty with concentration). Participants were asked to return at 24 and 52 weeks for follow-up IADL, MMT-R and CogState battery.

Laboratory Methods

Cerebrospinal fluid white blood cell (WBC) enumeration and CSF-VDRL reactivity were determined in a Clinical Laboratory Improvement Amendments (CLIA)-certified hospital clinical laboratory. HIV RNA and peripheral blood CD4+ T lymphocyte concentrations were obtained by medical record review. Serum RPR titers were performed in a research laboratory [19]. Detection of *Treponema pallidum* subspecies *pallidum* (*T. pallidum*) DNA in blood was determined as previously described [20, 21]. Only samples collected within 8 days of treatment of the current episode of syphilis were tested based on our experience that *T. pallidum* DNA is rarely detected in blood samples after this time (unpublished data).

Data analysis

Assessment of cognitive impairment was based on age adjusted normative data from CogState and was categorized as none (all test scores > -1 standard deviation [SD] of normative data), mild impairment (two test scores < -1 SD, or one test score < -2 SD), moderate impairment (two test scores < -2 SD) or severe impairment (three test scores < -2 SD). For the entry analysis, the latter two categories were combined. For the follow-up analysis, participants were categorized as improved if they had any impairment at study entry and improved by at least one category, or as

normalized if they improved to no impairment. Participants were categorized as declined if they were not severely impaired at entry and declined by at least one category.

For this study, we defined abnormal CSF as WBCs >5/ul. Because we included persons not infected with HIV and because our PLWH were largely on antiretrovirals with suppressed plasma HIV RNA, we were unlikely to overdiagnose neurosyphilis.

WRAT scores were normalized based on age [9]. Years of education was categorized as 9-12 vs. ≥13 years (high school or less vs. more than high school), BDI- II was categorized as 0-13 (none or mild depression) vs. ≥14 (moderate or greater depression), MMT-R was categorized as <5 vs. ≥5 [10, 22], and IADL was categorized as dependent vs. independent.

Descriptive statistics are expressed as number (percent) or median (interquartile range [IQR] or 95% confidence intervals). Proportions were compared by the Chi-square or Fisher's exact test, and comparisons of continuous variables by Mann-Whitney U test. Odds ratios (ORs) with 95% CI for categories of cognitive impairment at study entry were determined by univariate or multivariate ordinal logistic regression. Time to cognitive change was assessed by log rank test, and hazard ratios were determined by Cox regression. P-values <0.05 were considered statistically significant.