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Previous Syphilis Alters the Course of Subsequent Episodes of Syphilis

Christina M. Marra,[1,2] Clare L. Maxwell,[1] Sharon K. Sahi,[1] Lauren C. Tantalo,[1] Shelia B. Dunaway,[2] and Sheila A. Lukehart[2,3]

[1]Department of Neurology, University of Washington School of Medicine, Seattle, Washington, USA, [2]Department of Medicine–Infectious Diseases, University of Washington School of Medicine, Seattle, Washington, USA, and [3]Department of Global Health, University of Washington School of Medicine, Seattle, Washington, USA

Background. Individuals with previous syphilis may be more likely to be asymptomatic when they are reinfected with *Treponema pallidum*.

Methods. Individuals enrolled in a study of cerebrospinal fluid (CSF) abnormalities in syphilis were allowed to enroll in the study again with subsequent syphilis. For each participant, the index episode was defined as the most recent syphilis episode for which the study entry visit was performed within 30 days of the syphilis diagnosis date. Venipuncture and lumbar puncture were performed. The total number of syphilis episodes was determined by review of medical and public health records. *Treponema pallidum* DNA in blood and rRNA in CSF were detected using polymerase chain reaction (PCR) and reverse transcriptase PCR. Odds ratios (ORs) with 95% confidence intervals (CIs) were determined using logistic regression.

Results. 701 individuals had 1 (n = 478), 2 (n = 155), or ≥3 (n = 68) episodes of syphilis. The proportion of individuals whose index episode was asymptomatic significantly increased with increased number of syphilis episodes ($P < .001$). This difference was not explained by frequency of serological tests. Adjusted ORs (aORs) of detection of *T. pallidum* DNA in blood or rRNA in CSF at the index episode were significantly lower in those with previous syphilis (0.13; 95% CI, .08–.23, and 0.06, 95% CI, .02–.17). The aOR of neurosyphilis at the index episode was also significantly lower in individuals with previous syphilis (0.43; 95% CI, .27–.68).

Conclusions. Previous syphilis attenuates clinical and laboratory manifestations of infection with *T. pallidum*.

Keywords. syphilis; neurosyphilis; repeat infection; *Treponema pallidum*.

Since 2001, the rate of primary and secondary syphilis in the United States has steadily increased, particularly among men who have sex with men (MSM). In 2017, the rate was 11% higher than in 2016; 68% of infected individuals were MSM, of whom 46% were persons living with human immunodeficiency virus (PLWH) [1]. Similar observations have been made in other high-income countries [2, 3]. Identification of repeat episodes of syphilis in the same individual, particularly PLWH, is increasingly frequent [4–7], and these individuals are often asymptomatic [8–12]. This observation has sparked a debate regarding whether increases in asymptomatic syphilis are due to increased frequency of serological testing [5, 8, 12] or to differences in disease manifestations in individuals with repeat episodes of syphilis, perhaps due to acquired immune responses [10, 11], or to both factors [9]. Our goal in this study was to address this controversy within a cohort of PLWH and individuals not living with HIV enrolled in a study of cerebrospinal fluid (CSF) abnormalities in syphilis, many of whom returned to the study with subsequent episodes of syphilis.

METHODS

Study Participants

Participants were enrolled in a study of CSF abnormalities in syphilis conducted in Seattle, Washington, from September 1996 through June 2014 [13]. Eligibility for enrollment included clinical and serological evidence of syphilis and concern for neurosyphilis by the referring provider or by the patient. Reasons for referral to the study included, but were not restricted to, neurological symptoms or signs, particularly vision or hearing loss; serum rapid plasma reagin (RPR) titer ≥1:32; or for PLWH, peripheral blood CD4+ T-cell count ≤350/uL. The University of Washington Institutional Review Board reviewed and approved the study protocol, and written informed consent was obtained from all study participants.

Clinical Procedures

Participants underwent a standardized medical history and physical examination, blood draw, and lumbar puncture by a physician, nurse practitioner, or physician assistant in a hospital clinic or public health sexually transmitted diseases clinic examination room. Those with abnormal CSF and who were treated for neurosyphilis underwent follow-up visits that included

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Correspondence: C. M. Marra, Harborview Medical Center Box 359775, 325 9th Avenue, Seattle, WA, 98104 (cmarra@uw.edu).

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venipuncture at 3, 6, and 12 months after therapy; individuals who did not have abnormal CSF did not have follow-up visits. Individuals who had a subsequent episode of syphilis were eligible to enroll again into the study, regardless of whether they had neurosyphilis at a previous entry visit. Enrollment criteria and study procedures were identical to those of their previous study enrollment. At each entry visit, medical and laboratory records were reviewed, including a public health database that included serological test results, syphilis stage, and syphilis treatment.

Syphilis is a reportable disease in Washington State, and clinicians and healthcare facilities are required to submit a case report form for each individual diagnosed with syphilis. In addition, laboratories are legally required to report all reactive syphilis test results to public health departments in Washington State. As a matter of routine, negative test results on persons with a history of syphilis are also recorded in this database. All reactive syphilis serological tests are confirmed by the State Public Health Laboratory or the Public Health Seattle and King County Laboratory. Missing or incomplete case report forms are completed by disease intervention specialists. All information was recorded on standardized data collection forms.

An episode of syphilis was assigned based on identification of the first record of reactive serum syphilis serological tests, or a new diagnosis of primary or secondary syphilis, or newly reactive serological tests after previous negative results, or a 4-fold decline followed by at least a 4-fold increase in nontreponemal test titers occurring 90 days or more after a previously defined episode of syphilis. For each participant, the most recent syphilis episode for which the study entry visit was performed within 30 days of the syphilis diagnosis date constituted the analysis (index) episode, and this study visit is called the index visit.

Laboratory Methods

Cerebrospinal fluid white blood cell enumeration and CSF-Venereal Disease Research Laboratory (VDRL) test reactivity were determined in a Clinical Laboratory Improvement Amendments-certified hospital clinical laboratory. HIV RNA copy number and peripheral blood CD4+ T-lymphocyte counts were obtained by review of medical records, and only values obtained within 90 days of the index episode were considered. Serum RPR test titers determined while participants were on-study were performed in a research laboratory using published methods [14]. Otherwise, serum RPR test titers were obtained from medical and public health records. Detection of *Treponema pallidum* subspecies *pallidum* (*T. pallidum*) DNA in blood (n = 661) and rRNA in CSF (n = 678) were determined as previously described [13, 15].

Statistical Methods

Descriptive statistics are expressed as number (percent) or median (interquartile range [IQR]). Proportions were compared using the χ^2 or Fisher exact test. Odds ratios (ORs) with 95% confidence intervals (CIs) were determined using logistic regression. Covariates with P values ≤ .10 were included in multivariate models to determine adjusted ORs (aORs), with covariates removed if $P > .05$ in the initial multivariate model. P values ≤ .05 were considered statistically significant.

RESULTS

The characteristics of the 701 individuals at their index visit are shown in Table 1; 478 had 1 episode of syphilis, and the remaining 223 had at least 2 episodes of syphilis: 155 had 2, 43 had 3, 15 had 4, 8 had 5, 1 had 7, and 1 had 9 total episodes of syphilis recorded by the time of the index episode. At the index episode, most participants were men and 79.6% were PLWH. Among the PLWH, the median peripheral blood CD4+ T-cell count (available in 470 participants) was 439/uL (272–603), and median plasma HIV RNA (available for 476 participants) was 230 c/mL (40–33 065). Of all 701 participants, 51.2% had symptomatic syphilis (primary or secondary syphilis stages) and 48.8% had asymptomatic syphilis (early latent or late latent syphilis stages). About half were treated for the index syphilis episode before study entry. The median number of days between syphilis diagnosis and the index visit was 12 (6–19). We categorized the number of episodes as 1, 2, or ≥3 to have sufficient numbers in each group to allow comparisons. Compared with the other stages, the proportion of individuals diagnosed with asymptomatic (early latent and late latent) syphilis at their index episode increased with increased number of syphilis episodes ($P < .001$; Figure 1).

To address the possibility that the index episode was more likely to be asymptomatic in individuals with repeat episodes of

Table 1. Characteristics of 701 Study Participants at the Index Episode

Characteristic	Value
Male	687 (98.0)
Men who have sex with men	656 (95.6)[a]
Age, y	39 (33–46)
Persons living with human immunodeficiency virus	558 (79.6)
Index episode stage	
Primary	67 (9.6)
Secondary	292 (41.7)
Early latent	222 (31.7)
Late latent	120 (17.1)
Serum rapid plasma reagin titer	64 (32–256)
Treated for the index episode of syphilis before entry	338 (48.2)
Treponema pallidum DNA detected in blood	175 (26.5)[b]
T. pallidum rRNA detected in CSF	86 (12.7)[c]
CSF white blood cells >20/uL or reactive CSF-Venereal Disease Research Laboratory test	144 (21.2)[c]

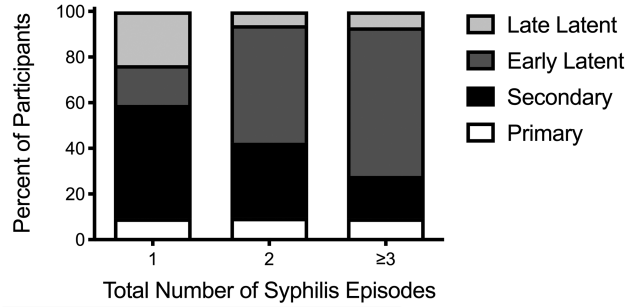
Values are expressed as number (percent) or median (interquartile range).

Abbreviation: CSF, cerebrospinal fluid.

[a]Sexual orientation was available for 686 men.

[b]Blood was available for 661 participants.

[c]CSF was available for 678 participants.



Number of participants			
Primary	42	16	8
Secondary	224	55	16
Early latent	79	86	56
Late latent	106	10	6

Figure 1. Syphilis stage at the index episode among individuals with 1, 2, or ≥3 total episodes of syphilis. Compared with the other stages, the proportion of individuals who were asymptomatic (early latent or late latent syphilis) increased with increasing number of syphilis episodes ($P < .001$). The box indicates the number of individuals in each of the 3 stacked bars by stage.

syphilis simply because of increased frequency of testing, we defined repeat nontreponemal tests as those that were performed 90 or more days after the previous episode. We chose a 90-day interval after an episode because the shortest recommended syphilis screening interval for high-risk individuals is 90 days [16] and tests within the 90-day interval after a syphilis episode were likely performed for follow-up and not for screening. We ranked the number of tests as 1, 2, or ≥3, and we considered days of follow-up as quartiles in logistic regression analysis. For the 223 individuals with more than 1 syphilis episode, the odds of the index episode being asymptomatic were higher for individuals with more tests, but this difference was not significant after taking into account duration of follow-up (aOR, 1.65; 95% CI, .81–3.35; $P = .17$ for those with 2 tests compared with 1 test and aOR, 2.05; 95% CI, .80–5.27; $P = .14$ for those with 3 or more tests compared with 1 test).

Next, we examined the impact of the number of episodes of syphilis categorized as 1, 2, or ≥3 on detection of *T. pallidum* DNA in blood or rRNA in CSF at the index visit. We ran multivariate logistic regression models that included terms for 1 vs ≥1 episode and a term for ≥3 episodes. One vs more than 1 episode was highly significant, but the term distinguishing ≥3 episodes from 1 vs more than 1 was not significant (data not shown). In our final models estimating the odds of detection of *T. pallidum* DNA in blood or rRNA in CSF at the index visit, we combined the number of episodes into 2 categories: no previous syphilis and any previous syphilis.

Compared with individuals without previous syphilis, the proportions of participants with detectable *T. pallidum* DNA in blood and rRNA in CSF at the index visit were significantly lower in those with previous syphilis ($P < .001$ for both; Figure 2). In univariate analyses (Table 2), the odds of detection of *T. pallidum* DNA in blood at the index visit were significantly lower in those with previous syphilis, in those with previous late latent syphilis, and in those treated for the index visit prior to the entry date. The odds of detection of *T. pallidum* in blood increased successively for every 2-fold increase in serum RPR titer and were higher in those with early-stage syphilis and in PLWH. In multivariate analyses, the relationships with all but previous late latent syphilis and HIV remained significant (Table 2). Similarly, in univariate analysis, the odds of detection of *T. pallidum* rRNA in CSF at the index visit were significantly lower in those with previous syphilis and in those treated for the index episode of syphilis before study entry and were higher in those with higher serum RPR titers (Table 2). In multivariate analyses, the relationships with all of these factors remained significant (Table 2). Among PLWH, including plasma HIV RNA or peripheral blood CD4+ T-cell concentrations in the multivariate models did not change the results (data not shown).

One possible explanation for the relationships we saw between previous syphilis and detection of *T. pallidum* DNA in blood or rRNA in CSF at the index visit could be inaccuracy in diagnoses of early latent or late latent syphilis, which are based solely on serological tests. Specifically, if increases in serum nontreponemal test titers can occur in individuals with previous syphilis as part of their natural history, or due to laboratory variability, and not because of reinfection, detection of *T. pallidum* DNA in blood or rRNA in CSF would not be expected. To address this possibility, we repeated the multivariate analyses restricting them to the 359 individuals with symptomatic syphilis (index episode stage was primary or secondary). Taking into account previous treatment and serum RPR titer,

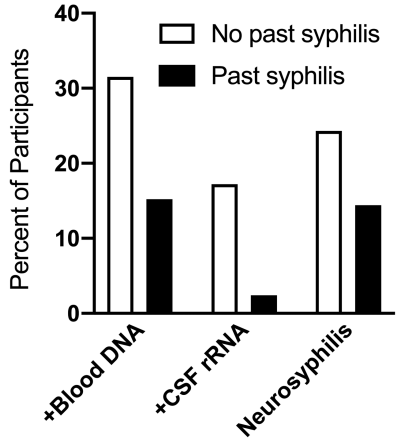


Figure 2. Proportions of participants with and without previous syphilis who had detectable *Treponema pallidum* DNA in blood or rRNA in CSF or neurosyphilis at the index visit. Compared with individuals without previous syphilis, those with previous syphilis were significantly less likely to have detectable *T. pallidum* DNA in blood or rRNA in CSF ($P < .001$ for both), and they were significantly less likely to have neurosyphilis ($P = .003$). Neurosyphilis was defined as CSF white blood cells >20/uL or a reactive CSF-Venereal Disease Research Laboratory test. Abbreviation: CSF, cerebrospinal fluid.

Table 2. Factors Associated With Detection of *Treponema pallidum* DNA in Blood or rRNA in Cerebrospinal Fluid at the Index Episode

	Treponema pallidum DNA Detected in Blood		*Treponema pallidum* rRNA Detected in Cerebrospinal Fluid	
Factor	OR (95% CI), *P* Value	aOR (95% CI), *P* Value	OR (95% CI), *P* Value	aOR (95% CI), *P* Value
Previous syphilis (any stage)	0.39 (.25–0.60), < .001	0.13 (.08–.23), < .001	0.12 (.05–.30), < .001	0.06 (.02–.17), < .001
Previous late latent syphilis	0.47 (.29–.77), .002	NI[a]	0.74 (.41–1.33), .31	NI[a]
Treated for the index episode of syphilis before entry	0.05 (.03–.09), < .001	0.02 (.01–.05), < .001	0.10 (.05–.20), < .001	0.07 (.04–.16), < .001
Serum rapid plasma reagin (per 2-fold titer increase)	1.25 (1.15–1.36), < .001	1.33 (1.20–1.48), < .001	1.34 (1.20–1.50), < .001	1.50 (1.30–1.73), < .001
Stage (early vs late)	2.00 (1.18–3.38), .01	5.84 (3.06–11.16), < .001	1.0 (.55–1.81), .99	NI[a]
People living with HIV vs people not living with HIV	1.84 (1.15–2.95), .01	NI[a]	0.81 (.47–1.39), .45	NI[a]

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; NI, not included in final model; OR, odds ratio.

[a]Not included in the final model because $P > .10$ in univariate analysis or $P > .05$ in the initial multivariate analysis.

the odds of detection of *T. pallidum* DNA in blood or rRNA in CSF remained significantly lower in those with previous syphilis despite the fact that their reinfection was symptomatic: aOR, 0.15; 95% CI, .07–.36; $P < .001$ for blood and aOR, 0.09; 95% CI, .02–.38; $P = .001$ for CSF.

We also examined the impact of previous syphilis on the odds of neurosyphilis at the index visit, which we defined as a reactive CSF-VDRL or CSF white blood cells >20/uL. Compared with individuals without previous syphilis, the proportion of individuals with neurosyphilis at the index visit was significantly lower in those with previous syphilis ($P = .003$; Figure 2). In univariate and multivariate models, the odds of neurosyphilis were significantly lower in those with previous syphilis (Table 3).

DISCUSSION

While some studies have suggested that individuals with a previous episode of syphilis are more likely to be asymptomatic with a subsequent episode [8–12], whether this finding reflects increased serological testing, acquired immune responses, or both has remained a topic of debate. The difference between these 2 explanations is not trivial. The finding that immune responses as a consequence of previous syphilis could alter the clinical manifestations of *T. pallidum* reinfection suggests that an effective syphilis vaccine may be possible, a goal that has thus far not been achieved. In this study, we found that compared with those without previous episodes of syphilis, individuals with repeated episodes of syphilis were more likely to have asymptomatic syphilis at their index visit. Importantly, this finding was not explained by testing frequency. This finding has important implications for public health and for clinical care and supports recommendations to screen high-risk individuals for syphilis regularly, regardless of symptoms.

We also found that the odds of detection of *T. pallidum* DNA and rRNA in blood and CSF at the index episode were 7.7 and 16.7 times lower in individuals with previous syphilis compared with those without previous syphilis, that this relationship held even when we restricted the analysis to those whose index syphilis episode was symptomatic (primary or secondary stages), and that the odds of neurosyphilis at the index visit were 2.3 times lower in individuals with previous syphilis compared with those without previous syphilis. These results support the concept that acquired immunity resulting from an initial syphilis infection can affect the presentation and course of subsequent episodes of syphilis. We had expected that those with prior late latent syphilis, in whom longer exposure to *T. pallidum* before treatment might lead to a more robust immune response, would have significantly lower odds of detection of *T. pallidum* DNA in blood or rRNA in CSF, but this was not the case. Importantly, our conclusions held regardless of HIV status and despite the fact that previous syphilis episodes were treated.

The concept that previous syphilis can confer protection from reinfection is supported by previous observations. Studies in the

Table 3. Factors Associated With Neurosyphilis, Defined as Cerebrospinal Fluid (CSF) White Blood Cells >20/uL or Reactive CSF-venereal Disease Research Laboratory Test at the Index Episode

Factor	Odds Ratio (95% CI), *P* Value	Adjusted Odds Ratio (95% CI), *P* Value
Previous syphilis (any stage)	0.52 (.34–.81), .004	0.43 (.27–.68), < .001
Previous late latent syphilis	1.66 (1.10–2.52), .02	NI[a]
Treated for the index episode of syphilis before entry	0.51 (.35–.75), .001	0.47 (.32–.70), < .001
Serum rapid plasma reagin (per 2-fold titer increase)	1.26 (1.16–1.38), < .001	1.29 (1.18–1.41), < .001
Stage (early vs late)	0.47 (.30–.73), .001	NI[a]
People living with HIV vs people not living with HIV	0.67 (.43–1.03), .07	NI[a]

Abbreviations: CI, confidence interval; NI, not included in final model.

[a]Not included in the final model because $P > .05$ in the initial multivariate analysis.

rabbit syphilis model showed that untreated animals infected for 3 or more months are completely protected from symptomatic reinfection with the same isolate, and they may or may not be protected from symptomatic infection with a different (heterologous) isolate [17]. Experiments on human prisoners, which would not be publishable in the modern era, showed that individuals with untreated or treated late syphilis were less likely to develop dark-field positive lesions after cutaneous inoculation with *T. pallidum* compared with individuals who had been treated for early syphilis [18]. Additionally, a mathematical analysis of reported cases of syphilis in the United States between 1960 and 1993 suggested that oscillations in syphilis incidence were consistent with development of immunity following treated infection [19].

Results similar to ours regarding less dissemination of organisms to blood in individuals with repeat episodes of syphilis were seen in a much smaller study, where, in 3 individuals with repeat episodes of syphilis, *T. pallidum* DNA was identified in skin lesions but not in blood [20]. The finding that blood and CSF bacterial burdens are lower in repeat episodes of syphilis is also supported by observations that the Jarisch-Herxheimer reaction, an acute febrile response after early syphilis treatment that is likely associated with bacterial burden, is less common in repeat episodes of syphilis [21, 22].

Limitations of our work should be considered in interpreting our results. The individuals in our study enrolled because of concern for neurosyphilis, which likely increased the proportion who were PLWH. However, we did not find a significant relationship between HIV status and our outcome variables in multivariate analyses (Tables 2 and 3). In addition, while enrollment was in no way dependent upon previous episodes of syphilis, our participants, who were mostly MSM, were representative of the populations that are at risk for *T. pallidum* reinfection. It is possible that some episodes of latent syphilis in those with more than 1 episode of syphilis, whose diagnoses were based solely on increases in serum nontreponemal test titers, were not truly examples of reinfection but rather represented fluctuations in titers or laboratory variation. As such, we may have overestimated the number of repeat infections classified as early latent. However, our conclusions regarding the impact of previous syphilis on detection of *T. pallidum* DNA in blood and rRNA in CSF were the same when we restricted the analysis to those whose index syphilis episode was symptomatic.

We demonstrate differences in symptomatic disease and in bacterial detection in blood and CSF in individuals with a new episode of syphilis who have had previous syphilis, regardless of previous syphilis stage and HIV status and despite treatment for their previous episodes of syphilis. Our study suggests that acquired immune responses play an important role. Future studies that compare host humoral and cellular immune responses during successive episodes of syphilis may help clarify the basis for our observations and may ultimately inform vaccine development.

Notes

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