The New England
Journal of Medicine

Volume 331 DECEMBER 1, 1994 Number 22

THE RESPONSE OF SYMPTOMATIC NEUROSYPHILIS TO HIGH-DOSE INTRAVENOUS PENICILLIN G IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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Abstract *Background.* Infection with the human immunodeficiency virus (HIV) may affect both the natural course of syphilis and the response to treatment. We examined the response to treatment with high-dose penicillin G in HIV-infected patients with symptomatic neurosyphilis.

Methods. Neurosyphilis was defined by reactivity in serum treponemal tests for syphilis, neurologic manifestations consistent with neurosyphilis, and a positive Venereal Disease Research Laboratory (VDRL) test on cerebrospinal fluid. We identified 11 HIV-infected patients with symptomatic neurosyphilis; 5 had been treated previously for early syphilis with penicillin G benzathine. Patients were treated with 18 million to 24 million units of penicillin G per day administered intravenously for 10 days. Cerebrospinal fluid was examined approximately 6 and 24 weeks after treatment, when the polymerase chain reaction and rabbit inoculation were used to detect *Treponema pallidum*.

Results. In four of the seven patients studied 24 weeks after treatment, the serum titers on rapid plasma reagin (RPR) testing decreased by at least two doubling dilutions, and four patients had reductions in the cerebrospinal fluid titers on VDRL testing or reverted to nonreactive results. In two patients there was no normalization or improvement in serum titers on RPR testing or cerebrospinal fluid titers on VDRL testing, cell counts, or protein concentrations. One patient relapsed with meningovascular syphilis six months after therapy. *T. pallidum* was detected by the polymerase chain reaction in cerebrospinal fluid from 3 of 10 patients before treatment, but in none of the 10 post-treatment specimens.

Conclusions. In patients with early syphilis who are also infected with HIV, therapy with penicillin G benzathine may fail, and neurosyphilis may develop. The regimen of high-dose penicillin recommended for neurosyphilis is not consistently effective in patients infected with HIV. (N Engl J Med 1994;331:1469-73.)

CONCURRENT infection with *Treponema pallidum* and the human immunodeficiency virus (HIV) is a growing public health problem because the incidence of both syphilis and the acquired immunodeficiency syndrome (AIDS) is increasing.[1] Infection with HIV may affect the natural course of syphilis or the response to treatment.[2-5] Several case reports document serious neurologic complications of early syphilis in patients with HIV infection, many of whom had previously been treated with recommended doses of penicillin G benzathine.[2,5-16] Even in the absence of neurologic symptoms, half of HIV-infected persons with serologic evidence of syphilis may have neurosyphilis.[17]

The efficacy of recommended therapy for neurosyphilis has not been extensively evaluated.[18] This report describes the clinical and laboratory results of our trial of a standard therapeutic regimen of high-dose intravenous penicillin G in HIV-infected patients with symptomatic neurosyphilis, in which we used quantitative nontreponemal serologic testing, the polymerase chain reaction (PCR), and rabbit-infectivity testing to detect *T. pallidum* in cerebrospinal fluid.

METHODS

Study Population

All the study patients received medical care at Grady Memorial Hospital, a large county teaching hospital serving the Atlanta metropolitan area. The study protocol was approved by the institutional review board of Emory University School of Medicine, and the patients were enrolled after giving informed written consent.

We included in the study any HIV-infected adult with newly diagnosed neurosyphilis, as indicated by reactive serum rapid plasma reagin (RPR) and fluorescent treponemal-antibody absorption (FTA-ABS) tests for syphilis, neurologic manifestations consistent with neurosyphilis, and a reactive Venereal Disease Research Laboratory (VDRL) test on cerebrospinal fluid. Cases were ascertained

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Supported by a grant from the Emory Medical Care Foundation Research Foundation and a Clinical Investigator Development Award (NS 01529) from the National Institutes of Health (to Dr. Marra).

Presented in part at the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, October 17-20, 1993.

through a review of all VDRL tests of cerebrospinal fluid processed in the hospital's clinical immunology laboratory.

All patients were enrolled by one of two staff physicians in infectious diseases. Evaluation included a physical examination with assessment of cranial-nerve function, motor function, reflexes, and mental status and a funduscopic examination. We assessed risk factors for HIV infection and evaluated previous syphilis infections and treatment, in part through a review of patient records at the Sexually Transmitted Disease Clinic of the Fulton County Health Department. To determine the stage of syphilis at the time of the diagnosis of neurosyphilis, we used the diagnostic criteria of Ronald et al.[19] Base-line helper T-lymphocyte (CD4) counts were obtained for all patients.

After they had been treated for neurosyphilis, the patients were evaluated by one of the two infectious-disease specialists. For those who agreed, we took sexual histories and performed physical examinations, serologic testing, and lumbar punctures approximately six weeks and six months after treatment.

Treatment

All patients with neurosyphilis were treated with 18 million to 24 million units per day of intravenous aqueous crystalline penicillin G potassium (Cilloral, Apothecon, Bristol-Myers Squibb, Princeton, N.J.) in doses administered every four hours for 10 days.

Serologic Tests in Serum and Cerebrospinal Fluid

Serum RPR and FTA-ABS tests and VDRL tests on cerebrospinal fluid were performed by standard methods.[20] Serum dilutions greater than 512 were not titrated to an end-point dilution.

Cellular, Protein, and Microbiologic Analysis of Cerebrospinal Fluid

Cerebrospinal fluid was examined to determine the absolute and differential cell counts and the protein concentrations according to standard techniques. Blood contamination of cerebrospinal fluid was assessed by measuring the concentration of erythrocytes; no specimen had more than 5 red cells per cubic millimeter. Cerebrospinal fluid pleocytosis was defined as more than 5 white cells per cubic millimeter. All specimens were assayed for cryptococcal antigen and cultured for bacteria, fungi, and mycobacteria.

PCR

We used the PCR to detect *T. pallidum* in cerebrospinal fluid, according to previously published methods.[21] Briefly, a 658-base-pair (bp) region of the gene encoding the 47-kd *T. pallidum* lipoprotein was amplified, and the PCR products were probed by DNA–DNA hybridization with a 496-bp fragment internal to the amplified DNA. Forty cycles were performed in a thermocycler (Perkin–Elmer Cetus, Norwalk, Conn.). To prevent false positive results due to contamination, all specimens were prepared under a laminar-flow hood in a dedicated facility. Specimens of cerebrospinal fluid obtained before and after treatment were stored at −20°C until they were used for PCR analysis.

Rabbit-Infectivity Test

To determine whether viable *T. pallidum* was present in post-treatment cerebrospinal fluid, serologically nonreactive New Zealand white rabbits were inoculated intratesticularly with 1 to 2 ml of cerebrospinal fluid within 120 minutes of collection.[4,22,23] The rabbits were maintained in separate cages in temperature-controlled rooms (18° to 20°C) on antibiotic-free food and were examined for orchitis on day 7 and every three days thereafter. Blood was drawn on days 18, 30, 60, and 90 for serologic testing for syphilis. Rabbits that remained serologically nonreactive and without evidence of orchitis were considered to be uninfected.

Criteria for Treatment Failure

Treatment was considered to have failed if the serum RPR titer did not decline by at least two doubling dilutions (i.e., dilutions in which the titer doubled) at six months. Neurologic impairment could persist indefinitely but could not progress. Finally, treatment was considered to have failed if pleocytosis in the cerebrospinal fluid did not resolve or improve within six months or if the cerebrospinal fluid VDRL titer increased by two or more doubling dilutions.

Results

Study Population

We tested 509 specimens of cerebrospinal fluid from November 1, 1992, through April 30, 1993, and identified 19 adults with reactive VDRL tests (3.7 percent). Five patients who tested negative for HIV, two patients who were being assessed for a response to earlier therapy for neurosyphilis, and one patient who died before entry were not enrolled. We report on the remaining 11 patients, all of whom met the criteria for inclusion and underwent at least one lumbar puncture during follow-up.

Clinical Presentation

The patients (nine men and two women with a mean age of 35 years [range, 24 to 60]) presented with the following neurologic manifestations: unilateral uveitis (in five), bilateral retinitis (one), stroke (two), behavioral changes (two), and meningitis (one). Five of the patients had not previously been known to be infected with HIV, and only two had a prior AIDS-defining illness. Nine patients had identified risk factors for HIV infection, including homosexual contact (seven) and injection-drug use (two). The median CD4 lymphocyte count when neurosyphilis was diagnosed was 344 per cubic millimeter (range, 22 to 972).

Four patients (Patients 1, 2, 8, and 10) had mucocutaneous lesions typical of secondary syphilis (papulosquamous or maculopapular rash involving the palms and soles). Three of them (Patients 1, 2, and 10) also had patchy alopecia.

Previous Therapy for Syphilis

Five of the patients (Patients 3, 5, 7, 9, and 11) had documented histories of treatment for early syphilis (early latent syphilis in three, secondary syphilis in one, and primary syphilis in one). Two patients had each been treated intramuscularly with 2.4 million units of penicillin G benzathine, and three patients had each received 7.2 million units of penicillin G benzathine (Table 1). The median interval between the last injection of penicillin G benzathine and the diagnosis of neurosyphilis was 8 months (range, 3 to 40). There was no sexual history to suggest reinfection in any patient.

Clinical Course

Table 1 summarizes the clinical presentations, serologic and cerebrospinal fluid findings, PCR and rabbit-infectivity results, and outcomes in the 11 patients with neurosyphilis. The median follow-up was 42 weeks (range, 8 to 54). All patients underwent lumbar puncture six weeks after treatment, and seven patients had second lumbar punctures at six months. The median serum RPR titer before treatment was 512 (range, 16 to ≥512), the median cerebrospinal

Table 1. Results of Serologic and Cerebrospinal Fluid Testing and Outcomes in HIV-Infected Patients with Symptomatic Neurosyphilis.*

Patient No.	Week of Examination	Clinical Presentation at Diagnosis	Previous Early Syphilis			Serologic Tests		Cerebrospinal Fluid Tests*				
			Dose of Penicillin G Benzathine	Serum RPR Titer	Months to Diagnosis of Neurosyphilis	CD4 Count	RPR Titer	VDRL Titer	Protein	White Cells	PCR	Rabbit Infectivity
			units			*cells/mm³*			*mg/dl*	*cells/mm³*		
1	0	Uveitis, rash	—	—	—	479	>512	2	26	20	+	ND
	6						256	NR	24	4	−	−
2	0	Uveitis, rash	—	—	—	200	>512	4	82	70	ND	ND
	6						128	1	46	4	−	−
	26						64	NR	38	0	−	−
	52						64					
3	0	Behavioral abnormalities	7.2 million	128	3	582	256	2	55	4	−	ND
	7						32	1	56	56	−	−
	26						32	NR	47	0	−	−
	52						32					
4	0	Uveitis	—	—	—	374	>512	16	76	10	+	ND
	8						128	4	51	80	−	−
	24						64	2	48	8	−	−
	52						32					
5	0	Stroke	7.2 million	128	8	972	16	4	208	30	−	ND
	6						32	2	113	30	−	−
	24						8	2	84	20	−	−
	32						32					
6	0	Retinitis	—	—	—	22	>512	2	36	4	+	ND
	6						256	NR	43	1	−	−
	22						256	NR	32	0	−	−
	56						256					
7	0	Behavioral abnormalities	2.4 million	256	3	440	128	4	152	20	−	ND
	8						128	8	173	10	−	−
	24						64	8	153	10	−	−
	56						64					
8	0	Stroke, rash	—	—	—	344	256	32	96	210	−	ND
	6						128	1	37	54	−	−
9	0	Meningitis†	7.2 million	128	13	77	>512	4	244	12	−	ND
	6						128	1	28	3	−	−
	16						64	1	130	5	−	−
	24	Meningovascular relapse					128	2	124	3	−	ND
10	0	Uveitis, rash	—	—	—	23	>512	64	250	40	−	ND
	6						>512	8	76	43	−	−
11	0	Uveitis	2.4 million	128	40	92	256	2	44	4	−	ND
	6						128	8	44	4	−	−
	40						128					

*Plus signs denote positive results, minus signs negative results, ND not done, and NR nonreactive.
†Blindness developed during treatment.

fluid VDRL titer was 4 (range, 2 to 64), and the median cell count in cerebrospinal fluid was 20 per cubic millimeter (range, 4 to 210). Six weeks after treatment, the serum RPR titers had decreased by two or more doubling dilutions in 4 of the 11 patients, and the cerebrospinal fluid VDRL titers had decreased by two or more doubling dilutions or reverted to nonreactive in 7 of the 11 patients. The VDRL titer remained unchanged (<2 doubling dilutions) in two patients and increased in two patients. Among the eight patients with initial cerebrospinal fluid pleocytosis, five had lower cell counts at six weeks, and in three the counts were unchanged or increased. Cerebrospinal fluid pleocytosis developed in one patient (Patient 3) at six weeks.

Twenty-four weeks after treatment, the serum RPR titers had decreased by two or more dilutions in four of seven patients, and the cerebrospinal fluid VDRL titers had decreased or reverted to nonreactive in four (Patients 2, 3, 4, and 6). The cerebrospinal fluid cell counts returned to normal in three of the six patients with pleocytosis. Two of seven patients (Patients 5 and 7) had no improvement in any of the following: serum RPR titers, cerebrospinal fluid VDRL titers, cerebrospinal fluid white-cell counts, and cerebrospinal fluid protein concentrations. Patient 9 had an initial decline in cerebrospinal fluid VDRL and serum RPR titers, but the titers increased at 24 weeks. Among the seven patients for whom serum RPR titers were available 32 to 56 weeks after treatment, three (Patients 5, 7, and 11) had no decline in titers as compared with base line.

T. pallidum was detected in the cerebrospinal fluid of 3 of 10 patients (Patients 1, 4, and 6) on pretreatment PCR. *T. pallidum* was not detected by PCR or isolated by rabbit-infectivity testing in any cerebrospinal fluid specimen after treatment. The neurologic impairment caused by syphilis improved in 10 of the 11 patients.

Patient 9, who had syphilitic meningitis, had progressive blurring of vision that led to irreversible blindness during the first 96 hours of penicillin treatment (dose, 24 million units per day). An orbital magnetic resonance imaging scan revealed generalized fullness of the optic nerves involving the optic chiasm and the proximal portion of the nerves bilaterally to the level of the optic canal. The findings were consistent with syphilitic ophthalmitis, although a Jarisch–Herxheimer reaction could not be ruled out. Follow-up examinations of cerebrospinal fluid at 6 and 16 weeks demonstrated a decline in pleocytosis and a decrease in the VDRL titer. At 24 weeks, headaches and left-sided weakness developed, and computed tomography revealed diffuse meningeal enhancement and thickening, consistent with meningitis, and infarcts in the right frontal and parietal–occipital areas. The cerebrospinal fluid showed 3 white cells per cubic millimeter, a protein concentration of 124 mg per deciliter, and reactive VDRL results at a 1:2 dilution. Cultures of cerebrospinal fluid for bacteria, fungi, and mycobacteria were negative. The patient was given a diagnosis of meningovascular syphilis and was retreated with 14 days of high-dose intravenous aqueous penicillin G. She had a persistent left hemiparesis after treatment and died two months later; permission for autopsy was not obtained.

Discussion

It has generally been assumed that high-dose regimens of intravenous aqueous penicillin G should be effective against neurosyphilis regardless of concurrent HIV infection. Our study examined the efficacy of high-dose aqueous penicillin G in HIV-infected patients with symptomatic neurosyphilis. Of the 11 patients with neurosyphilis, 5 had previously received 2.4 million to 7.2 million units of penicillin G benzathine and had no sexual history suggesting reinfection. A large proportion of our patients had recurrent infection in the central nervous system despite therapy for early syphilis that met or exceeded current recommendations. This finding supports the observations of others that recommended therapy for early syphilis may not be effective in patients with HIV infection.[2,5-16] The results of our study also raise serious questions about the efficacy of high-dose intravenous penicillin G for neurosyphilis in HIV-infected patients.

We assessed the efficacy of treatment in our patients using clinical, serologic, and biologic criteria and cell counts in cerebrospinal fluid. On the basis of clinical criteria, 10 of the 11 patients in our study had a resolution or stabilization of clinical manifestations after treatment, but a follow-up of more than six months is required to determine whether this clinical improvement represents successful treatment. For example, Patient 9 relapsed with severe meningovascular disease at 24 weeks.

Using the normalization of cerebrospinal fluid as a measure of therapeutic efficacy, we found that two patients (Patients 5 and 7) followed for six months had abnormal cell and protein concentrations and cerebrospinal fluid VDRL titers that did not change. These patients had not had more than two doubling dilutions in serum RPR titers. Two additional patients (Patients 4 and 9) had persistently abnormal cell counts and protein concentrations despite a substantial reduction or normalization of the cerebrospinal fluid VDRL and serum RPR titers.

There are no established guidelines for the appropriate rate of resolution of cerebrospinal fluid abnormalities in patients with neurosyphilis. In patients with concurrent HIV infection, persistently positive VDRL results and abnormal cell counts and protein concentrations in cerebrospinal fluid may be due to treatment failure, HIV infection, or a response to successful treatment. In patients without concurrent HIV infection, pleocytosis is considered to be the hallmark of active neurosyphilis, and the cell count may be the best indicator of a response to therapy.[1,24] Hahn et al. found that initial cerebrospinal fluid pleocytosis resolved six months after penicillin therapy in 80 percent of patients with asymptomatic neurosyphilis, and one year after therapy in 90 percent.[25] Dattner et al. stated that six months after adequate therapy for neurosyphilis, patients should have normal cerebrospinal fluid cell counts and decreased cerebrospinal protein concentrations.[26] Serial VDRL tests on cerebrospinal fluid can be used to follow the response to treatment; it may take years for the cerebrospinal fluid to become nonreactive on nontreponemal testing, although the titer should drop progressively.[26-29]

T. pallidum was not detected after treatment in any cerebrospinal fluid specimen by either rabbit inoculation or PCR, suggesting an absence of treponemes in the central nervous system. Although a positive result on either of these assays would be considered clear evidence of treatment failure, the converse is not true. *T. pallidum* was detected by PCR in cerebrospinal fluid from only three patients before treatment, suggesting that PCR is not a sensitive method for the diagnosis of neurosyphilis. Although we did not perform rabbit-infectivity testing of cerebrospinal fluid specimens obtained before treatment, *T. pallidum* was isolated by rabbit inoculation in only a subgroup of patients who had neurosyphilis in a recent study.[4]

Our patients had very high serum RPR titers when neurosyphilis was diagnosed (median titer, 512), a finding consistent with previous reports of high serum RPR titers and central nervous system involvement in early syphilis.[4,17] Three of seven of our patients (Patients 5, 7, and 11) did not have a decline of two or more doubling dilutions within six months after treatment. Patients with multiple episodes of syphilis may have slower declines in titer.[30,31] The established criteria for a decline in titer are based on patients without known central nervous system involvement, and the appropriate rate of decline has not been established for HIV-infected patients. Although the question has not been explored in a controlled study, there is speculation that titers may decline more slowly in patients

with HIV infection than in immunocompetent patients. If such speculation is true, caution should be used in accepting these slower rates as normal for this patient population. Because there is no microbiologic gold standard for cure, a slower rate of decline may actually be due to the presence of *T. pallidum* that persists after standard regimens.[4,32]

To treat HIV-infected patients with syphilis, careful and more frequent follow-up examinations have already been recommended. Clearly, this is a minimal requirement. Some experts recommend initial treatment with 4.8 million to 7.2 million units of penicillin G benzathine, rather than the 2.4 million units currently recommended for early syphilis. In our study and others, patients with HIV infection have relapsed after therapy, even with 7.2 million units. Some experts also advocate routine cerebrospinal fluid examination of all HIV-infected patients before therapy for syphilis in order to identify those in whom therapy for neurosyphilis is indicated.[3] Although this practice is likely to reduce the number of relapses, our results suggest that even regimens to treat neurosyphilis may not be completely effective in this population. Aqueous penicillin G procaine has not been rigorously examined in this population, and ceftriaxone has been associated with a substantial degree of failure.[17,33]

We could identify no obvious predictors of failure. The three patients with clear treatment failures did not have the highest RPR or VDRL titers at diagnosis, and their CD4 counts were not the lowest. This inability to predict treatment failure may suggest that all HIV-infected patients with syphilis should receive intensive evaluation, including cerebrospinal fluid examination, and very careful follow-up. A larger, well-controlled, prospective study is needed, and alternative therapies should be examined. Consideration should be given to periodic retreatment of patients with persistently reactive serum RPR titers or abnormal cerebrospinal fluid values.

We are indebted to Sandra Pryor, Pranda Tambe, M.D., Victoria Grosh, Diane Jeunnette, Karleen Davis, Anne Williams, and the entire staff of the Infectious Disease Clinic at Grady Memorial Hospital.

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