

CENTRAL NERVOUS SYSTEM INFECTION IN CONGENITAL SYPHILIS

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ABSTRACT

Background Identification of infants with *Treponema pallidum* infection of the central nervous system remains challenging.

Methods We used rabbit-infectivity testing of the cerebrospinal fluid to detect *T. pallidum* infection of the central nervous system in infants born to mothers with syphilis. The results were compared with those of clinical, radiographic, and conventional laboratory evaluations; IgM immunoblotting of serum and cerebrospinal fluid; polymerase-chain-reaction (PCR) assay testing of serum or blood and cerebrospinal fluid; and rabbit-infectivity testing of serum or blood.

Results Spirochetes were detected in the cerebrospinal fluid of 19 of 148 infants by rabbit-infectivity testing. Exposure of the infant to antibiotics before cerebrospinal fluid was obtained for rabbit-infectivity testing was associated with a negative test result ($P=0.001$). Spirochetes were detected in the cerebrospinal fluid in 17 of 76 infants (22 percent) who had no prior antibiotic exposure. These 17 infants included 41 percent (16 of 39) of those with some abnormality on clinical, laboratory, or radiographic evaluation; 60 percent (15 of 25) of those with abnormal findings on physical examination that were consistent with congenital syphilis; and 41 percent (17 of 41) of those with a positive result on IgM immunoblotting or PCR testing of serum, blood, or cerebrospinal fluid, or a positive result on rabbit-infectivity testing of serum or blood. Only one infant who had normal findings on clinical evaluation had a positive cerebrospinal fluid rabbit-infectivity test. Overall, central nervous system infection was best predicted by IgM immunoblotting of serum or PCR assay of serum or blood.

Conclusions Most infants with *T. pallidum* infection of the central nervous system can be identified by physical examination, conventional laboratory tests, and radiographic studies. However, the identification of all such infants requires the use of additional tests, including IgM immunoblotting and PCR assay. (N Engl J Med 2002;346:1792-8.)

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IN infants with suspected congenital syphilis, the detection of central nervous system infection by *Treponema pallidum* remains an elusive but important diagnostic goal. The diagnosis of congenital neurosyphilis has major therapeutic implications because penicillin G benzathine does not reach treponemicidal concentrations in the cerebrospinal fluid,^{1,2} even though this drug is one of the recom-

mended alternative treatments for infants at risk for congenital syphilis.^{3,4} In addition, establishing the prevalence of central nervous system infection among infants with congenital syphilis would help determine the extent to which the central nervous system constitutes a reservoir of infection.

Neurosyphilis is believed to occur in 60 percent of infants with congenital syphilis, as judged by the presence of cerebrospinal fluid abnormalities, such as reactivity on a Venereal Disease Research Laboratory (VDRL) test, pleocytosis, and elevated protein content.⁵ In infants, it is not known whether the results based on these criteria accurately reflect the prevalence of central nervous system infection by *T. pallidum*, since this approach has not been validated by rabbit-infectivity testing. Rabbit-infectivity testing involves the inoculation of clinical specimens into rabbits, and it has been used in research laboratories as the confirmatory test for the diagnosis of syphilis.⁶⁻¹⁰

Immunoblotting has facilitated the detection of neonatal IgM antibody directed specifically against *T. pallidum*, and the polymerase chain reaction (PCR) has been used to detect *T. pallidum* DNA.¹⁰⁻²⁶ In the current study, we used rabbit-infectivity testing of cerebrospinal fluid to identify infants with *T. pallidum* infection of the central nervous system. We compared the results of this test with the results of clinical, radiographic, and conventional laboratory examination; IgM immunoblotting of serum and cerebrospinal fluid; PCR assay of serum, blood, and cerebrospinal fluid; and rabbit-infectivity testing of serum or blood.

METHODS

Patients

Infants were prospectively enrolled if they were born between July 1989 and July 1999, their mothers had had syphilis during pregnancy, their evaluation for congenital syphilis included a lumbar puncture, and there was sufficient cerebrospinal fluid for rabbit-infectivity testing. The study was approved by the institutional review board of the University of Texas Southwestern Medical Center, and written informed consent was obtained from the mother of each patient.

Evaluation

Infants were evaluated for congenital syphilis with use of a standard protocol of conventional tests. A physical examination was

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performed, a nontreponemal test for syphilis in umbilical-cord blood or serum was performed (the VDRL or rapid plasma reagin test), radiographs of the long bones were obtained, and hematocrit and platelet count were determined. Lumbar puncture was performed to obtain cerebrospinal fluid for a VDRL flocculation test, white-cell and red-cell counts, and measurement of protein and glucose content. Findings on physical examination that were consistent with a diagnosis of congenital syphilis included characteristic rash, rhinitis, hepatomegaly, splenomegaly, and generalized lymphadenopathy.²⁷ No infant had seizures, cranial-nerve palsies, or other clinical evidence of central nervous system disease. Radiographic findings suggestive of congenital syphilis included osteochondritis or periostitis of long bones and pneumonia. Anemia was defined as a hematocrit of less than 35 percent in neonates (infants up to 28 days of age) or less than 30 percent in infants who were more than 28 days old, and thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter on at least two consecutive occasions.

In neonates, cerebrospinal fluid white-cell counts of more than 25 per cubic millimeter and protein concentrations of more than 150 mg per deciliter were considered to be elevated. In infants who were more than 28 days old, pleocytosis was defined as more than 5 cells per cubic millimeter, and an elevated protein concentration as more than 40 mg per deciliter. Cerebrospinal fluid specimens with a red-cell count of more than 100,000 per cubic millimeter could not be evaluated accurately and were therefore excluded from analysis. In cerebrospinal fluid samples with no more than 100,000 red cells per cubic millimeter, the white-cell count was adjusted for blood contamination by dividing the red-cell count by 500 and subtracting this value from the white-cell count, and the protein concentration was adjusted for blood contamination by dividing the red-cell count by 1000 and subtracting the value from the protein content expressed as milligrams per deciliter. A nontreponemal titer that was at least four times as high as the maternal titer or a positive cerebrospinal fluid VDRL test was considered diagnostic of congenital syphilis. Aerobic cultures of blood and cerebrospinal fluid were obtained as clinically indicated to determine whether a possible bacterial infection was present.

In addition to the conventional tests for congenital syphilis, IgM immunoblotting of serum and cerebrospinal fluid and PCR assay and rabbit-infectivity testing of serum or blood and cerebrospinal fluid were also performed, as previously described.^{10,26}

Statistical Analysis

We used SPSS software version 10.0 for Windows for the analyses. We used two-tailed Yates' corrected chi-square tests or Fisher's exact tests for categorical data and the Mann-Whitney test for nonparametric continuous data. We used Cohen's κ statistic to calculate the degree of agreement between two diagnostic tests after adjustment for chance; a κ value above 0.6 is considered to indicate strong agreement.²⁸ We used backward stepwise logistic-regression analysis to determine the best predictors of a positive cerebrospinal fluid rabbit-infectivity test. Candidate independent variables included birth weight, gestational age, maternal and umbilical-cord titers on VDRL tests, findings on physical examination, hematocrit, platelet count, radiographic findings, cerebrospinal fluid VDRL titer and indexes, results of IgM immunoblotting of serum and cerebrospinal fluid, and results of PCR assay of serum or blood and cerebrospinal fluid. The data entered in the final logistic-regression model were ranked or dichotomous. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Characteristics of the Patients

The study population consisted of 148 infants born to 146 mothers with syphilis (Table 1). The clinical

TABLE 1. CHARACTERISTICS OF THE INFANTS AND THEIR MOTHERS.*

VARIABLE	VALUE
Mothers (n=146)	
Race or ethnic group — no. (%)	
Black	100 (68)
Hispanic	31 (21)
White	13 (9)
Other	2 (1)
Age — yr	25 ± 6
Prenatal care — no. (%)	94 (64)
Cocaine use — no. (%)	48 (33)
HIV infection — no. (%)†	8 (6)
VDRL titer	
Median	1:16
Range	1:1–1:256
Stage of syphilis — no. (%)	
Primary	16 (11)
Secondary	30 (21)
Early latent (≤1 yr)	61 (42)
Late latent (>1 yr)	6 (4)
Unknown	33 (23)
Treatment of syphilis — no. (%)	
None	93 (64)
≤4 wk before delivery	29 (20)
>4 wk before delivery, but during pregnancy	23 (16)
Unknown	1 (1)
Infants (n=148)	
Birth weight — g	
Mean	2718 ± 605
Range	980–3930
Gestational age — wk	
Mean	37 ± 3
Range	26–42
Sex — no. (%)	
Male	81 (55)
Female	67 (45)
Nontreponemal-test titer‡	1:1–1:512
HIV infection — no. (%)†	1 (1)
Age at evaluation — no. (%)	
1 Day	136 (92)
2–28 Days	5 (3)
29–90 Days	7 (5)

*Plus-minus values are means ± SD. HIV denotes human immunodeficiency virus, and VDRL Venereal Disease Research Laboratory.

†A total of 131 mothers and infants were tested.

‡The nontreponemal test was a VDRL test in most cases and a rapid plasma reagin test in a few cases. Twelve infants had a titer on serologic testing that was at least four times as high as the maternal titer.

characteristics of these women reflected a population at high risk for vertical transmission of *T. pallidum*. At the time of delivery, the majority of the women (73 percent) had early syphilis, 64 percent of the women had received no treatment, and 20 percent had received treatment within four weeks before delivery. Ninety-two percent of the infants were evaluated for congenital syphilis at the age of one day. Nineteen of these infants have been described previously.¹⁰

Seventy infants (47 percent) had clinical, radiographic, or conventional laboratory findings consistent with a diagnosis of congenital syphilis. Sixty-five infants (44 percent) had a positive rabbit-infectivity test, PCR assay, or IgM immunoblot of serum, blood, or cerebrospinal fluid. The rabbit-infectivity test was positive in 31 infants (21 percent): spirochetes were detected in serum or blood samples from 27 of these infants and from cerebrospinal fluid samples from 19 of these infants. One infant who had normal results on conventional diagnostic evaluation and three infants with normal cerebrospinal fluid indexes and non-reactive cerebrospinal fluid VDRL tests had a positive rabbit-infectivity test of cerebrospinal fluid.

Infants who had a negative rabbit-infectivity test of cerebrospinal fluid were more likely to have been exposed to antibiotics prenatally or to have received antibiotics before undergoing lumbar puncture than were infants with a positive cerebrospinal fluid test (66 of 125 [53 percent] vs. 2 of 19 [11 percent], $P=0.001$). Data on antibiotic exposure were missing for four infants with negative cerebrospinal fluid rabbit-infectivity tests. The mother of 1 of the 19 infants with a positive cerebrospinal fluid rabbit-infectivity test had received a single dose of penicillin G benzathine within four weeks before delivery; another infant with a positive test had received penicillin before undergoing lumbar puncture.

Correlates of Central Nervous System Infection

Because antibiotic therapy could have caused a false negative result on the cerebrospinal fluid rabbit-infectivity test, the 76 infants without antibiotic exposure before lumbar puncture were included in subsequent analyses. When the infants with positive serum or blood PCR or rabbit-infectivity tests were analyzed, there were no significant differences in the median red-cell count of cerebrospinal fluid between the 17 infants with a positive cerebrospinal fluid rabbit-infectivity test and the 59 with a negative test (Table 2). No significant correlation was seen between cerebrospinal fluid red-cell count and the cerebrospinal fluid VDRL titer ($P=0.2$) or the results on IgM immunoblotting ($P=0.5$). It is therefore unlikely that contamination of cerebrospinal fluid by blood substantially affected the results of these tests.

Infants with infection of the central nervous system by *T. pallidum*, as shown by a positive cerebrospinal fluid rabbit-infectivity test, had a lower median gestational age and birth weight than infants without such infection (Table 2). The maternal stage of syphilis infection was not associated with the results of the cerebrospinal fluid rabbit-infectivity test ($P=0.53$) (Table 2).

Conventional and experimental diagnostic tests were compared with rabbit-infectivity testing of cer-

ebrospinal fluid to determine the relative accuracy of clinical and laboratory findings for the detection of central nervous system infection by *T. pallidum* (Table 3). An abnormal result on any conventional evaluation had a sensitivity of 94 percent, a specificity of 61 percent, and a positive predictive value of 41 percent; only one infant in whom spirochetes were detected in the cerebrospinal fluid by the rabbit-infectivity test was not identified by conventional evaluation. A combination of cerebrospinal fluid tests (white-cell count, measurement of protein, or VDRL test) had suboptimal sensitivity (82 percent) and specificity (65 percent). Three infants with positive cerebrospinal fluid rabbit-infectivity tests were not identified by conventional cerebrospinal fluid tests. On the other hand, a normal physical examination and normal results on conventional evaluations had good negative predictive values (96 percent and 97 percent, respectively). All eight infants born to mothers infected with human immunodeficiency virus type 1 had negative results on PCR and rabbit-infectivity testing of serum, blood, and cerebrospinal fluid.

IgM immunoblotting of serum identified all infants who had *T. pallidum* infection of the central nervous system. The sensitivity of serum or blood PCR assay (94 percent) was superior to that of cerebrospinal fluid IgM immunoblotting (47 percent) and cerebrospinal fluid PCR assay (65 percent) (Table 3). Statistical agreement was strongest between cerebrospinal fluid rabbit-infectivity testing and serum or blood PCR assay ($\kappa=0.76$), cerebrospinal fluid PCR assay ($\kappa=0.67$), serum or blood rabbit-infectivity testing ($\kappa=0.62$), and physical examination ($\kappa=0.61$) (Table 3). Among infants who had a negative cerebrospinal fluid rabbit-infectivity test, 11 had a positive result on cerebrospinal fluid IgM immunoblotting (4 with no prior antibiotic exposure and 7 with prior antibiotic exposure), and 2 had a positive cerebrospinal fluid PCR assay and no prior antibiotic exposure.

Logistic-Regression Analysis

When all variables (except the results of IgM immunoblotting of serum) were entered in a multiple logistic-regression model, the umbilical-cord VDRL test and the serum or blood PCR assay were the best predictors of central nervous system infection (odds ratio, 2.3; 95 percent confidence interval, 1.1 to 5.0; and odds ratio, 66.6; 95 percent confidence interval, 5.7 to 775). Serum IgM immunoblotting had 100 percent sensitivity and therefore could not be entered into the model, since one of the cells of the contingency table contained no subjects.

DISCUSSION

The possibility of central nervous system infection by *T. pallidum* is a major concern in the treatment

TABLE 2. CHARACTERISTICS OF 76 INFANTS WHO HAD NO EXPOSURE TO ANTIBIOTICS BEFORE CEREBROSPINAL FLUID WAS OBTAINED FOR RABBIT-INFECTIVITY TESTING.*

CHARACTERISTIC	POSITIVE RABBIT-INFECTIVITY TEST (N=17)	NEGATIVE RABBIT-INFECTIVITY TEST (N=59)	P VALUE
Sex — no. of infants			0.81
Male	9	27	
Female	8	32	
Median gestational age — wk	36	39	<0.001
Median birth weight — g	1980	2920	<0.001
Median age at enrollment — days	1	1	0.60
Stage of maternal infection — no./total no. (%)			0.53†
Primary	2/10 (20)	8/10 (80)	
Secondary	7/17 (41)	10/17 (59)	
Early latent (≤ 1 yr)	7/31 (23)	24/31 (77)	
Late latent (> 1 yr)	0/1	1/1 (100)	
Unknown	1/17 (6)	16/17 (94)	
Median VDRL titer			
Maternal	1:32	1:16	0.005
Umbilical cord	1:32	1:4	<0.001
CSF red-cell count — no./mm ³			
Positive serum or blood PCR‡			0.32
Median	1628	160	
Range	1–90,000	2–42,750	
Positive serum or blood rabbit-infectivity test			0.78
Median	1594	1280	
Range	1–90,000	2–69,000	

*CSF denotes cerebrospinal fluid, VDRL Venereal Disease Research Laboratory, and PCR polymerase chain reaction.

†Mothers with syphilis of unknown stage are excluded from the comparison.

‡The corresponding values for PCR testing of CSF are as follows: median, 1628, and range, 9 to 90,000, for positive tests; and mean, 1280, and range, 1 to 6450, for negative tests (P=0.24).

of infants born to mothers with syphilis. We used rabbit-infectivity testing to provide unequivocal evidence of viable *T. pallidum* in cerebrospinal fluid; the test can detect as few as 10 organisms in a clinical specimen.⁷⁻⁹ Among 76 infants with no exposure to antibiotics either in utero or after birth but before undergoing lumbar puncture, rabbit inoculation detected spirochetes in the cerebrospinal fluid of 22 percent, including 41 percent of those who had some abnormality on conventional clinical, laboratory, or radiographic evaluation; 60 percent of those with an abnormal result on physical examination that was consistent with a diagnosis of congenital syphilis; and 41 percent of those with a positive result on IgM immunoblotting or PCR assay of serum, blood, or cerebrospinal fluid or rabbit-infectivity testing of serum or blood. These results indicate that central nervous system involvement is common among infants infected with syphilis, and that once clinical, laboratory, or radiographic evaluation supports a diagnosis of congenital syphilis, therapy that is effective against

central nervous system disease is warranted. On the other hand, central nervous system involvement was not seen clinically, implying that the neurologic manifestations of congenital syphilis require more time to develop and are more prominent features of late congenital syphilis.

Six infants without prior antibiotic exposure and seven infants with prior antibiotic exposure had negative results on the cerebrospinal fluid rabbit-infectivity test, which was the diagnostic standard, but positive results on cerebrospinal fluid IgM immunoblots or PCR assays. The failure to identify spirochetes in the cerebrospinal fluid of these infants may indicate a true lack of infection with *T. pallidum* and therefore false positive IgM and PCR test results. A negative rabbit-infectivity test, however, may not exclude the presence of spirochetes in the central nervous system, since treponemes that were either killed by previous antibiotic therapy or localized to tissue sites would not be detected. Furthermore, the sample volume used for rabbit inoculation may be insufficient.

TABLE 3. COMPARISON OF DIAGNOSTIC ACCURACY OF LABORATORY TESTS AND CEREBROSPINAL FLUID RABBIT-INFECTIVITY TESTING IN 76 INFANTS WHO HAD NO ANTIBIOTIC EXPOSURE BEFORE CEREBROSPINAL FLUID WAS OBTAINED.*

TEST	SENSITIVITY	SPECIFICITY	POSITIVE	NEGATIVE	K VALUE
			PREDICTIVE VALUE	PREDICTIVE VALUE	
			no./total no. (%)		
Conventional tests					
Any abnormal result	16/17 (94)	36/59 (61)	16/39 (41)	36/37 (97)	0.38
Abnormal physical examination	15/17 (88)	49/59 (83)	15/25 (60)	49/51 (96)	0.61
Abnormality on bone radiograph	9/17 (53)	54/58 (93)	9/13 (69)	54/62 (87)	0.50
Anemia	4/16 (25)	57/59 (97)	4/6 (67)	57/69 (83)	0.28
Thrombocytopenia	8/16 (50)	56/58 (97)	8/10 (80)	56/64 (88)	0.54
CSF					
Reactive VDRL test	9/17 (53)	53/59 (90)	9/15 (60)	53/61 (87)	0.45
Elevated white-cell count	6/16 (38)	44/50 (88)	6/12 (50)	44/54 (81)	0.28
Elevated protein	9/16 (56)	39/50 (78)	9/20 (45)	39/46 (85)	0.32
Elevated white-cell count or protein	11/16 (69)	34/50 (68)	11/27 (41)	34/39 (87)	0.30
≥1 Abnormal CSF test	14/17 (82)	33/51 (65)	14/32 (44)	33/36 (92)	0.36
Other tests					
Any abnormal result	17/17 (100)	35/59 (59)	17/41 (41)	35/35 (100)	0.40
Positive serum or blood test					
Rabbit-infectivity test	13/14 (93)	40/49 (82)	13/22 (59)	40/41 (98)	0.62
IgM immunoblotting	17/17 (100)	39/59 (66)	17/37 (46)	39/39 (100)	0.47
PCR assay	16/17 (94)	53/59 (90)	16/22 (73)	53/54 (98)	0.76
Positive CSF					
IgM immunoblotting	8/17 (47)	54/58 (93)	8/12 (67)	54/63 (86)	0.45
PCR assay	11/17 (65)	57/59 (97)	11/13 (85)	57/63 (90)	0.67
IgM immunoblotting or PCR assay	13/17 (76)	53/59 (90)	13/19 (68)	53/57 (93)	0.64

*CSF denotes cerebrospinal fluid, VDRL Venereal Disease Research Laboratory, and PCR polymerase chain reaction.

Since all 21 infants who had positive results from IgM immunoblots of cerebrospinal fluid also had positive results from IgM immunoblots of serum, it is possible that the IgM antibodies diffused from the serum into the cerebrospinal fluid of these infants.²⁹ This possibility is supported by the finding that only 35 percent of these infants had positive cerebrospinal fluid PCR assays. On the other hand, 13 of 14 infants with positive cerebrospinal fluid PCR assays (93 percent) had positive results on serum IgM immunoblotting, suggesting that a positive cerebrospinal fluid PCR result indicates true infection.

Serum or blood PCR and serum IgM immunoblotting identified 94 percent and 100 percent, respectively, of infants with central nervous system infection by *T. pallidum*. On multiple logistic-regression analysis, blood PCR was the best predictor of central nervous system infection. Among 16 infants with a positive cerebrospinal fluid rabbit-infectivity test who were tested by simultaneous inoculation of rabbits with serum or blood, 15 (94 percent) had a positive result from testing of the blood or serum by rabbit-infectivity testing. In addition, 59 percent of infants with spirochetemia had central nervous system infection. These findings support the contention that *T. palli-*

dum invades the central nervous system by the bloodstream. In cerebrospinal fluid, the low sensitivity of IgM immunoblotting suggests that this test is of limited usefulness.^{10,18}

Our results document the low sensitivity of the cerebrospinal fluid VDRL test, white-cell count, and measurement of protein content for the identification of infants with central nervous system infection by *T. pallidum*. Sensitivity increased at the expense of specificity if there were one or more abnormal cerebrospinal fluid tests. When Platou's criteria were used (a cerebrospinal fluid white-cell count of more than 5 per cubic millimeter and a protein concentration of more than 40 mg per deciliter in infants of all ages),⁵ the sensitivity of both the cerebrospinal fluid white-cell count and measurement of protein increased to 100 percent, but the specificity was only 33 percent and 3 percent, respectively. Lukehart et al.⁹ reported similar findings in adults; no single abnormality or combination of abnormalities on testing of cerebrospinal fluid was significantly associated with the identification of *T. pallidum* on cerebrospinal fluid by rabbit-infectivity testing.

In our study population, central nervous system infection was documented in three infants who had

normal results on cerebrospinal fluid VDRL tests, cell counts, and protein measurements. One infant who had normal results on conventional evaluation had a positive result on serum IgM immunoblotting,¹⁰ whereas two infants had other abnormalities on conventional evaluation that were suggestive of congenital syphilis. These results, although confirming the need for a full evaluation of infants at risk, highlight the inherent difficulties in the assessment of cerebrospinal fluid indexes in neonates.^{30,31} Furthermore, the accuracy of a positive cerebrospinal fluid VDRL test in the absence of other diagnostic evidence of congenital syphilis is questionable, because transplacentally acquired nontreponemal IgG antibodies can pass from the infant's serum into the cerebrospinal fluid.³²

The high incidence of central nervous system infection by *T. pallidum* among infants with abnormalities on physical examination and on laboratory and radiographic studies supports the current recommendations of both the American Academy of Pediatrics³ and the Centers for Disease Control and Prevention⁴ that symptomatic infants receive a 10-day course of aqueous penicillin G or penicillin G procaine for presumed central nervous system infection. Our data also indicate that central nervous system infection is infrequent among infants with normal results on clinical, laboratory, and radiographic evaluations. Therefore, the current recommendation that these infants may receive a single intramuscular injection of penicillin G benzathine with appropriate follow-up serologic testing is justified.^{3,4,33,34} However, a full evaluation requires measurement of nontreponemal titers in the mother and infant, a physical examination, a complete blood count, bone radiography, and lumbar puncture. If the evaluation is incomplete or is not performed, the infant should receive empirical penicillin therapy that will eradicate *T. pallidum* from the central nervous system.^{35,36}

In conclusion, a combination of conventional tests identified the majority of infants with *T. pallidum* infection of the central nervous system in our study. However, the identification of all infants required additional tests, including IgM immunoblotting and PCR assay for *T. pallidum* DNA in blood and cerebrospinal fluid. We need more rapid and less expensive diagnostic tests, especially in countries where the prevalence of syphilis remains high and health care resources are limited.³⁷

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