Contrib. to Manag. Congenital Syphilis in Newborn Infant

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Objective: To determine the contribution of long-bone radiographs to the diagnosis and management of newborn infants at risk for congenital syphilis.

Design: Historical cohort.

Setting: Three large hospitals in Houston, Tex.

Patients: Eight hundred fifty-three live born infants who were evaluated for the presence of congenital syphilis.

Intervention: Long-bone radiographs done as part of the diagnostic evaluation for the presence of congenital syphilis.

Main Outcome Measure: Changes in diagnostic classification or management decisions that were based on radiographic findings in the long bones.

Results: For 450 infants, radiographic results did not affect management because clinical or historical factors were present that dictated treatment: 26 infants had clinical symptoms of congenital syphilis (65% [17] had abnormalities on radiographs); and 424 infants were born to mothers who were untreated or reinfected (5.9% [25] had abnormalities on radiographs). All of these infants required a full course of therapy regardless of radiologic findings. Born to mothers with possibly inadequate therapy (according to 1993 Centers for Disease Control and Prevention guidelines), 237 asymptomatic newborn infants were candidates for a single injection of penicillin G benzathine if the results of their evaluations were normal; of these, 2 (0.8%) had abnormal radiographic findings. Of the 166 infants born to adequately treated mothers with appropriately falling serologic titer levels, 1 (0.6%) had abnormal radiographic findings (P = .99 between groups). The results of the long-bone radiographs did not alter management for any of the 853 infants who were evaluated for congenital syphilis.

Conclusions: Long-bone radiographic findings, often abnormal in symptomatic infants, do not differentiate between active infection and past infection. The use of long-bone radiographs should be reconsidered in the routine evaluation of infants for congenital syphilis.

FOLL Owing the availability of penicillin in the early 1940s, there was a rapid decrease in the number of cases of congenital syphilis in the United States. By the early 1960s, when not a single case of florid congenital syphilis had been seen at Charity Hospital, New Orleans, La, for 6 years (with 10,000 births annually), concern was expressed that an entire generation of pediatric residents had never seen the disease. However, syphilis reappeared in the late 1960s, and following a decline in the late 1970s there has been a resurgence of the disease, probably related to the exchange of drugs such as crack cocaine for sex. The rise has been noted particularly in women of childbearing age with a resulting rise in the number of infants who require evaluation for possible congenital syphilis. The peak in congenital syphilis cases of 100 to 110 cases per 100,000 live births in 1991 reflects more than a 10-fold rise since 1987, only part of which was accounted for by the change in case definition that occurred in 1989. Since 1991, rates have begun to decrease in all but large urban areas and the rural South. The cost of evaluating infants born to seropositive mothers dictates that only those tests that are effective in diagnosis and management of congenital syphilis should be used.

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PATIENTS AND METHODS

Infants born at 3 large urban teaching hospitals in Houston, Tex, were included in the study. Infants born at these hospitals represent approximately 40% of the births and about 80% of the cases of congenital syphilis reported in the Houston metropolitan area each year. Stillborn infants were excluded from this study. Case finding methods differed among the hospitals. At Lyndon B. Johnson General Hospital (=6000 deliveries annually) and Hermann Hospital (=4000 deliveries annually), all infants who were evaluated for the presence of or treated for congenital syphilis from July 1990 to June 1993 were identified retrospectively from computerized medical record coding information. Coding practice at both hospitals was to code for congenital syphilis if any serologic test was performed (even a negative rapid plasma reagin) or treatment given (because of positive maternal serologic test results). At Ben Taub General Hospital (=6000 deliveries annually) infants were identified by retrospective identification of all seropositive mothers for the period January 1992 through December 1995 from serology laboratory logs of all serologic tests positive for syphilis. No additional patients from any of the hospitals were found by a cross-check with health department records of mothers with positive serologic test results.

Medical records were retrieved for identified infants and reviewed for maternal serologic test results and maternal treatment history. For infants of mothers with confirmed syphilis, the physical findings, laboratory test results, long-bone radiographic findings, and infant treatments were recorded. Infants were excluded if no evaluation was performed because the infant was found not to be at risk for congenital syphilis.

Infants were classified first according to positive clinical signs (prior to any laboratory evaluation). Infants were classified as symptomatic if they had physical findings consistent with congenital syphilis such as typical rash, lymphadenopathy, hepatomegaly, or splenomegaly. Infants without physical findings (asymptomatic infants) were further classified into 3 groups by maternal treatment and response according to CDC guidelines then in use: (1) clearly inadequate therapy if there was no documented treatment, or there was documented treatment but serologic evidence that the mother was reinfected after treatment (at least a 4-fold increase in titers); (2) possibly inadequate therapy if therapy was administered within 30 days prior to delivery, if therapy consisted of a nonpenicillin regimen, or if therapy was documented but a 4-fold decrease in serologic titers was not documented; and (3) documented adequate therapy according to CDC guidelines with at least a 4-fold decrease in serologic titers at the time of delivery. Maternal treatment history was considered confirmed if it was documented in available medical records or was obtained from the local health department’s records of diagnosis and treatment of sexually transmitted diseases in the state of Texas.

Long-bone radiographic films were interpreted at each hospital by pediatric radiologists who knew only that the patient was being evaluated for possible congenital syphilis. For this study, the results of official radiology reports were used. Our radiologists considered metaphyseal luencies and periostitis to be abnormalities consistent with congenital syphilis. The number of abnormal radiographic findings was determined for each group of infants described earlier. It was then determined whether the radiographic result changed the management (ie, treatment vs no treatment, or single-dose therapy vs multiple-dose therapy) for each infant. The rate of abnormal radiographs was determined for each group described, and Fisher exact tests were used to determine whether the rate of abnormal radiographs differed between groups.

This study was approved by the Institutional Review Committees at the University of Texas Medical School at Houston and Baylor College of Medicine, Houston.

Many different tests have been recommended in the past for evaluation of congenital syphilis, including physical examination, infant serology tests, complete blood cell counts with differential cell counts, Coombs test, hepatic enzymes, urinalysis, cerebrospinal fluid evaluation, and radiographs of the chest and long bones, but there has been little research regarding the usefulness of most of these tests. In 1993, the Centers for Disease Control and Prevention (CDC) published guidelines for the evaluation and management of infants born to mothers with positive serologic tests for syphilis that were consistent with the existing surveillance and clinical case definitions.56 Guidelines in the American Academy of Pediatrics 1994 Red Book67 also stated that every infant whose mother does not have documented evidence of adequate treatment for syphilis should be evaluated by physical examination, serologic testing, cerebrospinal fluid evaluation, and radiographs of the long bones. The American Academy of Pediatrics 1997 Red Book makes similar recommendations. Other tests are recommended if the clinical situation warrants. For asymptomatic infants, the need for therapy and the choice of a therapeutic regimen is based on maternal treatment history and the results of laboratory tests. Recommendations for evaluation and management are summarized in the Figure.

Among the tests that are recommended, long-bone radiographs are the most expensive (up to $250 per patient) and time consuming, and their importance in the management of infants evaluated for congenital syphilis has not been confirmed. The purpose of this study was to determine the extent to which long-bone radiographs contribute to the diagnosis and management of infants at risk for congenital syphilis.

RESULTS

Medical records were available for a total of 1109 liveborn infants of seropositive mothers. Medical records could not be located for 71 infants, and 185 infants received no evaluation because they were found not to be at risk for congenital syphilis. Physical examination findings that were consistent with congenital syphilis were present in 26 infants; 17 (65%) had abnormalities seen on long-bone radiographic films. Of these 26 infants, 19 were born to untreated mothers, 13 of whom had positive results from long-bone radiographs; 5 were born to women treated less
than 30 days before delivery, 4 of these 5 infants had radiographic findings consistent with congenital syphilis; and 2 infants were born to adequately treated mothers, 1 without documented decreasing titer levels. Neither of these 2 infants had abnormalities seen on long-bone radiographs.

Of the 827 infants who were evaluated for congenital syphilis but did not have physical findings suggestive of infection, 340 were born to untreated mothers and 84 were born to mothers with serologic evidence of reinfection after treatment. Of the total 424 infants born to women whose treatment was clearly inadequate, 25 (5.9%) had abnormal long-bone radiographic findings. Twenty-two of these 25 infants were born to untreated mothers, with the other 3 born to women who were reinfected after treatment.

There were 237 infants born to mothers with possibly inadequate therapy according to CDC guidelines. Eighty-nine infants were born to women treated less than 30 days prior to delivery, 5 infants were born to mothers treated with a nonpenicillin regimen, and 143 infants were born to mothers who did not have a documented 4-fold decrease in serologic titers after treatment. Two (0.8%) of these 237 infants showed nonspecific metaphyseal lucencies on long-bone radiographic films. Both were born to women with high serologic titers (1:256, 1:64) who were treated less than 1 week before delivery. A spinal tap was successful in 1 of these infants; findings were normal. Of the 143 infants born to women whose treatment regimen was appropriate but in whom decreasing titers had not been documented, none had abnormal findings on long-bone radiographic films. The serologic titers in these women ranged from 1.1 to 1.28.

There were 166 asymptomatic infants born to mothers whose treatment was adequate and who had responded to therapy appropriately according to 1993 CDC criteria. These infants were evaluated because of a misinterpretation of the term 4-fold fall at all 3 hospitals. The serologic titer levels of the mothers of these infants ranged from 1.1 to 1.64. One (0.6%) of these infants had metaphyseal lucencies seen on long-bone radiographs. This full-term infant was asymptomatic and had normal liver enzymes and cerebrospinal fluid values. The distribution of infants between groups and their long-bone radiographic findings are summarized in the Table. Long-bone radiographic results were unavailable for 85 infants.

The Fisher exact test for the difference between the rate of abnormal radiographic findings between the 237 infants of mothers with possibly inadequate therapy and the 166 infants of mothers with adequate treatment revealed a P=.99, demonstrating no difference between the groups.

### COMMENT

Since the late 1800s, abnormalities of the bones of infants with congenital syphilis have been noted, and by the turn of the century, bony changes had been identified on radiographs. Typical radiographic abnormalities included growth arrest lines, metaphyseal destruction, periostitis, and, rarely, osteitis, with abnormalities most frequently being found in infants with florid congenital syphilis. The bony abnormalities were originally thought to be due to direct infection by spirochetes, but the symmetrical nature of the changes and their consistent appearance in the metaphyses suggest that the lesions represent not local invasion and inflammatory response but rather alterations in osseous development in rapidly growing long bones, with the development of bone findings being proportionate to the rate of growth.

By the 1930s, radiologic studies were routinely used to diagnose congenital syphilis. It became evident, however, that many of the radiologic changes thought to be specific for syphilis could be seen not only with other perinatal infections, but also in noninfectious diseases such as rickets, hemolytic anemia, biliary atresia, and malnutrition. Before the advent of penicillin therapy, bony changes generally persisted past 6 months of age, with gradual improvement and complete resolution by 2 years.
of age. Penicillin-treated infants showed more rapid improvement, but mild changes persisted for longer than 6 months in most infants. Thus, abnormal bone findings would not be expected to distinguish an active infection from an infection that has been adequately treated within the last 6 months. Bone changes were found to worsen after treatment in some infants, and radiologic severity did not correlate with clinical symptoms such as pseudoparalysis. Because of these observations, the use of long-bone radiographs as a diagnostic criterion for the definitive diagnosis of congenital syphilis was discouraged. Recent studies underscore the lack of specificity of long bone changes.

Long-bone films were similarly nonspecific in our population. Infants in our study were classified by symptoms and by maternal treatment history in the manner suggested by CDC guidelines. Symptomatic infants and infants of untreated mothers (including those reinjected after a course of treatment) are considered presumptive cases.

The 1993 CDC guidelines recommended that these infants be treated with a full 10- to 14-day course of parenteral penicillin regardless of long-bone radiographic findings. For the 450 infants who were classified in these groups in our study, this test did not contribute to management decisions. In the 1997 Red Book, recommendations for treatment of these infants have been changed to allow the option of single-dose therapy for asymptomatic infants of untreated mothers, provided that all of the laboratory evaluation findings are negative. If a physician were comfortable with single-dose therapy for infants of untreated mothers, then the long-bone radiographs, if they were the only abnormal finding, would change management under these guidelines. Of the 26 symptomatic infants in our study, 9 (35%) had normal long-bone radiographs, including 1 of 4 infants whose serologic titer levels were greater than 4 times the maternal titer levels. Normal findings on radiographs clearly should not be taken as definitive evidence that an infant is not infected.

During our study, because of initial misinterpretation of what constituted an adequate serologic response to therapy, there were 166 asymptomatic infants who were fully evaluated despite documented appropriate maternal therapy and documented 4-fold decrease in serologic titer levels. These infants constituted the adequately treated group, who were at extremely low risk of having congenital syphilis, and in whom no workup was indicated according to either CDC or Red Book guidelines. One of these infants was born to a mother with a rapid plasma reagin titer of 1:64 at 20 weeks’ gestation who was treated appropriately at that time and followed up until delivery with documented decreasing maternal titer levels. This infant had very mild metaphyseal lucencies found on long-bone radiographic films but no other clinical or laboratory findings. This case is similar to another described in the literature whose mother had received appropriate therapy beginning 12 weeks before delivery, and in which the infant had metaphyseal lucencies noted on radiographic films. It is our belief, based on the natural history of bone changes in congenital syphilis, that both of these infants suffered from intrauterine infection prior to maternal treatment and had bone changes present when maternal treatment was instituted. These lesions had not yet resolved at the time of delivery, representing past rather than present infection. The finding of long-bone abnormalities should not be interpreted to indicate a need for the evaluation of infants like these.

Only the possibly inadequate treatment group, whose mothers were treated with a nonpenicillin regimen, were treated less than 30 days before delivery, or in whom decreasing titers had not been documented, could have been treated in different ways depending on test results according to CDC treatment guidelines. In our study, 237 infants were classified in the possibly inadequately treated group. No radiographic abnormalities were identified in the infants of 5 mothers who were treated with a nonpenicillin regimen or in the infants of 143 mothers who had well-documented appropriate therapy but in whom adequate decrease in titers was not documented by the time of delivery. Eighty-nine infants were born to mothers treated in the last 30 days of pregnancy; 2 infants in this group had abnormal radiographic films. Both of these infants were born of mothers with high maternal serologic titers who were treated less than 1 week before delivery for probable secondary syphilis. This stage of infection in a pregnant woman is associated with almost 100% transmission to the fetus. The CDC guidelines would have permitted a single-dose regimen in these infants; however, these 2 infants were never considered by clinicians in our setting to be candidates for single-dose therapy, regardless of long-bone radiographic results. Imperfect tests, such as long-bone radiographs, are used to evaluate infants for congenital syphilis because there is no reliable, widely available, accurate test for congenital syphilis: the rabbit infectivity test is neither practical nor timely; and polymerase chain reaction and IgM immunoblotting tests have not yet been proven to be sufficiently sensitive or specific to use in the diagnosis of congenital syphilis. Clinicians must manage these infants in a way that maximizes the number of infected infants who are treated while minimizing the number of uninfected infants who are treated. The CDC guidelines base most decisions for both surveillance and therapy on maternal therapy and serologic response to therapy. According to 1993 CDC guidelines, only when maternal therapy or response is possibly inadequate is there an option as to whether an infant should receive less than...
a 10- to 14-day course of parenteral therapy. This group represented about one third of our patients (excluding the infants who did not require any evaluation). Long-bone radiographic films would not have changed the therapeutic approach in any group of infants except this one. Unfortunately, given the natural history of slow resolution of bone changes after treatment, false-positive test results are likely to occur, so that long-bone radiographic films are least likely to be useful in this group. In our study of 853 infants, the long-bone radiographic films did not change the management of any infant. No infant from this group was readmitted to any of these 3 hospitals for treatment of syphilis. However, we do not have specific follow-up information on these infants.

Limitations of this study include the retrospective nature of our data collection, and the limited follow-up data that were available for these patients. No patient had any of the newer tests such as specific IgM or polymerase chain reaction tests performed, nor did any have definitive rabbit infectivity testing. Since our study was performed, evaluation and treatment recommendations have changed, so that some infants who were not candidates for single-dose therapy in 1993 may now be considered by some physicians to be so if all of the evaluation findings are negative.

ECONOMIC IMPLICATIONS

The charge for long-bone radiographs ranges from $132 to $175, with interpretation charges adding $52 to $60. Additional costs attributable to long-bone radiographic films include the cost of nursing time to transport the infant to the radiology department, and the cost of additional time in the hospital while awaiting the test results. If long-bone radiographic films were eliminated from the evaluation of all infants who were obligated to a full course of therapy because of symptoms or clearly inadequate maternal treatment–two thirds of our cases–the savings in procedure charges alone at our institution for the evaluation of all infants who did not require any treatment would be $23,000 to $30,000 per year. With more than 2000 presumptive cases reported in the United States annually (≈10% of which occur in Texas), a savings of more than $400,000 per year might be realized by eliminating only this test from the evaluation of infants who are already obligated to a full course of therapy. If the test were eliminated altogether, much more money could be saved.

CONCLUSION

Although findings on long-bone radiographic films are frequently abnormal in symptomatic infants, and are sometimes abnormal in asymptomatic infants with congenital syphilis, the findings on long-bone radiographic films may also be abnormal in uninfected infants with other conditions and in infants with past syphilis infection up to 6 months after treatment. Long-bone radiographic films, even if abnormal, do not differentiate between active infection, past infection, or other conditions. Long-bone radiographic films obtained for the evaluation of congenital syphilis represent a substantial expenditure of both money and time. On both clinical and economic grounds, the use of long-bone radiographs in the routine evaluation of infants for congenital syphilis should be reconsidered.

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REFERENCES


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