Congenital syphilis in a newborn

Joshua Baalman, MD

C.S. Mott Children's Hospital

Ann Arbor, Michigan

The case

A male infant was born via spontaneous vaginal delivery at term. His mother was late to prenatal care during the pregnancy, presenting at 20 weeks and 4 days gestation for her initial prenatal visit. Laboratory evaluation at that time was notable for a reactive rapid plasma reagin (RPR) test with a titer of 1:8 and a reactive confirmatory fluorescent treponemal antibody - absorption test (FTA-Abs). The mother disclosed that she had been diagnosed with and subsequently treated for syphilis with 3 doses of intramuscular penicillin approximately 9 months previously by the health department, which her obstetrics team was able to confirm. Records also showed that she had a 1:8 titer at the time of initial diagnosis and did not have follow-up testing post-treatment to ascertain treatment response. Repeat RPR testing 2 months later was still reactive with the same titer of 1:8, which was interpreted as "serofast" and thought likely to be attributable to her previous infection. The decision was made not to treat again at that time. Approximately 2 weeks prior to delivery, repeat testing was notable for a nonreactive RPR, which was interpreted as successful treatment of her initial syphilis diagnosis. The rest of her prenatal labs and 3 prenatal ultrasounds were all normal. Mother denied any physical signs or symptoms that could be related to syphilis, and her partner at the time of her initial diagnosis had tested negative for syphilis by enzyme immunoassay and received a single dose of intramuscular penicillin.

The infant's delivery was without complication. Apgar scores were 9 and 9 at 1 minute and 5 minutes of life, respectively. Weight measured at the 47th percentile; length at the 67th percentile; and head circumference at the 30th percentile. Vitals signs were age appropriate in the newborn period and his physical examination was generally unremarkable, without any signs of congenital anomalies related to a possible syphilis infection.

Given the mother's history of a nonreactive RPR test prior to delivery, but reactive RPR tests during pregnancy, the newborn nursery team consulted the pediatric infectious diseases team for guidance on further evaluation of the infant. This case posed a management challenge as it did not quite fit into the existing guidelines from the American Academy of Pediatrics (AAP) and their pediatric infectious diseases division.[1] As it is known that transplacental transmission of syphilis can occur at any stage of maternal infection and at any time during pregnancy, it was decided to send screening RPR testing on the infant prior to discharge.[1] With the assumption that the mother had been previously adequately treated for syphilis given her most recent RPR result, our suspicion was low for congenital syphilis and therefore the infant was discharged home with parents and close follow-up with their pediatrician.

The following day, however, the infant's RPR returned reactive with a titer of 1:8. As expected, FTA-Abs was reactive as well, reflective of his mother's antibody status. This posed another management dilemma, as congenital syphilis is typically diagnosed with an infant titer that is at least 4-fold greater than the maternal titer; however, mother did not have a measurable titer on recent testing. Ultimately, given the morbidity of untreated congenital syphilis, the decision was made to readmit the infant and perform a full evaluation and complete a course of treatment. Additional diagnostic testing that was pursued included complete blood count (CBC), comprehensive metabolic panel (CMP), cerebrospinal fluid (CSF) evaluation, and radiographs of upper and lower extremities. His CBC was notable for mild leukopenia with a lymphocytic predominance and mildly elevated platelets. CMP was notable only for a glucose reading of 49 with a point of care recheck being within normal limits. CSF studies were notable for 3 whote blood cell count and 433 red blood cell count, Gram stain showed polymorphonuclear and mononuclear leukocytes but no organisms, low glucose at 46 (in setting of serum glucose 49), and mildly elevated protein at 73. CSF venereal disease research laboratory (VDRL) testing was negative. Radiographs did not show any evidence of congenital syphilis or other pathology.

The infant's hospital course was largely uncomplicated. He completed a 10-day course of intravenous penicillin G for probable congenital syphilis. On discharge, it was recommended he have repeat RPR testing every 2 to 3 months until nonreactive. He was scheduled to follow-up with his pediatrician and in the pediatric infectious diseases clinic.

Discussion

Congenital syphilis is caused by transmission of the spirochete *Treponema pallidum* either transplacentally or at birth via contact with infected maternal lesions. As stated above, it can occur at any stage of maternal infection and at any time during the pregnancy, although the rate of maternal-fetal transmission is highest with primary and secondary syphilis.[1] In severe cases, it can lead to stillbirth, hydrops fetalis, or preterm delivery. Infants, however, are most commonly asymptomatic at birth. Early congenital syphilis refers to the development of symptoms prior to the age of two years, and may present with a diffuse rash most prominent on the hands and feet, rhinitis or "snuffles", hemolytic anemia, thrombocytopenia, hepatosplenomegaly, pneumonia, and chorioretinitis. Late congenital syphilis refers to the development of symptoms after the age of two years, and may present with intellectual disability, cranial nerve palsies, bone and teeth abnormalities, interstitial keratitis, sensorineural hearing loss, and arthritis.[1,2]

Early treatment of congenital syphilis can prevent the late manifestations of the disease. The Centers for Disease Control and Prevention and the US Preventive Services Task Force recommend universal screening of all pregnant women for syphilis.[1,2] Importantly, the rate of primary, secondary, and congenital syphilis have all increased in recent years. Primary and secondary syphilis increased by almost 73% nationally between 2013 and 2017, with an increase of almost 156% among women specifically. Similarly, the number of infants with congenital syphilis also increased during this time period, with an increase from 9.2 cases per 100,000 live births to 33.1 cases per 100,000 live births.[1] In order to identify those at risk for congenital syphilis, all infants born to mothers who were seropositive during pregnancy should be evaluated with a nontreponemal test, like an RPR or VDRL. Evaluation and treatment then depend largely on the relationship between the mother's RPR titer and the infant's RPR titer but also take into account the infant's exam and the mother's treatment history. Existing guidelines from the AAP recommend that if the infant's RPR is 4-fold higher than the maternal titer, the infant should undergo an extensive evaluation for congenital syphilis that includes bloodwork, CSF analysis, and potentially neuroimaging, long bone radiographs, ophthalmologic exam, and auditory brainstem response. Even in the absence of abnormal results, the infant should be treated with a complete course of intravenous or intramuscular penicillin for 10 consecutive days. There is also guidance available for "possible congenital syphilis" and "unlikely congenital syphilis", which is when the infant's RPR titer is less than 4-fold the maternal titer. In those situations, intervention depends on the details of the mother's treatment course.[1]

Our case posed a management challenge as it did not fit well into any of the guidelines detailed above, given the mother's treatment course and nonreactive RPR at delivery. The mother in this case was confirmed to have been treated with 3 doses of intramuscular penicillin. Although we do not know why she was given a 3-dose regimen, it is typically provided for syphilis of unknown duration, late latent syphilis, or as re-treatment of syphilis.[1,3,4] Treatment failure can occur, but studies have shown that *T. pallidum* remains extremely susceptible to penicillin, with a 90% or better treatment response to a single dose of intramuscular penicillin for early syphilis. Nontreponemal serologic titers (eg, RPR titers) should decline steadily by 6 months for early syphilis, but may take up to a year or longer to decline in latent syphilis. Although it is known that some individuals remain "serofast" after treatment, meaning they fail to revert to "non-reactive," the variability in how long it takes for titers to decline confounds this diagnosis and makes it difficult to ascertain if there has been a treatment failure or re-infection.[5] Given that the mother did revert to nonreactive prior to delivery, it is possible that she was truly adequately

treated by her initial course of antibiotics. The fact that the infant's RPR was reactive at a moderately high titer (defined as > 1:4) indicates that the infant may have been infected despite the mother's adequate treatment history and was making his own antibodies. It is possible for infants to develop congenital syphilis despite maternal treatment, but it is less likely when the mother has been treated greater than 4 weeks prior to delivery[1].

The AAP does acknowledge that a nonreactive maternal RPR at delivery does not rule out the possibility of an infant having congenital syphilis; however, it is considered a rare occurrence.[1] The nontreponemal tests are thought to be highly sensitive for all stages of syphilis.[4] There is a rare phenomenon called the "prozone phenomenon" where a nontreponemal test may be falsely negative in the setting of high concentrations of antibodies. A case report published in 1998 detailed a case of fetal hydrops fetalis due to overwhelming congenital syphilis in the setting of a nonreactive initial maternal RPR, although postpartum re-examination of the mother's blood revealed a reactive RPR with a titer of 1:1024.[6] This occurrence would not be expected in this case, though, given the titers we do have available on mother are not suggestive of markedly elevated antibody levels.[1,4] Alternatively, it is possible that this patient's mother was reinfected and her titers increased from 1:8 as opposed to truly declining, but we would then expect the infant's titers to be higher as well to reflect the mother's status.

Our infectious diseases team recommended that the mother be retested to reevaluate her RPR status and titer level. Although the existing guidelines define congenital syphilis according to a comparison between mother's and infant's RPR titers, we were in a unique situation given that the only information we had was that the mother had a nonreactive result shortly before delivery and no additional titers were measured. Ultimately, we decided to treat the infant based on his positive titer alone, given the consequences of not treating an actively infected infant.

Patient outcome and follow-up

Unfortunately, repeat RPR testing on the infant has not yet been performed, which poses a limitation to our case study. Existing guidelines recommend careful follow-up evaluation of an infant with congenital syphilis at their well child visits and serial nontreponemal antibody titers every 2 to 3 months until titers become nonreactive. Titers should be nonreactive by 6 months of age, whether the infant was truly infected and adequately treated or noninfected and seropositive because of transplacentally acquired antibodies. Infants with increasing titers or persistently

positive titers after 6 to 12 months should be re-evaluated and re-treatment should be considered.[1]

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