The Genetics Corner: A Genetics Consultation for Congenital Syphilis

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Case History:

This 25 week 6-day old female infant was born by C-section for premature labor and breech presentation to a 22-year-old G2P1 mother who had no prenatal care. The father of the baby was incarcerated. A fetal US was performed on the day before delivery when she presented with contractions. It revealed anhydramnios without confirmed rupture of membranes, echogenic bowel, scalp edema, ascites, fetal hydrops, and nuchal thickening. The mother was treated with Ampicillin and Gentamycin. Maternal syphilis was confirmed one day prior to delivery with a positive RPR and syphilis antibody test of 1:64. She smoked 1 ppd. The newborn responded poorly after delivery and required resuscitation with vigorous stimulation, suctioning, bagged ventilation and finally endotracheal intubation and positive pressure ventilation. Apgar scores were 1, 5 and 6 at 1, 5 and 10 minutes respectively. BW 1080 grams (97th%ile), BL 33 cm (41st%ile), HC 23 cm (36th%ile). The placental histology was pertinent for acute necrotizing chorioamnionitis. The maternal urine drug screen was positive for methamphetamine. Her HIV/AIDS screen was negative.

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The infant's RPR test was positive, >10. She was treated with Penicillin for ten days. Early radiographs showed hepatomegaly with hepatic calcifications (Figure 1), and long bones showed a periosteal reaction and metaphyseal changes consistent with congenital syphilis (Figure 2). She had chronic anemia, thrombocytopenia, and total and direct hyperbilirubinemia. Hypophosphatemia, hypocalcemia, hypomagnesemia, and elevated PTH levels were noted. Over time, she developed radiographic findings of metabolic bone disease of prematurity and bronchopulmonary dysplasia. On day 57, she was endotracheally intubated and mechanically ventilated with FiO_2 36%, PEEP 7, Rate 30. Head US and echocardiogram were normal. She tolerated enteric feedings with a 24 cal/oz formula but grew poorly. On day 60, her head was small: HC 27 cm, Z score -2.61. Hydrops had resolved, but hepatomegaly persisted. Ophthalmology exam revealed Stage 3, posterior zone 2 ROP with plus disease. Initially, facial features supported intrauterine compression from oligohydramnios but later dysmorphic features were evident: deep infraorbital folds, depressed nasal bridge, and protruding tongue.

Chromosome microarray revealed a small 51Kb duplication of chromosome 11p13, classified as a variant of unknown significance. The duplicated region contains two annotated genes: PAX6 and ELP4, the latter gene being disrupted by the duplication. Parental studies have been requested to determine if this is a de novo or familial variant.

Consultant's Report:

This baby's features are most consistent with congenital syphilis, microarray results notwithstanding. Duplication of PAX6 has rarely been reported, while deletion of PAX6 and ELP4 cause aniridia, which is not present in this infant. The baby's clinical course is no doubt further compromised and complicated by her extreme prematurity, her mother's lack of prenatal care and exposure to tobacco and methamphetamine.

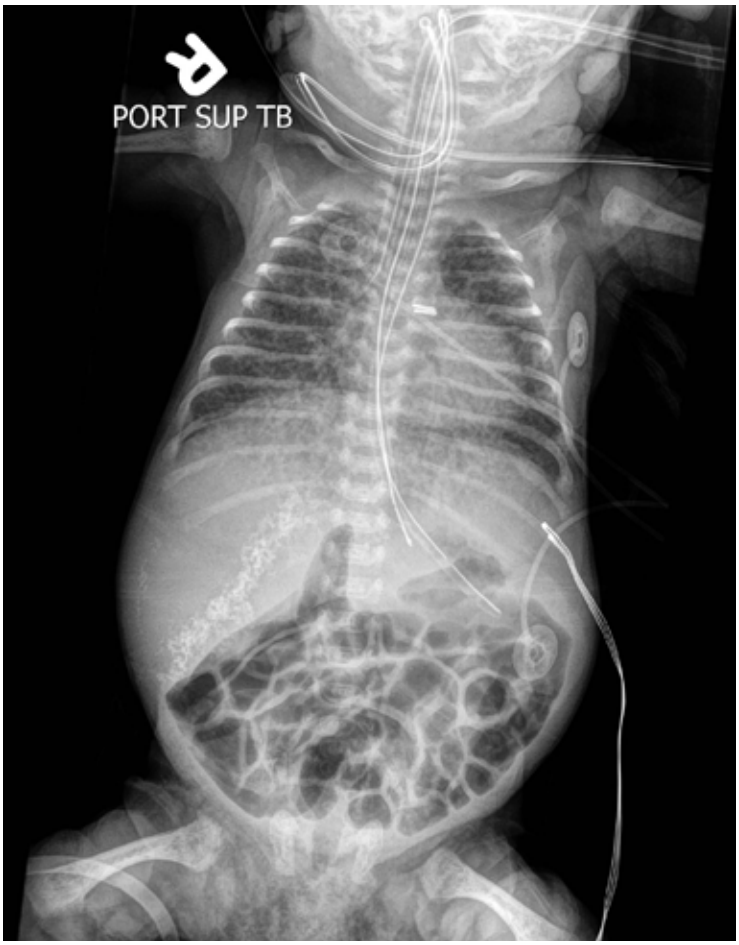

Figure 1: Multiple punctate calcifications in the liver of this infant with congenital syphilis illustrate the hepatic injury that is caused by this devastating infection.

Congenital syphilis alone is enough to account for most of this baby's serious problems. It is a devastating disease that is responsible for hundreds of thousands of stillbirths and neonatal deaths each year throughout the world. In 2016, the Centers for Disease Control and Prevention reported that the incidence of congenital syphilis was 15.7/100,000 live births, which followed a steady increase in reports since 2012 when the rate was 8.4/100,000 live births.

Syphilis can be vertically transmitted from the mother to the fetus at any time during pregnancy and within the first four years of maternal infection, when the chance of fetal transmission is about 70%. The highest transmission rates from mother to child occur in the early (primary, painless chancre, and regional lymphadenopathy) and secondary (rash, fever, malaise, arthralgias, lymph-

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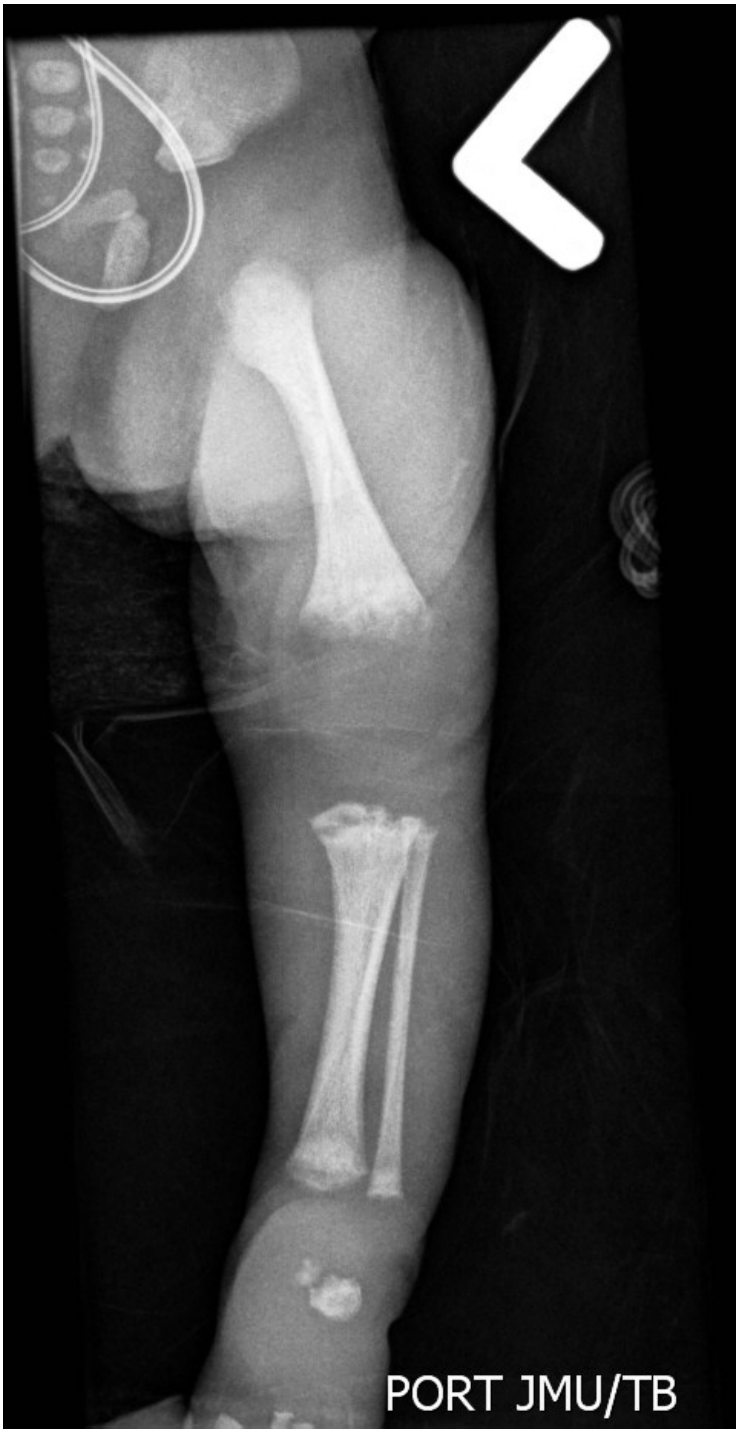

Figure 2: Periosteal reaction and metaphyseal irregularities are signs of congenital syphilis in these long bones.

adenopathy) phases of the mother's syphilis infection. During the latent phase of syphilis infection, after 1-3 months when signs of primary or secondary syphilis have resolved, and there are no symptoms, but antibody tests are positive, only about 2% of exposed fetuses become infected.

Congenital syphilis causes perinatal death in more than 40% of untreated affected pregnancies. Of the deaths caused by congenital syphilis, 75% are stillborn, and 25% are in the neonatal period. Infected infants, especially term infants can be asymptomatic at birth. If untreated, symptoms of poor feeding and rhinitis ("snuffles") develop by five weeks of age, which are followed by a papular desquamative rash of the palms, soles, mouth, and anus.

Infected preterm infants are more often symptomatic at birth, and their symptoms are generally more severe than infected term infants. Severely ill infected infants have non-immune hydrops fetalis and often present with hepatomegaly, splenomegaly, anemia, and pneumonia. Characteristic facial features include frontal bossing, high arched palate, and depressed nasal bridge. More than 90% of symptomatic infants have radiographic changes of the long bones, specifically metaphyseal irregularities and periosteal thickening. So-called saber shins are late sequelae of periostitis of the tibia. The CNS is involved in about 50% of symptomatic infants. Neurosyphilis, which is not necessarily confined to late syphilis, is nevertheless rare in the newborn period. It may present with deafness, cranial nerve palsies, diabetes insipidus, leptomeningitis, hydrocephalus, paresis, and convulsions and intellectual disability. The late manifestations of congenital syphilis, which are evident after age 2, include the dental anomalies (Hutchinson teeth, mulberry molars), uveitis, and eight nerve deafness that makeup Hutchinson's triad.

Effective prenatal care may mitigate many of the worst aspects of congenital syphilis by diagnosing and treating with antibiotics and other interventions. The *hydrops fetalis* associated with syphilis, which is secondary to fetal anemia, has been effectively treated with intrauterine transfusion. In this case, even with effective antibiotic therapy, the effects of congenital syphilis, which in this case, should include the ramifications of the preterm delivery, will have

serious and life-long consequences for this child.

Practical Applications:

1. The incidence of congenital syphilis is rising in the United States and throughout the world.
2. Seven percent of nonimmune hydrops is due to infection. Consider congenital syphilis in any infant with *hydrops fetalis*.
3. Because maternal syphilis is highly correlated with fetal loss, check the results of maternal syphilis tests when evaluating a stillborn infant.
4. Syphilis and HIV infection are correlated so test for both when either is suspected, especially in the context of lack of prenatal care, incarceration, high-risk sex behaviors, sex work, and illicit drug use.

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The authors have no relevant disclosures.

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