SWISS SOCIETY OF NEONATOLOGY

A chameleon in the night: early congenital syphilis with cholestatic liver disease and osteitis



Cripe-Mamie C, Büttcher M, Stranzinger E, Schibli S, Department of Neonatology (CMC), Department of Infectious Diseases (BM), Department of Pediatric Radiology (SE), Department of Gastroenterology (SS), University Children's Hospital, Inselspital Bern, Switzerland

Title figure:

Treponema pallidum (source: www.viralglobalnews.com)

This term male infant, born vaginally with a birth weight of 2980 g (P10) to a healthy 22-year-old G2/ P1 of Central African origin, adapted well with Apgar scores of 8, 9, 10 at 1, 5 and 10 minutes, respectively. The placenta weighed 730 g (P75) and was not examined histologically for lack of indication at the time of delivery. Timely antibiotic prophylaxis for positive group B streptococcus screen had been administered and the baby went to the regular postnatal ward.

At eight hours of life, he presented with a dusky skin color, subtle signs of respiratory distress, SaO₂ of 88% on room air, with prompt response to supplemental oxygen, a capillary refill time < 2 seconds, hypothermia (35.8 °C), hypoglycemia of 1.4 mmol/l and listlessness. His abdomen was slightly distended with discrete organomegaly but non-tender with normal bowel sounds. His skin showed multiple erythematous maculae on the palmar and plantar surfaces, with a maximum diameter of 5 mm, a bluish center, a hyperpigmented border and some desquamation (Fig 1-3). The mother's serologies were reported to be negative for syphilis, HIV, hepatitis B and showing immunity for rubella and toxoplasmosis. We admitted the infant with suspected early-onset sepsis for further investigations and immediate intravenous antibiotic treatment with amoxicillin and amikacin.

CASE REPORT



Skin lesions on the left foot (first day of life).



Fig. 2

Skin lesions on the right hand (first day of life).



Family history was noteworthy for the mother having arrived in Switzerland at the age of 12 years. She had a homozygous alpha+ thalassemia. No information was available from the father, who was also of Central African origin.

The CRP was highly elevated (178 mg/l), interleukin-6 was not detectable and the white blood cell count was 25.3 G/l with a marked left shift of 53%. A babygram (Fig. 4) and cerebrospinal fluid analysis were normal. Initial laboratory values were remarkable for cholestasis, transient lactic acidosis and hypoglycemia; the latter normalized rapidly with intravenous glucose administration of 3.6 mg/kg/min and enteral feeds. Echocardiography was normal apart from moderate persistent pulmonary hypertension of the newborn (PPHN). Blood cultures remained negative.

At this stage, our working hypothesis was that of neonatal early-onset sepsis with concomitant hepatopathy, suggestive either of an antenatal infection or congenital liver disease. Ultrasound examination of the abdomen on the 2nd day of life confirmed mild hepatosplenomegaly. The biliary tree was well visualized and there was some sludge in the gall bladder (Fig. 5). Given that the infant had neither vertebral nor cardiac anomalies, Alagille syndrome seemed unlikely. Screening for cystic fibrosis (immunoreactive trypsinogen) was also normal. Alpha-1antitrypsin levels, ammonia levels, urinary reducing substances as well





Abdominal ultrasound demonstrating sludge in the gall bladder.

as serum amino acid profile were all within normal limits. Total iron (46 µmol/l) and ferritin (2248 µg/l) were elevated while transferrin values were normal. Neonatal hemochromatosis was considered, however alpha-fetoprotein was within normal limits, the infant did not develop liver failure and improved with antibiotic treatment, intravenous glucose and enteral feeds supplemented with ursodeoxycholic acid.

On day of life 2 and 3, he developed thrombocytopenia (minimal 27 G/l) without evidence of coagulopathy and received 3 platelet transfusions. This prompted us to rule out additional congenital infections (enterovirus, cytomegalovirus, toxoplasmosis, hepatitis B, hepatitis C, HIV, parvovirus B19). On ophthalmologic examination, there was no evidence of, posterior embryotoxon (as seen in Alagille syndrome), or cataract (as seen with galactosemia or congenital infections).

Upon further questioning, the mother remembered a non-pruritic bronze-colored flat rash on her forearms one month prior to delivery, which is compatible with secondary syphilis (Fig. 6). Maternal syphilis serology was repeated and seroconversion was demonstrated (TPHA titer of 1:81'920, VDRL titer of 1:128). There was evidence of metaphyseal osteitis on x-rays (Fig. 7). A repeat cerebrospinal fluid (CSF) analysis showed no pleocytosis, borderline protein content, normal glucose value, negative PCR reaction for T. pallidum and a slightly positive CSF-VDRL test. Thus, CNS involvement could not be ruled out. Cranial ultrasound images were normal. The infant received a ten-day-course of intravenous penicillin for confirmed early congenital syphilis. By the age of 6 months, VDRL-test had turned negative and cholestasis had resolved completely. Neurodevelopment was normal.



12

Maternal skin lesions.



X-ray of the right hand: band-like transparencies of multiple metaphyses consistent with syphilis-associated metaphysitis.

DISCUSSION

The initial presentation of the infant was felt to be compatible with early-onset sepsis complicated by PPHN. When hepatosplenomegaly, thrombocytopenia and cholestasis were noted, the differential diagnosis was expanded to include congenital infections. However, since the extent of cholestasis was particularly pronounced compared to values described in case series in the literature (1-3), cholestasis due to extrahepatic obstruction and in the context of certain metabolic diseases was excluded (4, 5).

Syphilis, though easily diagnosed and treated, still poses a global health threat. It is estimated that about 1.5 million pregnant women are infected yearly, half of whom experience adverse pregnancy outcomes, such as spontaneous abortions, stillbirth, prematurity, low birth weight, neonatal and infant death, congenital disease among newborn infants with typical sequelae (6, 7).

Since the late 1990s there has been a steady increase of syphilis amongst the adult population. This resurgence – also among women of childbearing age – is not readily recognized, since mother-to-child transmission had almost disappeared with rates as low as 8-10 per 100'000 births in the US and Europe (6, 7, 11, 12). Transmission of syphilis to the fetus results in far greater morbidity and mortality than the primary infection of the adult (3, 6–8). Early syphilis is diagnosed before the age of 2 years (3, 6–9, 13). As many as 65% of infants with congenital syphilis will be asymptomatic at birth. The clinical presentation in most cases is non-specific and can encompass signs of a congenital infection, a typical skin rash in 10–70%, hepatomegaly in 25–70%, central nervous system involvement in 25%, and long bone involvement in 60-80% (Fig. 7) (3, 8, 9, 13). The most frequent skin manifestation is that of small copper colored maculopapular lesions very similar to the secondary syphilitic lesions seen in adults (8, 9). With fetal infection, any organ can become involved. Typically, hepatitis develops with hepatomegaly and abnormal liver function tests. Cholestatic jaundice is common and most often transient (1, 2, 8).

The treatment of choice for congenital syphilis is intravenous penicillin for 10-14 days (10, 13). In a rabbit model amoxicillin has been shown to be treponemicidal, but penicillin is still regarded as the first line treatment for syphilis (7, 13).

REFERENCES

- Shah MC, Barton LL. Congenital syphilitic hepatitis. Ped Inf Dis J 1989;8:891-892 (no abstract available)
- Anand NK, Chellani HK, Wadhwa A, Prasanna SB, Mohan M. Congenital syphilitic hepatitis. Ind Ped 1991;28:157-159 (Abstract)
- Zhou Q, Wang L, Chen C, Cao Y, Yan W, Zhou W. A Case series of 130 neonates with congenital syphilis: preterm neonates had more clinical evidence of infection than term neonates. Neonatology 2012;102:152-156 (<u>Abstract</u>)
- McKiernan P. Neonatal jaundice. Clin Res Hepatol Gastroenterol 2012;36:253-256 (*Abstract*)
- 5. De Bruyne R, Van Biervliet S, Van de Velde S, Van Winckel M. Neonatal cholestasis. Eur J Pediatr 2011;170:279-284 (*Abstract*)
- Newman L, Kamb M, Hawkes S, et al. Global estimates of syphilis in pregnancy and associated adverse outcomes: analysis of multinational antenatal surveillance data. PLoS Med 2013;10:e1001396 (<u>Abstract</u>)
- World Health Organization. Investment case for eliminating mother-to-child transmission of syphilis, 2012; ISBN 978 92 4 150434 8
- Woods CR. Syphilis in children: congenital and acquired. Semin Pediatr Infect Dis 2005;16:245-257 (Abstract)
- 9. Lago EG, Vaccari A, Fiori RM. Clinical features and follow-up of congenital syphilis. Sex Transm Dis 2013;40:85-94 (*Abstract*)
- Patton ME, Su JR, Nelson R, Weinstock H. Center for Disease control and Prevention. Congenital syphilis - United States, 2003-2008. MMWR 2010;59:413-417 (<u>Abstract</u>)

- Meldepflichtige sexuell übertragbare Infektionen (STI) in der Schweiz: Chlamydiose, Gonorrhoe, Syphilis. Überwachungssystem und epidemiologische Situation Ende 2010. BAG Bulletin 2011;12:253-261 (no abstract available)
- Meyer Sauteur PM, Trück J, Bosshard PP, et al. Congenital syphilis in Switzerland: gone, forgotten, on the return. Swiss Med Wkly 2012;141:w13325 (<u>Abstract</u>)
- Walker G, Walker DG. Congenital syphilis: a continuing but neglected problem. Sem Fetal Neonatal Med 2007;12:198-206 (Abstract)

SUPPORTED BY **EVifor Pharma**

CONTACT Swiss Society of Neonatology www.neonet.ch webmaster@neonet.ch