

Dangerous bugs:
sepsis and perinatal acidosis
in a preterm neonate

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HIERONYMVS FRACASTORIUS

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This 1300 g male preterm infant was born by emergency caesarean section at 31 5/7 weeks of gestation because of fetal bradycardia, reverse flow in the umbilical artery, and suspected maternal infection. Maternal serologies were not available at the time of the delivery.

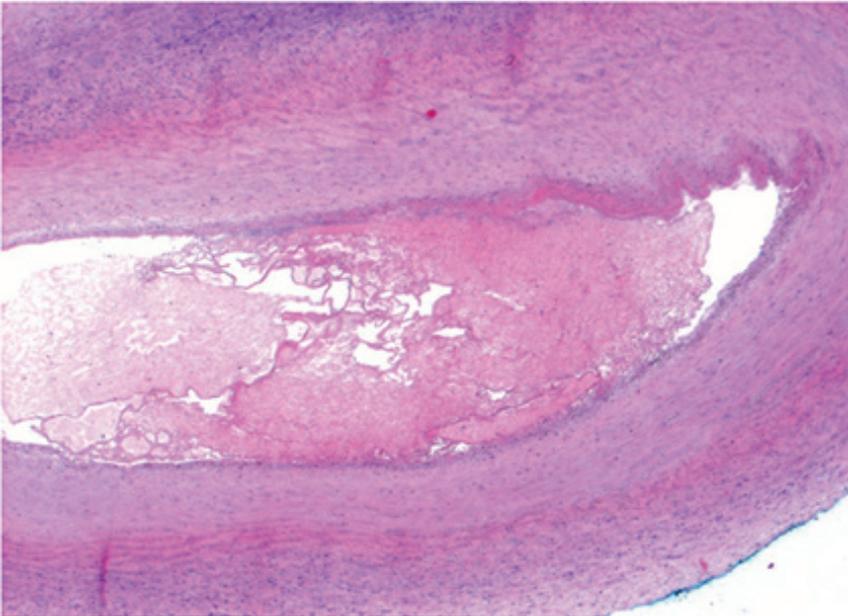
At ten minutes of age, there were some signs of respiratory distress (subcostal recessions, grunting), however, respiratory rate, heart rate and blood pressure were age-appropriate. Umbilical arterial pH was not available, umbilical venous pH was 7.06. Blood gas analysis at the age of 15 minutes revealed a mixed acidosis with a pH of 7.06, a pCO₂ of 76 mmHg (10.1 kPa), a base excess of -12.4 mmol/l, and a lactate concentration of 13.6 mmol/l. Further laboratory findings included hypoglycemia (0.3 mmol/l), thrombocytopenia (18 G/l), and evidence of hepatic dysfunction (ASAT 291 U/l, ALAT 343 U/l, GGT 389 U/l, INR 4.22). The C-reactive protein was 82 mg/l, and IL-6 was less than 50 pg/l. Cranial ultrasound on day one of life was normal.

The infant's respiratory distress responded well to continuous positive airway pressure without need for supplemental oxygen and resolved within four hours of birth. The infant was treated with intravenous glucose, empiric antibiotics (amikacin and amoxicillin), and a single platelet transfusion.

On day three of life, maternal VDRL and TPPA blood tests including syphilis FTA-IgM were reported to be positive. The results of serological tests in the boy showed a similar pattern and were consistent with a diagnosis of congenital syphilis. Histology of the umbilical cord showed necrotizing funisitis, and the presence of *Treponema pallidum* in the cord was confirmed by immunohistochemistry (Fig. 1- 3).

Antibiotic therapy was changed from amikacin/amoxicillin to penicillin G for 14 days based on recommendations from the Center for Disease Control and Prevention (CDC) (1). As expected, blood samples taken after two weeks of treatment showed a negative VDRL and TPPA tests and a decrease in syphilis FTA-IgM while syphilis FTA-IgG became positive.

In the context of serologically confirmed congenital syphilis, further diagnostic tests were initiated. X-rays of the chest and long bones as well as abdominal ultrasound were normal. Cerebrospinal fluid analysis was done twice and was without any pathological findings. Cranial ultrasound over the first two weeks of life was unremarkable, however, on day 28 of life, cystic periventricular leukomalacia was diagnosed (Fig. 4, 5). Neurodevelopmental follow-up at three, six, and twelve months revealed increasing peripheral spasticity and axial hypotonia along with severe global neurodevelopmental delay.



*Umbilical artery with intraluminal thrombus
(HE stain).*

Fig. 1

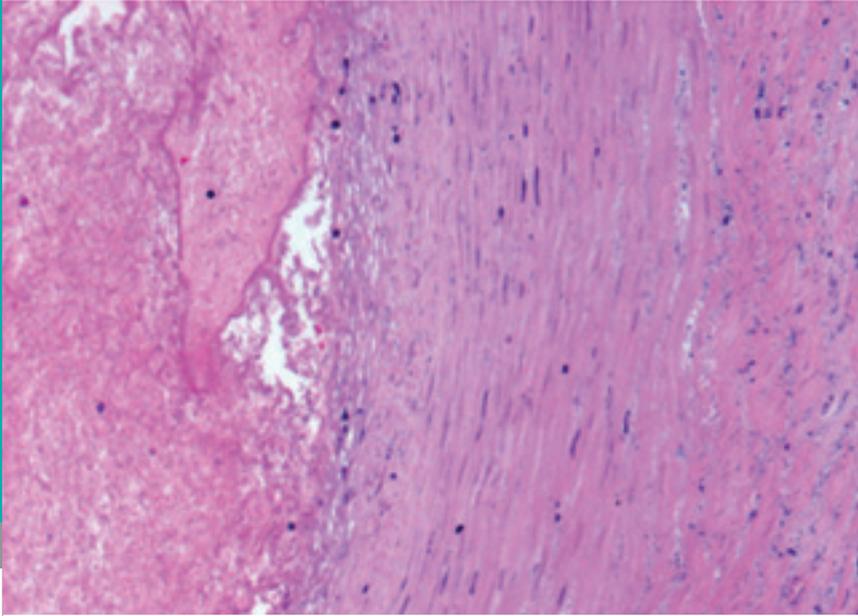
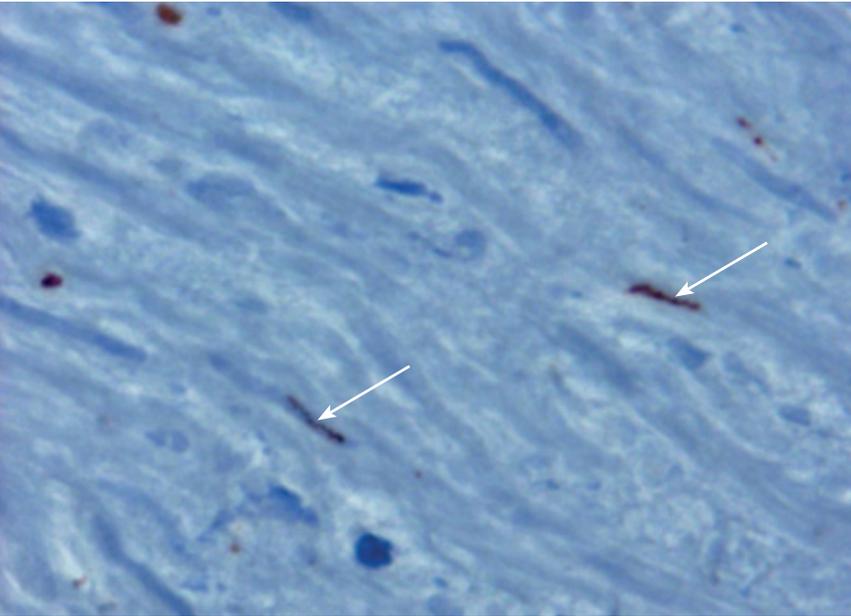


Fig. 2

*Umbilical artery with necrosis and spirochetes
(HE stain).*

**Fig. 3**

Umbilical artery with spirochetes (immunohistochemistry).

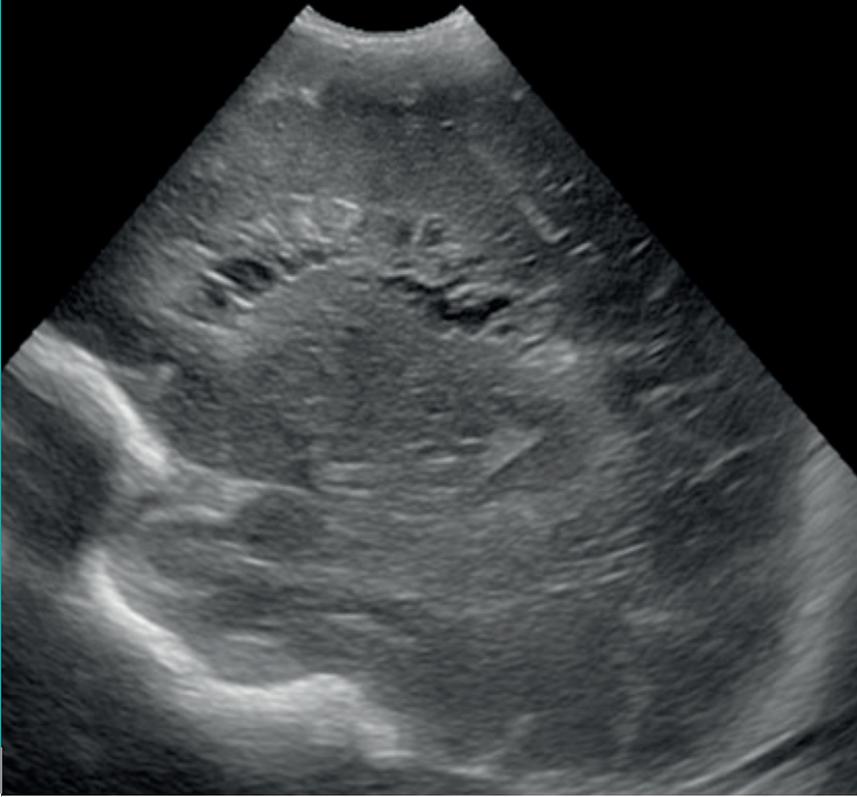


Fig. 4

Cranial ultrasound: periventricular leukomalacia (sagittal view).



Cranial ultrasound: periventricular leukomalacia (coronal view).

DISCUSSION

On a worldwide scale, about 2.1 million pregnant women have active syphilis and 1 million babies are born with congenital syphilis each year; most of these live in low- and middle-income countries (2, 3).

There are no current data on the incidence of congenital syphilis in Switzerland. The Swiss Federal Office of Public Health registers newly diagnosed syphilis cases in adults. Recent data clearly document an increase in the incidence of laboratory-based syphilis notifications, regardless of gender and age. Concomitantly, a rise in syphilis-diagnosed women of childbearing age is seen. These data suggest that congenital syphilis may become an increasingly prevalent problem in Switzerland (4).

Spirochetes are able to cross the placenta and infect the fetus from 14 weeks of gestation, with the risk of fetal infection increasing with gestational age (5). Clinical manifestations of congenital syphilis are influenced by gestational age at birth, stage of maternal syphilis, maternal treatment, and fetal immunological response (6).

More than 50% of pregnant women with untreated syphilis in pregnancy have adverse outcomes including early fetal loss, stillbirth, prematurity, low birth weight, neonatal and infant death, and congenital disease among newborn babies (7). Fetal death is primarily caused by transplacental infection and reduction

in blood flow to the fetus (5). Fojaco et al. found an association between necrotizing funisitis and congenital syphilis. Necrotizing funisitis is a deeply seated inflammatory process within the matrix of the umbilical cord, which may be accompanied by phlebitis and thrombosis (8).

Congenital syphilis can be classified into early congenital syphilis and late congenital syphilis. In early congenital syphilis, clinical signs appear during the first two years of life, whereas clinical signs in late congenital syphilis occur after two years and until the first two decades. Early congenital syphilis is caused by active infection and inflammation while late congenital syphilis is either a result of chronic inflammation or represents the scars induced by initial lesions of early congenital syphilis (5).

Early congenital syphilis

35% of fetuses infected with syphilis are born alive and about 60% of them are asymptomatic at birth (9). Clinical manifestations in symptomatic neonates are variable. About 40-60% of symptomatic infants show at least one of the following signs or symptoms: hepatomegaly, nasal discharge (sometimes blood-stained, containing spirochetes), rash, generalized lymphadenopathy, or skeletal abnormalities (metaphyseal and diaphyseal portions of the long bones, typically bilateral, symmetric and polyostotic) (10).

Hepatomegaly is present in almost every symptomatic infant with congenital syphilis and potentially accompanied by elevated serum transaminases and alkaline phosphatase, direct hyperbilirubinemia, and impaired coagulation (11). Generalised lymphadenopathy has been described in 50% of the patients. Large epitrochlear lymph nodes are highly suggestive of congenital syphilis (12).

Mucocutaneous manifestations are common in symptomatic infants. A disseminated bullous syphilitic rash containing spirochetes may be present at birth or may develop within one to two weeks of birth. Most commonly, the rash is maculopapular in appearance. It may present anywhere on the body but is typically located on the back, buttocks, posterior thighs, and soles. This proliferative stage lasts for about one to three weeks and is followed by desquamation, crusting, and fading towards a dusky red or copper color which may persist (11). Uncommon cutaneous lesions of congenital syphilis include fissures, mucous patches, and condylomata lata. All of these lesions contain spirochetes and should be considered to be infectious. Dark field microscopy of samples from these lesions may be diagnostic.

Acute syphilitic leptomeningitis or chronic meningo-vascular syphilis may develop during the first year of life. Other potential manifestations of early congenital syphilis include non-immune fetal hydrops, hematolo-

gic abnormalities (anemia, thrombocytopenia, leukopenia or leucocytosis), pneumonia, fever, myocarditis, ophthalmologic and gastrointestinal manifestations, and nephrotic syndrome (6, 8, 12).

Late congenital syphilis

Late congenital syphilis is a very rare clinical entity (6, 14). Approximately 40% of infants born to women with untreated syphilis in pregnancy develop late congenital syphilis (7). As mentioned above, late congenital syphilis is either a result of chronic inflammation or represents the scars of inflammation from early infection. The clinical symptoms and consecutive complications include (6, 7, 13): Hutchinson's teeth (hypoplastic, peg-shaped notched central incisors), dental caries, perforation of the hard palate, interstitial keratitis (usually bilateral), glaucoma, corneal clouding, optic nerve atrophy, eighth cranial nerve deafness, destruction of the nasal cartilage and perforation of the nasal septum, saddle nose, mental retardation, hydrocephalus, convulsive disorders, affection of cranial nerves, juvenile paresis, prolonged periostitis, frontal bossing, saber shin tibia, enlargement of the sternoclavicular portion or the clavicle (Higoumenakis sign).

Diagnosis

Laboratory criteria for the diagnosis of congenital syphilis were defined by the US CDC as follows: demonstration of *Treponema pallidum* by dark field microscopy, fluorescent antibody, or other specific

stains in specimens from lesions, placenta, umbilical cord, or autopsy material (8). If there are any possible syphilitic skin lesions or secretions, dark field microscopy is the most specific technique for diagnosing syphilis. Besides dark field and fluorescent antibody assays, different serological tests exist. These tests should be performed simultaneously in mother and infant. Serologic tests can be classified in nontreponemal and treponemal tests (table).

Nontreponemal tests detect antibodies against cardiolipin (a component of cell membranes and mammalian tissue) which may or may not be related to syphilis. The results of the tests may be false positive due to pregnancy, autoimmune disorders, or infections (6). Nontreponemal tests usually become negative within one year of adequate treatment, however, a small proportion of patients will show persistently positive titers despite adequate therapy.

Treponemal tests detect an interaction between serum immunoglobulins and surface antigens of *Treponema pallidum*. False positive results are possible in patients with Lyme disease, leptospirosis, and disease caused by different *Treponema* species. In contrast to nontreponemal tests, these test results will remain positive for life (6).

Proven or highly probable congenital syphilis is pre-

Nontreponemal Tests	
VDRL (Venereal Disease Research Laboratory) RPR (Rapid Plasma Reagin)	Screening and evaluation of treatment: <ul style="list-style-type: none"> • fourfold titre increase = active disease • fourfold titre decrease = successful therapy
Treponemal Tests	
FTA-ABS (Fluorescent treponemal antibody absorption) TPPA (Treponema pallidum particle agglutination test) MHATP (treponemal-specific microhemagglutination test)	Confirmation of the diagnosis

Table

Overview treponemal and nontreponemal tests.

sent if there is abnormal physical examination of the neonate with symptoms consistent with congenital syphilis, or a nontreponemal serologic titre in the neonate which is more than four times higher than the maternal titre, or a positive dark field or fluorescent antibody test, or a reactive nontreponemal test along with either reactive cerebrospinal fluid VDRL, pleocytosis or elevated protein concentration.

Treatment

Neonates with congenital syphilis should be treated with penicillin G intravenously for 14 days (13). The Jarisch–Herxheimer reaction is less frequent in newborn infants than in older infants. It occurs 2–12 hours after receiving therapy for active syphilis and is characterised by fever, headache, myalgia, and malaise. This reaction is caused by the release of treponemal endotoxin-like compounds during penicillin-mediated lysis. Benzathine penicillin is no longer recommended due to reported therapy failure in infants with congenital syphilis. Effectiveness of therapy can be verified by a fourfold titre decrease in nontreponemal tests (16).

Although congenital syphilis is a rare finding in Switzerland, recent data suggest that the incidence may rise in the future. Serological syphilis screening of pregnant women is recommended at their first prenatal visit and, in patients at high risk, during the third trimester and at delivery (8). Early diagnosis and prompt treatment are the key points for avoiding long-term complications of the disease.

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