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CASE REPORT

Early congenital syphilis and false-negative by Prozone Phenomenon

Sífilis congênita precoce e falsonegativo por Fenômeno Prozona

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Abstract

Objectives: Syphilis is an infectious, contagious, systemic and cosmopolitan disease , its evolution is chronic and curable, caused by a spirochete, Treponema pallidum, whose human is an exclusive transmitter.[1,2] Since 1960, an increase in the incidence of acquired syphilis has been observed, and as a consequence a proportional increase in its vertical transmission.[6] Given the relevance of the subject, the present work aims to report a clinical case in this context and to discuss the diagnostic methods. **Report:** Infant, male, 46 days, admitted with maculo-papular exanthema and diffuse circumscribed erosive lesions 24 hours ago, whose mother presented VDRL negative during prenatal and delivery. The infant was admitted for investigation and treatment, and VDRL of the mother and infant were performed, both positive, and the hypothesis of a false-negative at the moment of delivery due to the Prozone phenomenon was proposed. **Comments:** Given the high rates of congenital syphilis in Brazil, despite the control programs, it is possible to question the quality of prenatal care and delivery, the technical knowledge of health professionals about which method of diagnosis is adequate, but also regarding the interpretation of the result, and question the existence of a deficiency of the laboratory technique, because the Prozone phenomenon can be avoided if the VDRL is executed according to the operational protocols.

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INTRODUCTION

Syphilis is a curable, infectious, systemic, cosmopolitan, and potentially chronic disease caused by *Treponema pallidum*, a spirochete bacterium transmitted solely by humans. The disease may be transmitted during sex (acquired) or vertically (congenital) through the placenta or at the time of delivery, as the newborn passes through the birth canal.[1,2] Cases of infection by transfusion of blood or blood products have significantly decreased since the introduction of stricter control procedures at blood centers.[3] There is no vaccine for syphilis yet, and infection by *Treponema pallidum* does not grant patients protection against reinfection.[4]

Although syphilis was a known condition in the 15th century, it was properly treated only after penicillin was discovered in 1928 and the effects of the antibiotic agent against the disease elucidated after World War II[5]. In the 1950s there was hope that syphilis would be eradicated, but since 1960 the reported incidence of the disease has been on the rise on account of multiple factors, including sexual liberation, increased injecting drug use, growing number of cases of infection by HIV, the introduction of the contraceptive pill, and the greater number of tests ordered as individuals become more aware of the disease. The number of cases of acquired syphilis grew along with the number of cases of vertically transmitted disease.[6]

Data from the Information System for Notifiable Diseases (SINAN, Brazilian acronym) show that 104,853 cases of congenital syphilis affecting infants aged less than a year were reported between 1998 and 2014, and indicate that the incidence rates of congenital syphilis have increased from 1.7 in 2004 to 4.7 cases per 1,000 live births in 2013.[7]

The diagnosis of syphilis in infants is complex and must be based on epidemiological, clinical, and workup criteria.

In light of the relevance of the topic, this paper reports the case of an infant diagnosed with congenital syphilis.

CASE REPORT

A brown male infant aged 46 days was admitted to the emergency unit of a public hospital with diffuse skin lesions developing for 24 hours. He was born from an uneventful cesarean section after a full term pregnancy. The infant's weight was adequate for his gestational age, and he was discharged 48 hours after birth. His mother went to four prenatal care appointments and was tested for syphilis via the VDRL (Venereal Disease Research Laboratory) test during pregnancy and at the time of delivery, all of which came back negative. However, she reported that red spots appeared all over her body after delivery, and that her male partner had not sought treatment after being diagnosed with syphilis while she was pregnant. The infant was referred for additional testing and treatment at the hospital's pediatric ward.

Physical examination revealed the infant was generally in good condition, hydrated, with a healthy skin tone, anicteric, and afebrile. He presented with ring-shaped lesions with slightly elevated borders and early-stage ulcerations with crust, and some ulcerating lesions without effusion diffusely distributed throughout his body, including the palms of the hands and scalp (Figure 1). He did not have signs of secondary infection. His liver was palpated 3cm from the costal margin. No other alterations were observed.

The infant was referred to the pediatric ward, where he underwent additional testing and examination by abdomen ultrasound examination, long bone x-ray imaging, complete blood count, liver magnetic resonance imaging, renal function tests, and cerebral spinal fluid and blood VDRL tests. The patient had a positive blood VDRL test with a titer of 1:16, while the CSF-VDRL and HIV tests came back negative. No significant alterations were found in the other tests and images, and the infant was diagnosed with congenital syphilis without central nervous system involvement. The patient was treated with intravenous ceftriaxone, starting with a loading dose of 100mg/kg followed by 80mg/kg every 24 hours for 14 days, as specified in a Technical Note issued by the São Paulo State Health Secretary over the treatment of congenital syphilis in scenarios of unavailability of crystalline penicillin and procaine.[7]

The patient improved from the skin lesions and was discharged at the end of therapy. He was referred for outpatient care at the Reference Center for Sexually Transmitted Diseases.

DISCUSSION

The graph below shows that the incidence rate of congenital syphilis increased by 276% within the last ten years among infants aged less than a year. The number of cases is largely underestimated, since underreporting is still a significant issue despite the requirement to report cases of the disease set out in Ordinance No. 542 put into effect by the Ministry of Health in 1986.[7]



Figure 1. Photo of the infant before (upper) and after (lower) the treatment. Source: own author.

Diagnosing infants with congenital syphilis is no simple matter, since more than half of the infected individuals are asymptomatic at birth; and even when signs and symptoms manifest, they tend to be mild and unspecific[3], as in the case in question.

The Ministry of Health accounts for cases of congenital syphilis involving live births, miscarriages (up to 22 weeks of gestation or body weight ≤ 500g), and stillbirths (22+ weeks of gestation or body weight > 500g) from mothers with non-treponemal tests (CRDL) positive for syphilis of any titer, with or without confirmation by fluorescent treponemal antibody--absorption (FTA-ABS) tests for syphilis, performed during prenatal care or at the time of delivery or curettage, who have been treated inadequately or not treated at all.[4,6]

The diagnosis of congenital syphilis via laboratory tests may be performed directly (via identification of the spirochete bacterium) - indicated for early stage disease - or indirectly (via serology). Direct methods include dark-field microscopy - highly specific and moderately sensitive - and PCR to detect *Treponema pallidum* in amniotic fluid and diagnose fetuses with congenital syphilis, a procedure seldom used in clinical practice.[4]

VDRL is a serological diagnostic method that provides qualitative (positive or negative for syphilis antibodies) and quantitative (titers 1/8;1/16;1/32,...) results.[4,6] It is the most widely available test in the Brazilian Public Healthcare System. Ease-of-use and affordability have made it the test of choice in syphilis screening and response-to-treatment monitoring. Nonetheless, the test will at times produce false-positive (pregnancy, cancer, collagenoses, viral infections, etc.) and false-negative results in contexts of low antibody titers or due to the prozone phenomenon.[4]

The prozone phenomenon is a false-negative response caused by a disproportionate ratio between the levels of antigens and antibodies, in which high antibody titers interfere with the antigen-antibody reaction. In order to avoid it, in the VDRL test the sample must be tested in its pure state and at a dilution of 1:8.[4] The prozone phenomenon may occur in 1-2% of the patients, particularly in individuals with early-stage disease and patients diagnosed during pregnancy, as the case reported herein.[7]

Treponemal tests used to confirm the diagnosis of syphilis include FTA-ABS, enzyme-linked immunosorbent assay (ELISA), and the Treponema pallidum hemagglutination assay (TPHA). They are sensitive and specific for anti-treponemal antibodies and have also been indicated to rule out VDRL false-positive results.[4]

Rapid syphilis tests are also based on the detection of anti-treponemal antibodies. Patients with positive results must be investigated for prior treatment and the potential effects of serological memory on their test results.[4]

Lastly, the high rates of congenital syphilis recorded in Brazil in spite of the programs in place to control the disease places question marks on the quality of the care provided prenatally and at the time of delivery, on to what extent healthcare workers know which diagnostic test to use, on how well they interpret test results, and on the quality of the procedures carried out at diagnostic laboratories, since the prozone phenomenon can be prevented if the VDRL test is performed in accordance with testing standards.

Healthcare services must implement and encourage the adoption of protocols that introduce syphilis screening as an integral element in prenatal care so that an end is put to the progression of congenital syphilis in Brazil. Syphilis is a preventable disease when it is identified and adequate treatment is offered in a timely manner to infected pregnant women and their sexual partners[3].

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