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Diphtheria in two pregnant in the context of the epidemic in Venezuela

Difteria en dos embarazadas en el contexto de la epidemia en Venezuela

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SUMMARY

Diphtheria is an acute infectious disease caused by the bacterium Corynebacterium diphtheriae that encodes diphtheria toxin (DT) in susceptible human subjects during an outbreak. Venezuela has experienced a widespread resurgence of diphtheria since early 2016. Here, we describe the clinical characteristics of two cases of diphtheria in hospitalized pregnant women in 2017, in two cities in Venezuela. The clinical diagnosis was made according to the recommendations of the World Health Organization. Throat samples were cultured and diphtheria toxin was amplified by real-time PCR technique. The first case presented a severe and lethal form, while the second case presented a severe tonsillar form of the disease. Diphtheria remains a life-threatening infection, especially during pregnancy. Early diagnosis and treatment with antitoxin and antimicrobials are recommended for effective management.

Keywords: *Diphtheria, pregnancy, tonsillar membranes, severe disease, diphtheria toxin.*

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RESUMEN

La difteria es una enfermedad infecciosa aguda causada por la bacteria Corynebacterium diphtheriae que codifica la toxina diftérica (TD) en sujetos humanos susceptibles durante un brote. Venezuela experimentó un resurgimiento generalizado de la difteria desde principios de 2016. A continuación, describimos las características clínicas de dos casos de difteria en gestantes hospitalizadas en 2017, en dos ciudades de Venezuela. El diagnóstico clínico fue realizado de acuerdo con las recomendaciones de la Organización Mundial de la Salud. Las muestras de garganta se cultivaron y la toxina diftérica se amplificó mediante la técnica de PCR en tiempo real. El primer caso presentó una forma letal, mientras que el segundo caso presentó una forma amigdalina grave de la enfermedad. La difteria sigue siendo una infección potencialmente mortal, especialmente durante el embarazo. El diagnóstico precoz y el tratamiento con antitoxina y antimicrobianos es lo recomendado para un manejo eficaz.

Palabras clave*: Difteria, embarazo, amígdalas, enfermedad grave, toxina diftérica.*

INTRODUCTION

Diphtheria is an acute infectious disease caused by strains of *Corynebacterium diphtheriae* transformed to toxigenic by the introduction of a lysogenic phage carrying a gene encoding the diphtheria toxin (DT) in susceptible human subjects during an outbreak. The production of DT is strictly repressed by the diphtheria toxin repressor (DtxR) and iron ions from the extracellular environment (red blood cells derived) as a co-repressor factor (1). DT, which is the most prominent virulence factor of *C. diphtheriae*, inhibits protein synthesis by catalyzing NAD^+-dependent ADP-ribosylation of elongation factor-2, thus inducing apoptosis, resulting in cell death. (2) Historically, *C. diphtheriae* isolates have been typed phenotypically into four biovars (Belfanti, gravis, intermedius, and mitis) although genetic approaches have questioned the basis of biovar separation (3).

Humans, horses, and cats have known reservoirs (4) and transmission occurs primarily through direct contact with airborne respiratory secretions or exudation from infected skin lesions. After colonization, *C. diphtheriae* induces biofilm formation that causes local cellular damage, ulcer formation, and fibrin polymerization (also known as pseudomembrane) after bacterial colonization. Subsequently, DT exerts a distant toxic effect on the heart (causing myocarditis), peripheral nervous system (causing weakness progressing to paralysis), and kidneys, helping bacteria to evade immune defense mechanism (specific antibody response and phagocytosis) as well (1).

Although its is a well-controlled vaccine-preventable disease, cases of diphtheria are still endemic in countries with decreased immunization coverage and poor socioeconomic conditions (1) such as Ukraine, Russia, Latvia, India, Indonesia, Nepal, Angola, and Brazil, with few sporadic cases reported in developed countries. However, there has been an increase in the incidence of adult diphtheria in Venezuela as a consequence of the recent collapse of the Venezuelan healthcare system (5,6) attributable to the sharp reduction in oil revenue with the consequent shortage of the foreign currency income needed to import equipment, food, medicines and medical supplies (including vaccines), the reduction of its annual expenditure dedicated to public health-care spending, and the lack of regular information due to epidemiological silence imposed by the government, making the assessment of the impact of the crisis quite difficult. The last official report from the Venezuelan Ministry of Health was published in 2016 (7).

In Venezuela, the diphtheria outbreak began in July 2016 and, as of epidemiological week (EW) 34 of 2020, a total of 3 114 suspected cases have been reported (324 cases in 2016, 1 040 in 2017, 1 208 in 2018, 488 in 2019, and 54 in 2020). Of the total, 1 790 have been confirmed (582 by laboratory and 1 208 by clinical criteria or epidemiological link), including 294 deaths. Among confirmed cases, 58 cases including 17 deaths had symptom onset in 2016, 786 cases including 103 deaths in 2017, 775 cases including 151 deaths in 2018, 166 cases including 21 deaths in 2019, and 5 cases including 2 deaths in 2020. Since the beginning of the outbreak, a sustained increase in cases was observed until 2018, followed by a decrease in 2019; it is expected that in 2020, the number of cases will continue to decrease (8).

Additionally, because of the migratory movement, cases of diphtheria have been

confirmed in Venezuelan citizens in other countries, especially in Colombia and Brazil (9). In 2019 and 2020, Brazil, Colombia, the Dominican Republic, Haiti, and the Bolivarian Republic of Venezuela reported confirmed cases of diphtheria (8).

In this context, even though the occurrence of diphtheria during pregnancy or the puerperium is rare (with few known reports in the literature) (10,11), here we report two suspected cases of the disease during the outbreak in Venezuela, where people have limited access to health-care and doctors lack treatment and laboratory facilities, besides being unfamiliar with the disease as the last case report of diphtheria in the country was in 1992 (12,13).

The aim was to describe two cases of diphtheria in pregnant women, one of them hospitalized in the "Instituto Autónomo Hospital Universitario de Los Andes" (IAHULA) (case N°1), Mérida, Mérida state; and the second, in the "Hospital Universitario de Caracas" (HUC) (case N°2), Caracas, Capital District, during November 2017, in the context of the diphtheria epidemic that affects the Bolivarian Republic of Venezuela, since 2016.

Case Report

Case 1

In November 2017, a forty-four years-old pregnant woman (third gravity), resident of Merida State, contracted pharyngeal symptoms during the first trimester of gestation. A week later, she visited a private physician, because of worsening of her symptoms, with high fever, exudative tonsillitis, sore throat, dysphagia, and cough. She was referred to the University Hospital of Los Andes due to respiratory distress and laryngeal stridor. From her medical history, menarche occurred when she was 13 years old with regular cycles that lasted 3 days. She had a medical history of recurrent pregnancy losses (RPL) of unspecified origin and a previous cholecystectomy 6 years ago. She denied any immunization with toxoid in the last 10 years.

At admission, physical examination showed a blood pressure of 114/70 mmHg, heart rate of 118 beats per minute and her body temperature was within the normal range. The clinical examination revealed a left painful cervical adenopathy (2x2 cm) without swollen neck and an adherent gray-white asymmetrical pseudomembrane in the tonsils and pharynx. Chest examination revealed a respiratory rate of 16 breaths per minute and bilateral crackles on auscultation over upper lung fields. She did not have a cutaneous lesion or neurologic signs or symptoms. Other findings of physical examination were unremarkable.

She was admitted to the hospital with a diagnosis of high-risk pregnancy, suspected respiratory diphtheria, community-acquired pneumonia, advanced maternal age, and RPL. Laboratory blood tests revealed a white blood cell (WBC) count of 38 000/μL (65 % neutrophils) and a C-reactive protein (CRP) level of 12 mg/dL. Chest radiography documented right lobe infiltrates and the culture of pharyngeal exudates showed penicillin/macrolides-resistant *E. coli* susceptible to cephalosporins. Pharyngeal samples were collected and submitted for bacterial culture and diphtheria toxin real-time Polymerase chain reaction (PCR) amplification.

The patient was treated with diphtheria antitoxin (DTA)100 000 IU, IV infusion in 500 mL of 0.9 % sodium chloride), crystalline penicillin 4 million units, intravenous, four-times a day, ceftriaxone 2 g, Intravenous, twice a day, moxifloxacin 400 mg/d and adult Td vaccination. Close contacts were treated with penicillin G benzathine (1.2 million units, Intramuscular, unique dose) and adult Td vaccination.

After hospitalization, she rapidly developed difficulty breathing and pleural effusion despite medical treatment, causing transference to the intensive care unit (ICU) where she expelled a bronchial tree-shaped pseudomembrane (Figure 1). Oxygen was given as the patient's clinical prognosis worsened when she developed severe diphtheritic toxemia that quickly progressed to hemodynamic instability and respiratory failure causing her death six days later. Real-time PCR amplification of the diphtheria toxin gene resulted positive (performed at Instituto Nacional de Higiene Rafael Rangel" (INHRR), throat culture of *C. diphtheriae* was negative.

Case 2

A twenty-three-year-old patient, natural and from Cúa (Miranda State, Venezuela), with a single 30-week pregnancy, referred with non-quantified high body temperature, odynophagia even to solids, arthralgia, myalgia, and headache of moderate intensity. Two days later, a whitish plaque appears on her oropharynx. She received medical care without improvement, and therefore, was admitted 24-hrs later at the Hospital Universitario de Caracas. From her medical history, her last menstruation period date was imprecise, three previous pregnancies, two caesarean sections, no abortions. Uncontrolled pregnancy, with no previous diphtheria vaccination. Physical examination of admission showed a blood pressure of 100/50 mmHg, heart rate of 86 beats per minute and body temperature was within the normal range. Wide mouth opening, sialorrhea, a grayish membrane presence was seen on the soft palate, which was no detachable and extends to palatine tonsils and pharynx lateral and posterior faces (Figure 2). Her neck was swelling, without apparent local adenomegaly. Respiratory auscultation was normal without aggregates, rhythmic heart sounds without murmurs. The abdomen was soft, depressible. External genitals are shown normal configuration, showing a gravid uterus. Other findings of physical examination were unremarkable. She was admitted as a probable infection by Corynebacterium diphtheriae and treated with crystalline penicillin at doses of 3 million units every 4 hours, and two doses of DTA (60 000 units each), 24h apart, however, an allergic reaction was evidenced by multiple urticariform skin lesion throughout the body, that required intravenous steroids treatment. Nasofibrolaryngoscopy visualization showed a white-grayish membrane in valleculae and lateral wall of the pharynx, edema in the epiglottis, arythenoepiglottic fold that reduce the glottic lumen to 20 % wide. The blood test showed normal values range of arterial gases and electrocardiogram. Obstetrics evaluation shows normal fetal well-being, perinatal echo at discharge within normal. Later on, azithromycin 500 mg orally was added due to the slow evolution towards improvement, she was discharged 9 days later in good general conditions. Pseudomembrane culture of the pharynx was positive for *C. diphtheriae*, and real-time PCR amplify the diphtheria toxin gene was positive (performed at INHRR).

Figure 1. Bronchial membrane expelled in case 1. IAHULA, Mérida. Venezuela, November 2017.

Figure 2. Pharyngeal membrane of a pregnant 23-years old woman with, 30 weeks of pregnancy (Case 2). Cúa, Miranda State, Venezuela, November 2017.

Figure 3. Pharyngeal membrane in resolution state, observed in case 2, at day 7 of treatment. HUC, Caracas, Venezuela, November 2017.

DISCUSSION

Here, we describe the clinical evolution of two cases of diphtheria during pregnancy in a current ongoing outbreak of the disease in Venezuela. Information on diphtheria during pregnancy is limited, most of the publications are based upon immunization and its effects on the pregnancy and newborn. Some isolated reports on the clinical behavior of the disease in pregnant women had been reported in some countries of the former Soviet Union in the 1990s, one of the most important epidemics in the last years, it is scarce, even though in some of these countries the number of women affected was significant (14,15).

The description of some cases of diphtheria in pregnant women was published early in the 19th century, describing severe forms of the disease, with vaginal, anal, and pharyngeal involvement; maternal death, and neonatal death by diphtheria acquired in the postpartum period (10). There is also a description of pregnant women in the pre-antibiotic era with successful treatment only with DTA (10).

The clinical manifestations of our two cases are considered serious; case number 1, had seven days of the progressive evolution of a pharyngeal and systemic symptom and got complicate with laryngeal stridor, which is a symptom of severity (16,17). Some highlighting aspects of the case were her advanced maternal age, recurrent miscarriages, involvement of the lower respiratory tract, and sepsis, factors that probably contributed to death (18,19). The patient received DTA, antimicrobials, steroids, and ventilatory support; even so, the evolution was torpid, dying 6 days after admission. Probably the entire respiratory tree was upholstered by a pseudomembrane, which the patient partially expelled one day before dying (Figure 1). The observation of the pseudomembrane with the morphology of the bronchial tree is something that we had only seen in the books (17) so that the observation of this phenomenon was something completely unprecedented. The autopsy was not performed due to the "Complex Humanitarian Emergency" that the country is currently experiencing (5,20).

The mortality rates de la diphtheria still ~10 % and have changed little over time. Acute mortality is due to toxin-mediated diphtheritic cardiomyopathy, obstruction of the respiratory tract by the pseudomembrane, disseminated intravascular coagulation, and renal failure (21). In fatal diphtheria, pharynx, larynx, trachea, and the main bronchi may be covered by pseudomembranes that may or may not be firmly attached to the tissues. Smaller bronchi are often reddened and coated with a similar thin membrane. The lungs are hemorrhagic with moderately solid consistency. Edema and hyperemia of the affected epithelial surface appear first. This is followed by necrosis of the epithelium, accompanied by the outpouring of a fibrinosuppurative exudate. The coagulation of this exudate on the ulcerated necrotic surface creates the characteristic tough, dirty gray to gray-white superficial pseudomembrane (22).

Case number 2 also had criteria of severity, involving a significant obstruction of the respiratory tract; however, the patient received aggressive treatment including anti-toxin, antimicrobials combination, and steroids, slowly evolving to improvement, and without obstetric complications and withdrew in good general

conditions after 9 days of hospitalization.

None of the patients had cardiac complications such as myocarditis, this complication is potentially fatal, and usually occurs during the first week of the disease onset (23). The incidence of diphtheritic cardiomyopathy following diphtheria is 10 %–20 %, and the associated mortality is ~50 %. Clinical signs of diphtheritic cardiomyopathy become apparent by the end of week 2 of infection, it is more frequent in children (21).

Neurological complications usually occur 15 days after the onset of symptoms and manifest with cranial nerve alteration, mainly affecting the IX and X pair, causing problems in swallowing and associated with aspiration pneumonia. There may be disorders of sensation and motor alterations such as quadriparesis and quadriplegia (24), among others.

Diphtheria is a severe and serious disease in pregnant women. Respiratory dysfunction and/or vaginal infection might occur during any trimester of pregnancy or in the postpartum period (10,25). Pregnant women with severe diphtheria should be evaluated by a multidisciplinary team, as was done in our cases; regular cardiac and fetal monitoring, close monitoring of respiratory and cardiac function, and early detection of obstetric complications are recommended. Diphtheria can cause abortion, premature birth, neonatal death, and estimated maternal death in one-third of the survivors (26). Women with respiratory diphtheria at the end of pregnancy, in the puerperium, or during lactation may transmit the infection to infants, this microorganism spread through direct contact, respiratory droplets, and aerosols from infected mothers (26,27). When an outbreak of neonatal diphtheria occurs in a hospital facility, all newborns should receive diphtheria prophylaxis (28). Breastfeeding is not contraindicated; it is advisable to extract breast milk and offer the newborn until the mother stops being contagious.

In case number 1, the culture of the pseudomembrane was negative, but the diphtheria toxin was identified by the RT-PCR (polymerase chain reaction in retro transcription) technique. The patient had probably received antibiotics before admission, a factor that probably could have contributed to the negativity of the culture. In addition, the sample had to be transported from the interior of the country to the national reference center (INHRR, located in Caracas) for infectious agents' culture and identification. RT-PCR provides supportive evidence of diphtheria's toxin amplification, confirming the diagnosis (29). However, in a situation where there is an increased risk of infection, treatment should be given early during illness and without waiting for laboratory confirmation of the agent and its toxin (30). In case number 2, it enters the definition of the case confirmed by positive culture of *C. diphtheriae* and by identification of diphtheria toxin by the RT- PCR technique (16,29).

Our cases received antibiotics recommended in diphtheritic diseases, such as crystalline penicillin and, or macrolides (16,17). Case number 1 also received multiple antimicrobials due to the lower respiratory tract and sepsis involvement. In case number 2, a macrolide was added due to the slow evolution towards improvement, she also received steroids for edema of the neck, obstruction of the glottic lumen, and the severe allergic reaction that occurred secondary to the administration of DTA. Antibiotics are useful in eradicating the organism and thereby limiting both toxin production and transmissibility. However, diphtheria antitoxin should be administered promptly based on the clinical presentation and presumptive diagnosis and cannot wait for laboratory confirmation (16,17,30).

Delay in initiating antitoxin treatment is associated with an increased incidence of myocarditis, paralysis, and death. In the pre-antibiotic era, the treatment of diphtheria was carried out only with DTA, this medication being lifesaving (10,30). In severe cases of diphtheria, a maximum dose of DTA is recommended. In both cases described here, doses of 100 000 and 120 000 respectively were indicated; case number 2 received fractional doses of DTA, due to the non-availability of the medication at the time of patient's admission, and to a severe allergic reaction at the end of the administration of the second dose. DTA is recommended to be applied in one-time doses; fractionated dose is associated with a greater probability of allergic reaction since DTA is a heterologous protein of horse serum (30). In case of an allergic reaction, desensitization is recommended, and extreme caution should be exercised when administering

DTA in patients with a history of allergy and asthma (30).

None of our patients were immunized against diphtheria, the diphtheria vaccine is a formal recommendation during pregnancy, it has been shown that maternal antibodies are transferred efficiently to the fetus (26). Additionally, several studies indicate that transplacental maternal antitoxin (maternal antibodies) provides newborns protection against diphtheria at birth if their mother is immune (31).

Due to the continuing increase in pertussis disease since 2013, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) recommends women in the United States, a dose of Tdap during each pregnancy, regardless of the patient's prior history of receiving Tdap (32). To maximize the maternal antibody response and passive antibody transfer and levels in the newborn, the optimal timing for Tdap administration is between 27 weeks and 36 weeks of gestation, although Tdap may be given at any time during pregnancy. Tdap administration during pregnancy is not associated with an increased risk for frequency of major malformations, stillbirth, preterm birth, small for gestational age, or hypertensive disorders (32,33).

In Venezuela, there is no availability of the Tdap vaccine; only the Td vaccine is available and recommended for adults, including pregnant women. The vaccination rate against diphtheria in Venezuela, in susceptible groups, remains low (34).

Finally, we mention the study carried out by Strauss et al. (35), on the diphtheria outbreak in Venezuela; of 51 patients evaluated in different parts of the country, they studied ten samples for molecular characterization: Nine samples corresponded to *C. diphtheriae* and 1 to *C. ulcerans*. Two Sequencing Types (ST), ST174 and ST697 (the latter not previously described) were identified among the eight *C. diphtheriae* isolates from Carabobo state. Cg-MLST revealed only one cluster also from Carabobo. The Whole Genome Sequencing analysis revealed that the outbreak seemed to be caused by different strains with *C. diphtheriae* and *C. ulcerans* coexisting. The predominant biotype of *C. diphtheriae* was mitis.

CONCLUSIONS

In pregnant women, diphtheria should be promptly diagnosed and treated with diphtheria antitoxin, antibiotic therapy, and toxoid, as well as continuous monitoring and supportive therapy in case of serious complications (management of the airway and heart, neurological and renal failure) to prevent maternal deaths. Likewise, health authorities should intensify the training of health personnel to improve medical care and vaccination, as well as epidemiological surveillance, research, and education of the population to prevent future diphtheria outbreaks.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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