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Neonatal tetanus

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Neonatal tetanus, also known as tetanus neonatorum, occurs in young infants of inadequately immunized mothers. It is a kind of generalized tetanus that is exhibited mainly by prevention of the release of the inhibitory neurotransmitters (i.e., disinhibition) and is initiated by tetanospasmin, an exotoxin created by *Clostridium tetani*. Contamination of the umbilical cord stump is the main cause. The typical, early manifestations are weakness and lack of ability to suck, continuing within hours to trismus, risus sardonicus, and ultimately generalized tetanic spasm, rigidity, and opisthotonus. Without treatment, neonatal tetanus has a poor outcome with a mortality rate above 90%. Mortality can result from asphyxia due to the spasm and hypersympathetic state. The managing goals are to neutralize its toxin, eradicate *C. tetani*, care for wound, and offer supportive care, such as mechanical ventilation, parenteral nutrition, sedation, neuromuscular blockade, and management of autonomic dysfunction.

Key words: Immunization, Passive; Infant, Newborn; Seizures; Tetanus; Vaccination

Introduction

Tetanus is caused by tetanospasmin, also known as tetanus toxin, an exotoxin produced by *Clostridium tetani*. Neonatal tetanus (NT), also known as tetanus neonatorum, is a chief cause of infant mortality in developing countries[1-3]. It is estimated that the entity led to 787,000 and 200,000 deaths worldwide in 1988 and in 2000, respectively[3]. The latest World Health Organization estimate shows is 25,000 deaths from NT in 2018, which means an 88% reduction from the situation in 2000[3]. Maternal tetanus and NT have not yet been eliminated by July 2019 in 12 countries[3]. Unlike in low and middle-income countries, NT is rare and was reported in only 2 newborns from 2009 to 2015 in the United States[3].

Main subject

1. Bacteriology and pathogenesis

C. tetani is a thin, gram-positive, non-encapsulated, motile, obligated anaerobic bacillus that exists in vegetative and sporulated forms. The spores are

terminal and drumstick in appearance, and withstand heat or chemical disinfection. However, the vegetative forms can be killed by chemical disinfectants (glutaraldehyde, iodine, and hydrogen peroxide), heat, and some antimicrobials[4]. Spores are present in soil and the gastrointestinal tract of mammals; they are nonpathogenic in earth or contaminated animal tissues until conditions are suitable for alteration to the vegetative (pathogenic) forms. Such conditions emerge when oxygen concentration decreases in the devitalized tissue by either foreign body, injury (primarily crush) or suppuration.

Although *C. tetani* itself does not invade the tissue, this bacterium induces illness through production of tetanospasmin[4-7]. Toxigenic *C. tetani* strains encode tetanospasmin on a plasmid[5], and the toxin is produced by the proliferating *C. tetani* at the location of infection. The toxin acts in the central nervous system to prevent the discharge of inhibitory neurons, thereby disinhibiting the motor neurons. Unlike botulinum toxins, it has no action at the neuromuscular junctions. Its action is as a metalloprotease preventing the release of glycine and γ-aminobutyric acid[5]. The neuromuscular endplates and motor nuclei of the central nervous system are stimulated by tetanospasmin, thus generating muscle spasm and convulsions.

The absorption and transport of tetanospasmin have 2 mechanisms[7]. When a large amount of the toxin is produced, it spreads to the neurons via the circulation and lymphatics, causing spasm at distant sites and initially affecting the muscles with shortest neural path. The toxin undergoes transcytosis and interneural transfer, resulting in effects distant from the toxin production sites[5]. Lockjaw and risus sardonicus are manifestations of this fast-developing illness. The inception of muscular involvement relates to the neural distance from the toxin production sites[5-7].

Nidogen-1 and nidogen-2, extracellular matrix proteins, are the receptors of tetanospasmin that reach the nervous system through the neuromuscular junctions. These proteins spread backward transsynaptically, shielded from neutralizing anti-toxins, to the inhibitory synapses where the proteins bind and permanently prevent the secretion of acetylcholine[8]. The lower motor neurons become uninhibited, increasing the tone of agonist and antagonist muscles. This increase in muscle tone produces the typical confined spasm and rigidity.

Tetanospasmin also can generate paralysis by stopping transmission at the neuromuscular junctions[9]. Some clinical manifestations indicate the involvement of the sympathetic nervous system. The lasting effect of the toxin may be reduced by the neuronal generation of additional branches and the creation of new links among the surviving neurons[5,7].

2. Clinical manifestations

NT is a generalized tetanus that usually occurs only in infants delivered from unimmunized or inadequately immunized mothers. Causes of this entity include infection of the umbilical stump, inadequate obstetric care, delivery away from medical facilities, poor obstetrical care following delivery, and cultural routines such as application of cow stool or soiling over the umbilical stump. The incidence of NT may be reduced by the immunization of adolescent and adult women, and local use of antimicrobials on the stump.

Weakness and failure to suck are the most frequent initial manifestations that usually occur in 5-7 days (range, 3-24 days) after birth. These symptoms continue to develop from an initial trismus and sucking difficulty to risus sardonicus within hours, and subsequently to generalized tetanic spasm, rigidity, and opisthotonus (Fig. 1)[6]. Affected infants stay awake despite the spasm.

NT has a poor prognosis with a mortality rate over 90%. This outcome can be caused by the hypersympathetic state. The most frequent causes of mortality are apnea during the first 7 days and septicemia in 7-14 days often due to infection starting at the umbilical stump[6]. Other complications include pneumonia, atelectasis, hemorrhage from the lung or central nervous system, renal failure, electrolyte imbalance, and laryngospasm. Younger age and lower

Fig. 1. An infant with neonatal tetanus presenting with opisthotonus (provided by the Centers for Disease Control and Prevention).

weight are associated with death[10]. Earlier onset, leukocytosis, and longer time between first symptom and admission are also indicators of mortality and longer hospital stay[10].

Improvement is heralded by defervescence (usually within 3-7 days), reduction in spasm episodes, and improvement of muscular rigidity. Resolution may take up to 45 days. Survivors often exhibit developmental disabilities. Newborns with severe umbilical infection are prone to bacteremia due to Enterobacteriaceae, gram-negative anaerobic bacilli (e.g., *Bacteroides fragilis* group), and *Staphylococcus aureus*[11].

3. Diagnosis

The diagnosis is made on clinical grounds in the settings of increased risk, and by ruling out other potential reasons for tetanic spasm in newborns. The isolation of *C. tetani* from the stump may not be related to production of tetanospasmin. NT can be suspected once the aforementioned initial manifestations emerge. Laboratory tests are only helpful in excluding other causes. Thus, management of NT cannot be delayed pending the laboratory findings[6].

The differential diagnosis includes pseudo-tetanus, birth injury, rabies, hypocalcemic tetany, seizure, meningitis, encephalitis, dystonic reactions to antipsychotics or other central dopamine antagonists, and strychnine poisoning[12,13].

Neonatal tetany differs from NT. Newborns with tetany are well between convulsive episodes. Carpopedal spasm and laryngospasm appear in tetany, but trismus is rare. The diagnosis is established by confirming hypocalcemia[11,14].

The rigidity of newborns due to birth injury usually exhibits signs of brain injury before the initial signs of tetanus emerge. Extraocular palsies generally exist, abdominal rigidity is lacking, and response to stimulation is suppressed[15].

4. Management and outcome

The managing goals are to neutralize its toxin, eradicate *C. tetani*, care for wound, and offer supportive care, such as mechanical ventilation, parenteral nutrition, sedation, neuromuscular blockade, and management of autonomic dysfunction[16]. Most data on this topic are based on observation or studies in adults. Survival rests on the various measures for supportive care with emphasis on intubation, administration of neuromuscular blocking agents, and providing assisted ventilation[17,18]. It is difficult but necessary to administer forceful, but calculated, and supportive care that eliminates any stimulus. Affected infants to an adequate setting should be transferred early in the course of illness.

1) Neutralization of tetanospasmin

The newborn should receive human tetanus immunoglobulin (TIG) without delay[11,18]. TIG should be given as a single intramuscular (IM) dose of 500 U to bind the circulating toxin. However, the exact dose has not been determined, and total doses as high as 3,000-6,000 U are also recommended. Part of the dose can be infiltrated around the identified wound. If TIG is unavailable, equine tetanus antitoxin can be administered. When this antitoxin is given, immediate and delayed reactions to the antitoxin may take place. Although intravenous (IV) immunoglobulin offers passive immunization, there is insufficient familiarity with its dose and efficacy. Since tetanus itself does not confer an antibody response, those who underwent NT should be immu-

nized with the series of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), following complete recovery from the active illness[11,18].

Intrathecal administration of TIG or tetanus antitoxin enables higher concentration of TIG or antitoxin within the nervous system than IM administration. Despite the conflicting evidence on superiority of intrathecal over IM administration, a meta-analysis using 12 clinical trials involving 942 patients suggested that intrathecal administration is more beneficial than the latter[19]. A randomized controlled trial shows a reduced mortality in neonates who received intrathecal lyophilized human immunoglobulin while also receiving IM tetanus antitoxin[20].

2) Eradication of *C. tetani*

C. tetani is susceptible to several antimicrobials: penicillins, cephalosporins, metronidazole, macrolides, tetracyclines, and imipenem[21-23]. It is recommended that specific antimicrobial therapy should be given with one of these modalities: per os or IV metronidazole (< 7 days of age, 15 mg/kg/day in divided doses; > 7 days, 30 mg/kg/day in divided doses, for 10-14 days); or IV penicillin G (100,000 U/kg/day administered at 6-hour intervals, for 10-14 days).

3) Wound care

In the presence of an umbilical stump infection, it may be necessary to obtain the adequate antimicrobial coverage against polymicrobial aerobic-anaerobic pathogens[11]. Topical application of antimicrobials or disinfectants to the umbilical cord can serve as an effective preventive measure[16]. It is important to clean the wound by removing dirt, foreign object, and the dead tissue.

4) Sedation and neuromuscular blockade

Clinical experience has demonstrated that mortality rate was lowest in those treated with combined therapy of diazepam, phenobarbital sodium, and/or chlorpromazine[21]. Omphalectomy has also been used to eliminate the toxin production[21].

Sedation and muscle relaxation in mild cases are achievable with diazepam. An initial dose of 0.1-0.2 mg/kg IV is given to release an acute spasm, followed by a continuous IV infusion of 15-40 mg/kg/day, titrated to control the spasm. After 5-7 days, it can be decreased by 5-10 mg/day and given orally or nasogastric[11].

Concomitant phenobarbital is given with a loading dose of 20 mg/kg and maintenance dose of 5 mg/kg/day to reach a serum phenobarbital concentration of 30-50 mg/dL. Substantial apnea occurs in about 10% of treated patients and respiratory support should be given immediately. Assisted ventilation is vital at higher doses. Other benzodiazepines, such as lorazepam and midazolam, are also acceptable. Further sedation with phenothiazines may be needed. If spasm cannot be suppressed, therapeutic paralysis is required[10].

Curariform agents, such as vecuronium, can induce neuromuscular blockade. Since these agents are often administered for extended period of time, the doses should be reduced slowly to prevent withdrawal symptoms[10].

5) Management of autonomic dysfunction

Decreasing production of catecholamines can reduce the autonomic dysfunction. Labetalol (0.25-1.0 mg/minute) that possesses both α- and β-blockade can be given. Providing only β-blockade (e.g., propranolol) is not advised because it may lead to sudden death[18]. Morphine sulfate (0.5-1.0 mg/kg/ hour, continuous IV infusion) is frequently used to sedate and control the autonomic dysfunction by diminishing cardiac and vascular sympathetic tone. This drug adjusts cardiac instability without compromising[24]. Only magnesium sulfate has been evaluated in a randomized clinical trial of severe tetanus[25], and in several series for managing spasm including NT[26-29]. Thus, magnesium sulfate is given as a first-line agent in the management of NT. It relaxes the vascular smooth muscles and decreases catecholamine release from the adrenal medulla[30] and the adrenergic nerve endings[31]. Other medications to control the autonomic dysfunction are atropine, clonidine, and

epidural bupivacaine[32,33].

6) Other measures for supportive care

Nutritional support is important, and should be provided early to satisfy the neonates' high caloric and protein demands[34]. Enteral feeding is rarely utilized. Instead, a percutaneous endoscopic gastrostomy tube is frequently used in decreasing gastroesophageal reflux than a nasogastric tube. Central venous hyperalimentation may also be used. Heparins or other anticoagulants are given to prevent thromboembolism. Flotation bed or frequent position changes can prevent skin breakdown and peroneal nerve palsies[26,27].

7) Outcome

Many survivors from NT experience developmental handicaps. Only a few studies evaluated the long-term effects of this entity. Furthermore, actual rates of sequelae are likely to be greater. A Kenyan study shows that 20%–40% of survivors sustained permanent brain damage, manifested as microcephaly, and neurological, developmental, and behavioral difficulties[35]. A Nigerian case series shows cerebral palsy, cognitive-developmental delay, and deafness in 20% of survivors[36]. These complications might have been caused by the hypoxia and hypoglycemia that are frequent throughout the illness.

5. Prevention

The World Health Organization recommends the administration of 6 doses (3 primary plus 3 booster ones) of tetanus toxoid-containing vaccines to each child. The 3-dose primary series should start at the age of 6 weeks, followed by 3 boosters given 4 weeks apart[37]. It is recommended that the 3 boosters are given in the second year of life, and additional single booster doses at 4–7 years and at 9–15 years. Ideally, there should be at least 4 years between booster doses.

To prevent the occurrence of NT, pregnant women should receive 1 dose of reduced diphtheria and pertussis toxoids (Tdap) during each pregnancy, preferably during 27–36 weeks of gestation[37,38]. Previously unvaccinated pregnant women should receive 2 doses of tetanus toxoid (at least 1 dose of Tdap) given 1 month apart, with the first dose as early as possible in pregnancy[2,37]. Further doses should be given in subsequent pregnancies or at intervals of at least 1 year, up to a total of 5 doses that is considered sufficient for the lifelong protection[2].

Conclusion

NT is one of the most common life-threatening consequences of unhygienic deliveries and umbilical cord management. This entity is an indicator of inadequate availability of immunization and other maternal and neonatal care. NT-related mortality rates are high mainly when inadequate health care is provided as often occurs in developing countries. The managing goals are neutralization of toxin, eradication of *C. tetani*, wound care, and specific supportive care. Mortality can be averted easily by practicing sanitary delivery and adequate cord care or by vaccinating children and women with tetanus toxoid-containing vaccines.

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Conflicts of interest

Acknowledgements

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