Diphtheritic Polyneuropathy: A Rare Complication that Needs to be Acknowledged

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Abstract
Globally, diphtheria still poses a burden on public health, predominantly in developing countries. Poor vaccine coverage and boosters are the main factors in the diphtheria outbreak that should have been obliterated as the vaccine was invented a century ago. Health services are particularly burdened by diphtheria because it can lead to both short-term complications like acute airway obstruction and long-term complications like myocardial toxicity and diphtheritic polyneuropathy. Data about diphtheritic polyneuropathy is scarce, and physicians may not be aware of this condition. Herein we present the pathophysiology, clinical manifestation, diagnosis, and treatment of diphtheritic polyneuropathy.

Keywords: complication; clinical manifestation; diphtheria; diphtheritic polyneuropathy; treatment

Introduction
First described by Hippocrates (5th century B.C.), diphtheria is a potentially lethal disease caused by Corynebacterium diphtheriae or other toxigenic strains (C. ulcerans and C. pseudotuberculosis) (Acosta et al. 2021). In the pre-vaccine era, diphtheria used to be one of the primary causes of death in the population, especially in children. If left untreated and without the immunity of the patients (the unvaccinated ones), the mortality rate is about 50%, whereas if being treated, the rate drops to somewhere around 10% (Faulkner et al. 2019). A higher case-fatality rate, up to 20%, is observed in children under the age of 5 and adults over 40 years old (Centers for Disease Control and Prevention 2022a).

Although the diphtheria vaccine was first introduced in 1921, approximately a million cases of diphtheria and over 60,000 deaths were reported every year in the 1970s. After the addition of the diphtheria toxoid vaccine to the global Expanded Programme on Immunization (EPI), the prevalence of diphtheria declined by more than 90% from 1980 to 2000 (Blumberg et al. 2018). It was shown through analysis of the diphtheria, tetanus, and acellular pertussis (DTaP) immunization program in the United States that in a cohort of 4.1 million children, 276,750 cases of diphtheria and 27,675 deaths would have occurred in the absence of the program. The estimated cost of these cases would have been roughly US $18,772.4 million (Ekwueme et al. 2000).

Despite the availability of effective vaccinations, diphtheria has the potential to resurface. Poor immunization coverage, interruption of the cold chain, inadequate living conditions, delayed reporting to the health center, and non-availability or delay in the administration of antitoxin are likely to contribute to the recurrence of the disease and higher mortality (Gowda et al. 2022; Jammar et al. 2021). The waning of immunity in adults is playing a part as a risk factor for this condition. As people get older, their immunity to diphtheria decreases, making them more vulnerable to infection (Sunarno et al. 2021). Only 31.2 percent of adults aged ≥ 19 years in the United States received the Tdap vaccine booster between 2010 and 2018 (Lu et al. 2021). Significant decreases in vaccination status were found in children and adolescents during the COVID-19 pandemic. This delay in catch-up immunization could pose a serious public health risk and lead to vaccine-preventable disease outbreaks (Brooks, McLendon, and Daniel 2021; Hong et al. 2021; Murthy et al. 2021; Saxena et al. 2021).

The major threats of diphtheria include respiratory obstruction in laryngeal diphtheria, acute systemic toxicity, myocarditis, and neurologic complications, primarily peripheral polyneuropathy (Tiwari and Wharton 2018). Diphtheritic polyneuropathy (DP) is a major, but rare, complication of
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Diphtheria and is correlated with the severity of diphtheria (Kanwal et al. 2012). It is reported to occur in up to 15% of diphtheritic patients (Logina and Donaghy 1999).

Health care workers are usually not aware of DP due to the disease's limited distribution to areas of the nation with low vaccination rates. Neurological dysfunction is also a notoriously severe case among diphtheria complications (Mateen et al. 2013; Prasad and Rai 2018). All neurological symptoms are included under the umbrella term "diphtheritic polyneuropathy," with the emergence of palatal paralysis being the initial symptom. Palatal paralysis is a highly frequent neurological complication that can emerge alone or in conjunction with bulbar dysfunction (Jammar et al. 2021; Prasad and Rai 2018).

The neurologic symptoms of DP are biphasic, causing early bulbar disturbances from the toxin's direct spread and late generalized demyelinating neuropathy from the toxin's hematogenous spread (Gowda et al. 2022; Suresh et al. 2012). Every patient with a diphtheria diagnosis needs to start receiving diphtheria antitoxin (DAT) immediately and be monitored for neurological complications for three to six months after treatment (Prasad and Rai 2018). Most DP patients have a complete recovery or only mild deficits at discharge so, the prognosis of DP is good (Logina and Donaghy 1999; Piradov et al. 2001). Hence, prompt identification and distinction from other neuropathies is necessary for appropriate treatment and contact tracing (Jammar et al. 2021; Prasad and Rai 2018).

Epidemiology

A few case studies of diphtheritic polyneuropathy have been reported, but no publications describing the precise prevalence of DP worldwide have been published. Three case series of adult DP were reported: 50 cases (aged 41–60) in Latvia by Logina and Donaghy (Logina & Donaghy, 1999), 32 cases (aged 21–54) in Russia by Piradov et al. (Piradov et al., 2001), and 20 cases (aged 18–24) in Latvia by Krumina et al. (Krumina et al., 2005). The majority of cases of DP involving children were reported from India, a developing country. In total, 48 cases (aged 1.5–11) were reported by Kanwal et al. (Kanwal et al., 2012); Mateen et al. reported 15 cases (aged <15) (Mateen et al., 2013); Manikyamba et al. reported 13 cases (aged 5–13) (Manikyamba et al., 2015); Prasad and Rai reported 28 cases (aged 3–18) (Prasad & Rai, 2018); Jammar et al. reported 60 cases (aged 3–18) (Jammar et al., 2021); and Gowda et al. reported 35 cases (aged 3.9–17) (Gowda et al., 2022).

Pathophysiology

Diphtheria toxin (DT), whose gene (tox) is carried in the genome of a family of corynebacteriophages, is the primary virulence factor of C. diphtheriae. C. diphtheriae becomes toxigenic by acquiring tox genes through lysogenic integration of the β-prophage genome into their chromosome (Sharma et al. 2019). Only the C. diphtheriae strains that carry the tox bacteriophage gene are accountable for polyneuropathy and cardiomypathy (Carod-Artal 2018; Sanghi 2014). Diphtheria toxin is an exotoxin that, at concentrations below 0.1 g/kg of body weight, can be fatal to humans (Frattelli et al. 2011; Sharma et al. 2019).

Diphtheria toxin is comprised of two chains, A and B. While the A chain contains a catalytic domain, the B chain contains two portions of domains, which are the R (receptor-binding) domain and the T (membrane-inserting translocation) domain. The R domain plays a role in the endocytosis of toxins by acting as a ligand for plasma membrane heparin-binding epidermal growth factor (HB-EGF) receptors (Sanghi 2014; Sharma et al. 2019). HB-EGF receptors are abundantly expressed by Schwann cells, so they are more vulnerable to diphtheria toxin (Katriji 2022; Sanghi 2014).

DT enters the cell through clathrin-coated pits. DT subunit bond is partially cleaved by endosome-associated proteases, and a conformational change occurs when the subunit is exposed to acidic conditions, allowing the T domain to enter the endosomal membrane and resulting in the translocation of the A-subunit across the endosomal membrane into the cytosol. In the cytosol, the toxin A chain then irreversibly inhibits protein synthesis synthesis by NAD+-dependent ADP ribosylation elongation factor 2 (EF-2), which for cell protein synthesis, is a crucial factor. By inhibiting EF-2 function through ADP-ribosylation, the toxin causes protein synthesis inhibition that leads to host cell death (Sanghi 2014; Sharma et al. 2019).

As the toxin enters Schwann cells, it results in the inhibition of the synthesis of myelin proteolipid, axon cylinders, and other proteins, leading to toxic myelopathy with paranoid demyelination (Hadfield et al. 2000). Early palatal and bulbar dysfunction followed by generalized polyneuropathy in DP, suggests that, prior to hematogenous dispersion in the late stage of the disease, diphtheria toxin locally damages nerve endings in bulbar muscles at an early stage (Gowda et al. 2022; Logina and Donaghy 1999; Suresh et al. 2012).

Clinical Manifestation

The manifestation of diphtheritic polyneuropathy usually appears weeks to months later (Gowda et al. 2022; Suresh et al. 2012; Truelove et al. 2020). Patients with severe infections have a higher risk of developing DP. Approximately 10% of mild cases and 75% of severe cases develop DP (Gowda et al. 2022). Data from a previous diphtheria study found that 5% to 15.2% of patients developed DP during the course of the disease (Kadirova, Kartoglu, and Strebel 2000; Logina and Donaghy 1999).
Diphtheritic polynuropathy has a typical biphasic course of disease. Lower cranial neuropathies appear a few weeks following pharyngeal infection, causing dysphagia, dysphonia, and insensibility of the face, tongue, and gingiva (Piradov et al. 2001). Several weeks later, as cranial neuropathies get better, limb symptoms start to emerge (Logina and Donaghy 1999; Piradov et al. 2001).

A study by Logina et al. (1999) in 50 patients with DP and a study by Piradov et al. (2001) in 32 patients with DP during the diphtheria epidemic in the former Soviet Union described the clinical characteristics of DP in adults (Logina and Donaghy 1999; Piradov et al. 2001). Adults are especially vulnerable to these epidemics because their childhood vaccination-induced immunity is waning (Logina and Donaghy 1999).

The latency of DP, the time between the onset of the initial diphtheria symptoms and the emergence of DP, ranged from 2 to 50 days (a mean of 30±8 days in one study (Piradov et al. 2001) and the median of 10 days in another (Logina and Donaghy 1999)). The basic symptoms of DP comprises cranial nerve palsy (dysarthria/dysphagia, facial weakness, oculomotor disturbance, impaired visual acuity, dysfunction of CN XII, XI, and V; lesions in CN VIII and I are absent), weakness of respiratory and abdominal muscle, quadriparesis, and peripheral sensory disturbances (Logina and Donaghy 1999; Piradov et al. 2001).

During weeks 1–3 of DP, respiratory tract disturbances also appear due to paresis and paralysis of the pharynx, larynx, and tongue, combined with paresis and paralysis of the respiratory muscles, as indicated by disconcretion of the cough reflex and obstruction in the conducting airways. Motor disturbances (mostly muscular hypotonia and tendinous arreflexia) are apparent during weeks 2–3 of DP in one study (Piradov et al. 2001) and at 5 weeks in another study (Logina and Donaghy 1999). The motor symptoms reach their peak severity during 7 weeks of disease (Piradov et al. 2001).

Sensory disturbances include hypoesthesia and hypesthesia, disturbances in proprioception, tactile discrimination, vibration, and sensory ataxia. During the progression of the illness, autonomic disturbances such as sinus tachycardia, arterial hypotension, urine retention, significant xeroderma, and hyperkeratosis, and hyperemia and hyperhidrosis may appear (Piradov et al. 2001). The clinical manifestations of DP in children are not different from adults (Gowda et al. 2022; Kanwal et al. 2012; Manikyamba, Satyavani, and Deepa 2015).

The majority of DP patients had completed a complete recovery or only mild deficits upon discharge (Logina and Donaghy 1999; Piradov et al. 2001). Nevertheless, even though 91% had mild deficits after a year, 41% of these patients were still unable to restart manual labor, despite being able to walk (Logina and Donaghy 1999). The case-fatality rate of DP in these series ranged from 6% to 16%, but it is predominantly due to cardiopulmonary complications (Logina and Donaghy 1999; Piradov et al. 2001).

**Diagnosis**

The diagnosis of diphtheritic polynuropathy should be based on a patient’s history and a detailed neurological examination, as the cultures are likely to be negative when the symptoms appear (Logina and Donaghy 1999; Piradov et al. 2001). Studies on the cerebrospinal fluid (CSF) may reveal normal values, lymphocytic pleocytosis, or elevated protein levels (albumin-cytologic dissociation) (Piradov et al. 2001; Sanghi 2014). Segmental demyelination with axon sparing is commonly found in histological examination (Katirji 2022; Logina and Donaghy 1999). Axonal degeneration can be seen in severe cases due to secondary damage from swollen neurons (Logina and Donaghy 1999; Prasad and Rai 2018). In accordance with demyelinating neuropathy, nerve conduction studies showed slowed motor and sensory conduction velocities, prolonged distal latencies, conduction blocks, and prolonged F latencies (Carod-Artal 2018; Logina and Donaghy 1999; Sanghi 2014).

Besides GBS, other infectious diseases could have polynuropathy as a manifestation of the disease. Distal Symmetrical Polyneuropathy (DSPN) and CMV-associated polynuropathy are usually seen in the late stages of HIV infection. DSPN usually involves the lower extremities, with paresis, weakness, and dysesthetic pain as the main complaints. Lyme disease, associated with a tick bite, can manifest with cranial neuropathies and polyradiculoneuropathies, but often has an acute onset and painful clinical features (Carod-Artal 2018). DP differs from these neuropathies due to the fact that it is not associated with HIV infection or tick bites, and DP usually presents as early cranial neuropathies followed by muscle weakness, sensory and autonomic disturbance without painful features.

**Treatment**

Antibiotics and diphtheria antitoxin (DAT) are the mainstays of therapy in acute pharyngeal diphtheria (Acosta et al. 2021). Although no formal clinical trial of DAT administration has been conducted, an early administration of DAT (in the first 3 days of the acute pharyngeal phase) could reduce the incidence and severity of neuropathy (Krumina et al. 2005; Logina and Donaghy 1999). However, when a patient first shows symptoms of neuropathy, it’s unclear whether giving DAT will be beneficial.

Diphtheritic polynuropathy is managed conservatively, as there is no specific treatment for this condition. Hemodynamic monitoring, vasopressors, endotracheal tube intubation, ventilation support, and nasogastric feeding may improve survival (Logina and Donaghy 1999).
Diphtheria Vaccine

It is generally known that vaccines are the best way to prevent diphtheria and have protective effects on humans against the disease. Non-vaccination, lack of completed vaccination since the pre-puberty period, as well as the absence of further boosters in adulthood, or occurring in immunocompromised people, are the main causes of the soaring number of infected people. In several countries, the prevalence of childhood diphtheria has decreased since the DPT vaccination program was implemented. For instance, in the Netherlands, the recorded cases of diphtheria decreased by 82.4 percent during the first 13 years of the mass vaccination period (1919–1931) (Van Wijhe et al. 2018). According to an analysis of the global epidemiology of diphtheria, 65% of case-patients from 2000–2017 were unvaccinated, 13% were partially vaccinated, and 22% were vaccinated with >3 doses of diphtheria toxoid-containing vaccine. It should be clarified that although immunization protects against clinical diphtheria, it does not stop the transmission of Corynebacterium spp., including the Corynebacterium that does not express DT (Sharma et al. 2019).

According to the WHO, the first 3 doses of vaccination in infants provide a protective level of antibodies in 94–100% of infants (Truelove et al. 2020). In order to prevent the diphtheria outbreak, the coverage of primary immunization (DPT3) in infants must reach a minimum of 95%, and the coverage of boosters for 18-month-olds and primary school children must reach 95% (Kementerian Kesehatan Republik Indonesia 2017). Despite that, vaccination coverage is still low in a lot of countries. India only has coverage of three primary diphtheria vaccines, ranging between 55.1% (1998–1999) and 78.4% (2011–2016) (Murhekar 2017). According to studies on urban Australian indigenous children, 72% of children received their first dose of the DPT vaccination on time (at two months old), but just 59% of them got their third dose on time (at six months old) (Lovie-Toon et al. 2016). Similar issues exist in Indonesia, where diphtheria vaccination rates are still below the target (as >90% coverage can be seen as successful), 67.7% in 2007, 61.9% in 2010, 75.6% in 2013, and 61.3% in 2018 (Karyanti et al. 2019).

Nowadays, diphtheria vaccines are made from a modified version of the diphtheria toxin, which is called a toxoid that’s usually absorbed into an adjuvant such as aluminum hydroxide or aluminum phosphate. Before this method, a different approach was first used in the USA in 1914 with a mixture of toxoid and antitoxin. In 1923, the formaldehyde detoxification of diphtheria toxin method was developed. Later on, a more immunogenic alum-precipitated diphtheria toxoid was used in 1926. By the 1940s, the combined vaccine DPT (diphtheria-tetanus-pertussis vaccine) was widely used around the world. Diphtheria has four kinds of vaccines, which include DTaP and DT, which are used in infants and children under 7 years of age, and TdP and Td, which are used for older children and adults (WHO 2017).

Primary vaccination for infants based on WHO recommendations consists of 3 doses of the DPT-HB-Hib vaccine. By 6 weeks of age, the first dose must be administered. The second dose should be administered within an interval of at least 4 weeks after the first dose, and the third dose should be completed by 6 months of age. The missing doses should be given at the earliest opportunity, with an interval of at least 4 weeks between doses if there are delays in primary vaccination. Booster is given at 12–23 months of age, 4–7 years of age, and 9–15 years of age. Injection of the toxoid-containing vaccines is usually administered intramuscularly, with 0.5 mL as the standard dose (WHO 2017). Further periodic boosters are recommended every 10 years, as immunity decreases with age because of the weakening of the immune system and/or the lack of proper vaccination at an early age (Manikyamba et al. 2015). A booster with a higher antigen content should be evaluated, as they usually only contain a low antigen content, which is ≥ 2 IU of diphtheria antigen, compared to a primary dose containing ≥ 30 IU. This might not provide enough protection for population immunity, and the answer to that problem is to increase the amount of diphtheria toxoid, at least in the booster vaccines (Blumberg et al. 2018).

Apart from the primary vaccination and the boosters, pregnant women should also be given Td [this vaccine is more recommended than monovalent tetanus toxoid (TT)] for prenatal care. Transplacental maternal antibodies give the newborn infant passive immunity during the first several months of life, which is one of the significances of this vaccination (WHO 2017). Once diphtheria-infected patients are clinically stable, a post-infection booster dose of diphtheria toxoid-containing vaccine should be administered to improve immunity (Gower et al. 2020).

Gender-based susceptibility to the disease could also be seen in several studies, showing that deficiency of seroprotection was more common in women than in men due to gender-specific immune responses subsequent to vaccination (Hasselhorn et al. 1998; Marlovits et al. 2000; Völzke et al. 2006). However, recent studies in Singapore (Ang, James, and Goh 2016) and Thailand (Hanvatananukul et al. 2020) showed that there is no significant difference in seroprotection between genders. Therefore, the interval between boosters is the same for both genders.

Although diphtheria vaccine is considered one of the safest vaccines available, sometimes there are mild adverse events associated with the DTwP administration in both infants and children, which include local reactions at the site of injections (50%), systemic reactions such as fever >38°C and irritability (40–75%), drowsiness (33–62%), loss of appetite (20–35%), and vomiting (6–13%). Severe reactions might occur as well, but they happen in less than one in a million doses (WHO 2017).
Conclusion

Physicians should be aware of the neurological complications of diphtheria. When encountering diphtheria patients, long-term patient follow-up and monitoring should be conducted to assess the early phase of diphtheritic polyneuropathy. Diphtheritic polyneuropathy should be distinguished from other acute polyneuropathies, as the management of the disease differs. The availability of DAT should be maintained, as early administration of DAT in acute pharyngeal diphtheria could reduce the incidence and severity of diphtheritic polyneuropathy.

References


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Saleeb, Paul G. 2022. 204 - Corynebacterium Diphtheriae (Diphtheria). Ninth Ed. Elsevier Inc.


