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DIPHTHERIA AS A SYSTEMIC DISEASE: ANALYSIS OF COMPLICATIONS ASSOCIATED WITH DIPHTHERIA TOXIN

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ABSTRACT

Diphtheria is a contagious disease caused by the bacteria Corynebacterium diphtheriae. This disease, although morbidity has significantly decreased in developed nations thanks to immunizations, continues to provide a substantial health risk in areas with low immunization rates. Diphtheria, with the acute inflammatory phase of the upper respiratory tract, can result in severe organ problems, mainly due to the effects of diphtheria toxin. Cardiac involvement, manifested as myocarditis, constitutes the most severe consequence of diphtheria and is the primary cause of mortality in affected persons. Diphtheritic polyneuropathy represents a considerable portion of post-diphtheritic sequelae and has a positive prognosis; therefore, timely diagnosis is crucial for efficient treatment. Renal impairment in diphtheria is less commonly reported than cardiac and neurological sequelae, necessitating greater investigation in this domain. This article reviews the current knowledge on the mechanisms of action of diphtheria toxin, the epidemiology of complications, their clinical manifestations, and possible diagnostic and therapeutic strategies. The significance of prophylaxis and the increasing danger of illness recurrence due to diminishing vaccination rates in some communities was also emphasized.
Aim of the study: This article aims to elucidate the current state of knowledge on organ complications of diphtheria, focusing on the mechanisms of diphtheria toxin, prevalent clinical manifestations, and potential implications in the cardiovascular, neurological, and renal systems. The paper seeks to highlight the significance of early diagnosis and underscore the need for a multidisciplinary approach in the management of respiratory diphtheria.
Materials and methods: A review of the literature available in the PubMed and Google Scholar database was performed, using the key words: „diphtheria", „cardiac complications", „neurological complications", „myocarditis", „polyneuropathy", „Corynebacterium diphtheriae".

KEYWORDS

Diphtheria, Cardiac Complications, Neurological Complications, Myocarditis, Polyneuropathy, Corynebacterium Diphtheriae

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1. Introduction

Diphtheria is a contagious disease resulting from infection with the bacteria *Corynebacterium diphtheriae*. It was a predominant cause of pediatric mortality until the early 20th century. Due to extensive vaccination efforts, diphtheria is predominantly managed globally; yet, it remains endemic in certain areas. The disease is presently found in India, Southeast Asia, Latin America, the Caribbean, and sub-Saharan Africa. Significant outbreaks may arise where immunization rates are insufficient. The migration of certain people with inadequate vaccination rates has resulted in a rise in the disease's incidence in developed nations. Specifically, the rise in immigration to Europe has correlated with an uptick in occasional diphtheria infections. In Europe, several instances of diphtheria are documented annually, with approximately fifty percent being "imported" from endemic regions (Mangion et al., 2023). The WHO indicates that since 2015, there has been a yearly rise in diphtheria cases (*Diphtheria Reported Cases and Incidence. WHO. (2024)*).

Corynebacterium diphtheriae, the etiological agent of diphtheria, is a Gram-positive, non-encapsulated, non-spore-forming aerobic bacterium linked to a significant death rate of roughly 10%. The symptoms of the disease, both localized and systemic, result from an exotoxin generated by bacterial strains infected with a bacteriophage that has the gene responsible for the toxin. Diphtheria toxin induces systemic problems by obstructing protein synthesis, resulting in cellular apoptosis (Ott, 2018)(Weerasekera et al., 2019) . The exotoxin exhibits the highest affinity for myocardial cells, the cardiac conduction system, the peripheral nervous system and renal tubular cells. The proliferation of bacteria at the infection site results in toxin release and localized destruction of respiratory epithelial cells, leading to inflammation and culminating in the formation of a pseudomembrane, necrotic tissue adhered to the substrate, a hallmark symptom of diphtheria

(Ott et al., 2022). Local tissue damage promotes the dissemination of the toxin by lymphatic and hematological pathways to multiple organ systems, including the cardiac muscle, neurological system, and kidneys.

The reservoir refers to a human being, either an ill individual or a carrier. Infection transmits primarily by droplets, and less commonly through direct contact with respiratory secretions or the skin. The incidence of disease typically rises during winter and spring. The incubation phase typically spans 2 to 5 days, but the contagious period extends from 2 to 4 weeks in the absence of antibiotic therapy. The illness typically commences with nonspecific flu-like manifestations, such as fever, pharyngitis, and cervical lymphadenopathy. Cervical adenopathy and mucosal edema frequently result in the distinctive "bull neck" appearance observed in numerous infected individuals. A dense, gray, leathery membrane envelops the tonsils, throat, soft palate, nasopharynx, and uvula. Efforts to excise the pseudomembrane result in hemorrhage from the subjacent mucosa (Truelove et al., 2020).

The foundation for **diagnosing** diphtheria in typical situations is the clinical presentation. Bacteriological testing is crucial for diagnostics, utilizing bacterial culture to identify *Corynebacterium diphtheriae* in a smear preparation obtained from the pseudomembrane or other observable alterations. Special Loeffler, Tindale, or tellurium media are frequently employed for this purpose. The production of toxins by bacteria can be verified using laboratory procedures like the Elek precipitation test, polymerase chain reaction (PCR) test, and enzyme immunoassay (EIA) (Rosana et al., 2020). Serological assays are additionally employed. Tests are conducted to facilitate the early identification of systemic issues arising from infection, including ECG, assessment of cardiac muscle damage markers, or analysis of CSF fluid when symptoms suggest nervous system involvement.

The cornerstone of diphtheria **treatment** is the prompt injection of diphtheria antitoxin and antibiotics. Equine antitoxin is administered. In suspected diphtheria cases, antitoxin must be delivered promptly based on clinical evaluation, without awaiting laboratory confirmation, as it neutralizes only the toxin present in the bloodstream, not that which is already attached to target cells. It is delivered intravenously, with vigilant monitoring of the patient for anaphylactic shock (Pérez & Brisse, 2024a).

The preferred antibiotics for treating diphtheria are erythromycin or penicillin G for 14 days. Alternatively, rifampicin or clindamycin may be utilized. They are administered chiefly to suppress additional formation of the exotoxin, alleviate local symptoms, and avert further transmission of the infection. Experiencing diphtheria does not confer enduring immunity; hence, during the convalescence phase, the patient must be advised of the necessity of vaccination against diphtheria, tailored to their present vaccination status.

Post-exposure prophylaxis for individuals in contact with a diphtheria patient is also crucial. Contact prophylaxis entails a single intramuscular dose of penicillin G or a 7-10 day course of oral erythromycin. If over five years have elapsed since the last diphtheria vaccination, a booster dose is recommended.

The subsequent chapters of this work include a comprehensive discussion on the suitable treatment for systemic problems.

The primary cause of fatality is airway blockage or hypoxia, predominantly resulting from the aspiration of pseudomembranes. In the cutaneous variant of the disease, ulcerative skin lesions enveloped by a gray membrane may be evident. Diphtheria, if not promptly identified and treated, can result in considerable mortality and morbidity due to severe consequences including myocarditis, obstructive airway disease, polyneuritis, cranial nerve palsies, disseminated intravascular coagulation, and secondary pneumonia (Jain et al., 2016). The mortality rate is approximately 5-10%, but for children under 5 years and people over 40 years, it is elevated, estimated at nearly 20%. Cardiac complications occur in around 10-25% of persons with respiratory diphtheria. The mortality rate of diphtheria myocarditis ranges from 50% to 75%, signifying a markedly elevated risk. Neurological complications manifested in 15-27% of diphtheria cases, with moderate respiratory diphtheria resulting in neurological symptoms in 20% of patients, whereas severe respiratory disease was associated with neurological issues in 75% of patients. They account for as much as 15% of fatalities.

The foundation of diphtheria prevention is **immunization**. Healthcare practitioners must inform parents about the advantages of regular immunization in illness prevention. Considering that immunity diminishes with time, prompt vaccination and booster doses are essential to mitigate mortality linked to diphtheria infection, ultimately protecting the health and well-being of vulnerable populations worldwide (Loiacono et al., 2021).

This paper emphasizes the systemic impacts of diphtheria and stresses the importance of a multidisciplinary approach in the management of respiratory diphtheria. Vigilant monitoring, prompt administration of immunoglobulins and antibiotics, and supportive care are crucial for improving patient outcomes and reducing mortality risk.

2. Cardiac complications of diphtheria

Cardiac problems arise in around 10-25% of individuals with respiratory diphtheria. Cardiac involvement in diphtheria typically manifests as myocardial dysfunction and arrhythmia; however, pericarditis and endocarditis may also arise in some instances (Samdani et al., 2018) .

Myocarditis is the most severe manifestation of diphtheria and the predominant cause of mortality associated with this infectious disease. The mortality rate of diphtheria myocarditis is between 50% and 75%, indicating a significantly high risk (Ilyas, Khan, et al., 2024) .

The recurrent incidence of cardiological issues during diphtheria is attributable to the diphtheria toxin's strong affinity for cardiac myocytes and the cells of the cardiac conduction system. The fundamental **mechanism** underlying all systemic symptoms in diphtheria is the suppression of protein synthesis by diphtheria toxin. Diphtheria toxin exhibits direct cardiotoxicity, inducing DNA fragmentation and cytolysis by blocking the function of elongation factor 2 in protein synthesis. The degradation of actin filaments triggered by diphtheria toxin results in myocarditis and diminishes contractile performance. In convalescents, a progressive substitution of injured cardiomyocytes by fibrous tissue is noted. This may lead to long-term cardiac effects following diphtheria. Given this understanding, it is challenging to elucidate the reports of myocarditis in individuals infected with non-toxigenic strains of *Corynebacterium diphtheriae*.

The conduction system of the heart may be impacted by acute inflammation of the sinoatrial and atrioventricular nodes during heart illness resulting from diphtheria infection. Conduction system abnormalities in the heart signify severe cardiac injury and may be fatal despite ventricular pacing (Maghrabi, 2024).

Myocarditis is deemed more severe when it manifests early in the progression of diphtheria. This complication may arise during the acute phase of infection or may insidiously manifest several weeks after the onset of diphtheria. The initial **manifestations** of myocarditis encompass nonspecific weakness, malaise, fever, dyspnea, chest discomfort, palpitations, and tachycardia that is disproportionate to the fever; however, these early symptoms may also indicate the onset of congestive heart failure.

Myocardial involvement results in a range of **ECG alterations** in 50-67% of individuals infected with *Corynebacterium diphtheriae*. The ECG may exhibit sinus bradycardia or tachycardia, ST-T alterations (including ST segment depression or elevation, T wave inversion), numerous atrial ectopies, bundle branch blocks, and significant heart blocks necessitating pacemaker insertion. Severe conduction problems, particularly complete heart block, are the most feared complications, indicating significant cardiac damage, with nearly all instances resulting in mortality despite the use of ventricular pacing. The existing literature is limited regarding this perilous aspect of diphtheria progression. Research indicates that left bundle branch block and T wave inversion are prognostic factors for diminished long-term survival in these patients. Due to the elevated risk of cardiac mortality associated with these ECG alterations, patients must be meticulously watched even after the acute phase of the illness has subsided.

Presently, **echocardiography** is one of the most prevalent techniques for evaluating cardiac function in developed nations. Nonetheless, due to the predominance of diphtheria patients in low- and middle-income nations, where access to suitable equipment and specialists is not readily available, there are scant studies regarding potential alterations in ECHO in diphtheria myocarditis. Documented ECHO abnormalities encompass diastolic and systolic dysfunction, with less frequent occurrences of pericardial effusion, mitral and tricuspid regurgitation, left ventricular dilation, and augmented left ventricular wall thickness.

Myocardial inflammation results in the time-dependent production of cardiac damage indicators, specifically **CK-MB and troponin T**. An elevated level of cardiac enzymes correlates with the onset of serious heart failure. A notable positive link exists between elevated CK-MB and cardiac troponin levels and cardiac mortality during diphtheria. Cardiac troponin exhibited the highest sensitivity at 80%, while CK-MB demonstrated the greatest specificity at 95.56%. Cardiac troponin levels are posited to indicate disease severity and myocardial damage intensity; yet, this correlation remains inadequately comprehended. Additional research on this element is required to establish a definitive association.

Histopathological analysis of the myocardium during autopsy of individuals who succumbed to diphtheria demonstrated active inflammation in the interstitial spaces, alongside extensive cardiac necrosis and hyaline degeneration. Mononuclear cell infiltrates with eosinophilic cytoplasm were also seen. Tissue slices stained with fluorescent antibodies demonstrate that diphtheria toxin is heterogeneously distributed over the cardiac fibers. Electron micrographs reveal notable ultrastructural alterations in the affected myofibers, primarily concerning mitochondria, which exhibit enlargement, matrix loss, and disordered cristae, alongside glycogen depletion and lipid droplet formation. Patients who underwent cardiac biopsy due to cardiac symptoms during diphtheria exhibited mononuclear cell infiltrates with eosinophilic cytoplasm. In the patient

detailed in the case report, cardiac MRI revealed subepicardial T2 hyperintensity (edema) and late gadolinium enhancement (necrosis) in the anteroseptal section of the basal left ventricle, indicating myocarditis (Arvind et al., 2022).

Treatment alternatives for diphtheria myocarditis are exceedingly restricted. The therapeutic strategy primarily emphasizes supportive care and aims to sustain normal hemodynamic parameters (Chanh et al., 2022) . Ongoing surveillance is essential, encompassing serial ECGs, hydration administration, airway safeguarding, respiratory assistance, and management of heart failure. In instances of persistent tachyarrhythmias, the use of antiarrhythmic medications may be warranted. Intervention for arrhythmias with a high risk of negative outcomes is necessary. Prophylactic intervention for subclinical arrhythmias is not advised. Patients exhibiting bradyarrhythmias and significant symptoms of diphtheritic myocarditis may derive advantages from the implantation of a temporary pacing mechanism (TPM). In the initial phases of the disease, antitoxin demonstrates effectiveness; nevertheless, its efficacy is constrained against penetrating toxins or those already internalized by the cell. Since diphtheria myocarditis is typically identified in advanced stages, the significance of antitoxin in the management of these individuals seems improbable. It is advisable to deliver antitoxin to all individuals suspected of having diphtheria myocarditis, as it is the sole specific antidote available and can eliminate any unbound diphtheria toxin molecules. Consequently, one must exercise caution when a patient exhibits a painful throat, tonsillar webbing, and a bull's neck, particularly if these symptoms coincide with inexplicable tachycardia. In such instances, if diphtheria is suspected, antitoxin must be delivered promptly, without awaiting diagnostic confirmation, since this may mitigate cardiac problems and mortality in individuals infected with *Corynebacterium diphtheriae*. Insufficient data exists to substantiate the advantages of treatment with steroids and immunoglobulins.

Notwithstanding considerable progress in medical treatment, managing diphtheria consequences continues to pose challenges, particularly in regions with insufficient healthcare facilities and resources (Ilyas, Yousafzai, et al., 2024). The significance of diphtheria immunization must be underscored in this context. While vaccination does not ensure immunity against the disease, those who have received the vaccine generally experience less severe and less lethal diphtheria infections.

3. Neurological complications of diphtheria

Neurological complications occurred in 15-27% of diphtheria cases, with moderate respiratory diphtheria leading to neurological symptoms in 20% of patients, but severe respiratory illness was linked to neurological difficulties in 75% of patients (Jammar et al., 2022).

The diphtheria toxin is accountable for the manifestation of neurological symptoms. Schwann cells are vulnerable and specifically targeted by diphtheria toxin because they possess receptors that facilitate toxin endocytosis (Prasad & Rai, 2018). Local toxic effects manifest via direct dissemination of the toxin and are characterized by first bulbar dysfunction. Generalized polyneuropathy arises from hematogenous spread. Diphtheria toxin causes reversible degeneration of the myelin sheaths and axons of peripheral nerves. Axonal damage is thought to be secondary to external compression by swollen neurons. Neuronal integrity is usually preserved, but complete degeneration leading to axon and myelin destruction can sometimes be observed. Experimental studies increasingly suggest that the loss of sensory and motor neurons also affects neuronal function (PLEASURE & MESSING, 2005) .

Initial neurological **manifestations** encompass paralysis of the palate and pharynx (Prasad & Rai, 2018). **Bulbar symptoms** may manifest within the initial days of the illness, whereas peripheral sensory and motor neuropathy may develop between the third and sixth weeks. Preliminary symptoms may encompass tongue and facial numbness, dysphonia, hoarseness, and dysphagia (Manikyamba et al., 2015). These symptoms manifest in nearly all individuals with diphtheritic polyneuropathy and can vary from moderate to severe. Dysphagia may be associated with hyper salivation and the regurgitation of liquid food through the nasal passages or its aspiration into the respiratory tract, occasionally necessitating the use of a nasogastric tube for alimentation. Bulbar symptoms often resolve within a period of 5 to 10 weeks. During the progression of diphtheria, additional cranial nerves are impacted, particularly the oculomotor nerve and the ciliary nerves. Ocular motor abnormalities, characterized by ptosis, anisocoria, and diplopia, are reported with differing frequency. Paresis and paralysis of peripheral motor nerves are detected, initially affecting proximal regions and progressively descending. Symptom intensity may vary from minor ambulation difficulties to profound weakness and the inability to walk unaided. A significant risk may arise from paralysis of the breathing muscles, especially the diaphragm. This symptom manifests during the first to third week of the illness, peaking in intensity during the third to fourth week, necessitating the need of continuous mechanical breathing.

Alongside motor weakness, sensory disturbances manifesting as paresthesia, hypoesthesia, hyperesthesia, or diminished proprioception and vibratory sensation in the distal extremities are present in nearly all individuals with diphtheritic **polyneuropathy**. Sensory ataxia may manifest in some patients. Deep tendon reflexes may exhibit diminished strength [8].

Autonomic dysfunction is an additional consequence of diphtheria that affects the neurological system. Autonomic system symptoms encompass circulatory system diseases resulting from diminished vasomotor tone, including tachycardia, arrhythmias, and hypotension (Prasad & Rai, 2018). The symptoms may be challenging to distinguish from those of diphtheritic myocarditis outlined in the preceding chapter of this text. Additional symptoms encompass urinary system malfunction, including urine retention necessitating frequent catheterization, and hazy vision resulting from compromised accommodation and atypical pupillary responses. The body of information regarding the neurological consequences of diphtheria is limited. Isolated instances of diphtheritic encephalitis have been reported.

Cerebrospinal fluid analyses in patients with diphtheria affecting the neurological system may be entirely normal or have higher protein concentrations with normal cell counts. **Nerve conduction investigations** reveal diminished conduction velocities (both sensory and motor), extended distal motor latencies, numerous conduction blocks, and prolonged F-response latencies. These results align with the pathogenic characteristics of demyelinating polyneuropathy. Abnormalities in these studies exhibit peak severity 3-10 weeks following the initial symptoms of diphtheria, with subsequent gradual recovery. Conduction dysfunction may endure for over 3 months following the initial manifestations of polyneuropathy, occasionally extending to a year. In 2017, the inaugural account of an MRI brain scan conducted on a patient with diphtheria encephalitis was published (Foo et al., 2017) . **Magnetic resonance imaging** of the brain conducted on the eighth day of sickness revealed patchy hyperintensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences in the cortical and subcortical white matter of the anterior cingulate gyri, insular cortex, and both cerebellar hemispheres (Fig. 1). Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping revealed vasogenic edema in the cerebellar lesions. No focal enhancing brain lesion or aberrant leptomeningeal enhancement was observed. The authors of this publication emphasize that the MRI findings correlate significantly with the histological data obtained from autopsies of individuals who succumbed to central nervous system disorders related to *Corynebacterium diphtheriae* infection.

No specific **treatment** exists for neurological problems. The foundation is, similar to cardiac problems, the prompt administration of diphtheria antitoxin, which is beneficial alone if given at an early stage of the disease. The administration of glucocorticosteroids has not demonstrated a reduction in the incidence of polyneuropathy. Symptomatic treatment encompasses airway protection and, in instances of throat muscle paralysis, tube feeding and positioning with the upper body elevated. Individuals afflicted with diphtheria polyneuropathy may derive advantages from physiotherapy.

Diphtheria polyneuropathy is linked to a favorable prognosis (Jammar et al., 2022). Timely diagnosis facilitates the swift initiation of suitable treatment, underscoring the need of general physician awareness in this domain. A patient diagnosed with diphtheria should be observed for approximately 3-6 months for the emergence of neurological problems.

4. Kidney injury

Renal impairment during diphtheria is significantly less documented than cardiac and neurological consequences. Potential etiologies for the manifestation of renal impairment symptoms (such as renal dysfunction, proteinuria, and hematuria) encompass direct injury to the renal tubules by diphtheria toxin resulting in acute tubular necrosis, alongside the involvement of renal interstitial tissues leading to interstitial nephritis (Pérez & Brisse, 2024b). The magnitude of this devastation remains inadequately comprehended. In 2024, Mahamadou et al. (Mahamadou et al., 2024) released a study examining the probable pathomechanisms of acute kidney damage (AKI) linked to diphtheria infection and its effects on illness progression and treatment results. Renal impairment was delineated in accordance with the 2012 KDIGO guidelines. This study revealed a substantial incidence of acute kidney injury (59%) in patients with diphtheria, markedly beyond the 13-35.4% rates documented in previous research. The authors suggest that prior data may be undervalued owing to the absence of a standardized definition of AKI. The identified predictors of acute kidney injury (AKI) in patients with diphtheria included: age under 60 months (indicating renal immaturity), administration of oxygen therapy (associated with hypoxia and free oxygen radicals), and ibuprofen (due to its nephrotoxic potential linked to its mechanism of action). An increased prevalence of AKI was seen in patients administered dexamethasone, however the etiology of this occurrence remains challenging to ascertain. The incidence of

AKI during diphtheria elevated the mortality risk by 3.55%. The onset of AKI correlates with worse outcomes attributable to metabolic abnormalities, fluid overload, and injury to remote organs. This indicates the necessity of monitoring renal function in diphtheria patients, particularly in the pediatric demographic, and the prudent administration of dexamethasone and ibuprofen.

5. Conclusions

Diphtheria is an infectious disease caused by *Corynebacterium diphtheriae*, with its severe course resulting from the action of diphtheria toxin. Despite widespread vaccination, the disease persists in some regions and can be transmitted to developed countries by unvaccinated individuals. The disease is characterized by localized and systemic symptoms due to an exotoxin generated by bacteria. Diagnosis of diphtheria involves clinical presentation, bacterial testing, laboratory procedures, and serological assays. Treatment involves prompt injection of antitoxin and antibiotics, with erythromycin or penicillin G being the preferred antibiotics. Post-exposure prophylaxis is also crucial for individuals in contact with a diphtheria patient. The primary cause of fatality is airway blockage or hypoxia, predominantly resulting from pseudomembranes. The most serious systemic complications include severe cardiac damage, nervous system, and kidneys.

Myocarditis is the most common and dangerous complication, occurring in 10–25% of patients. The bacterial toxin damages the heart muscle and conduction system, potentially leading to arrhythmias, heart failure, and sudden death. Symptoms include fatigue, shortness of breath, chest pain, and tachycardia, with ECG changes present in most patients. Treatment focuses on supportive care and administration of diphtheria antitoxin.

Neurological complications affect 15–27% of patients and may include cranial nerve palsies, polyneuropathy, and autonomic dysfunction. These injuries are usually reversible but may require rehabilitation and intensive symptomatic treatment.

Renal complications are less common and may result from direct toxin-induced tubular injury, potentially leading to acute renal failure.

Effective prevention relies on vaccination, which significantly reduces the severity and risk of complications. Healthcare practitioners must inform parents about the benefits of regular immunization and provide timely delivery of immunoglobulins and antibiotics. A multidisciplinary strategy is necessary to enhance patient outcomes and mitigate mortality risk.

Disclosure

Author's contribution

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