Neurologic manifestations of diphtheria and pertussis

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DIPHTHERIA
Diphtheria, an infectious disease caused by Corynebacterium diphtheriae, affects the nasopharynx and skin. C. diphtheriae is a Gram-positive bacillus. It does not form spores, is nonmotile, and is transmitted via aerosol pathways. Typically, the incubation period for respiratory disease is 2–5 days. Toxigenic strains of C. diphtheriae release a toxin that leads to formation of a pseudomembrane in the pharynx – pharyngeal diphtheria. In addition, the toxin also results in systemic toxicity, myocarditis, and polyneuropathy. Nontoxigenic strains commonly cause cutaneous diphtheria.

Epidemiology
Before the development of a vaccine, diphtheria was a major cause of morbidity and mortality in children, especially in crowded urban areas. The development of diphtheria toxoid vaccine has led to the near elimination of diphtheria in Western countries (Bishai and Murphy, 2008). The annual peak incidence rate was 191 cases per 100,000 people in the US in 1921. Since 1980, this has fallen to fewer than five cases per 100,000 people. Between 1980 and 1995, only 41 cases of respiratory diphtheria were reported (Bisgard et al., 1998). However, pockets of colonization persist in North America, particularly in South Dakota, and Washington State in the US, and in the Province of Ontario in Canada. In the UK, the incidence of diphtheria is low. Since 1990, only 19 cases of toxigenic diphtheria have been reported in England and Wales and most of these were acquired abroad (McAuley et al., 1995). However, during the 1990s, diphtheria experienced a resurgence in both developed and developing countries where it had been well controlled. An epidemic that began in 1990 in the Newly Independent States (NIS) of the former USSR affected almost 150,000 people with nearly 5000 deaths by the end of 1996 (Vitek and Wenger, 1998). More than 97,000 cases with 2500 fatal outcomes took place in Russia (Piradov et al., 2001). In Latvia, an epidemic started in 1994, with a secondary peak of 574 cases (with 38 deaths) between 1998 and 2000 (Krumina et al., 2005). In 2000, 231 diphtheria cases were registered at the Infectology Center in Riga, Latvia, the majority of which were cadets, soldiers, and other defense personnel from a single closed community. In Belarus, a total of 965 cases were reported from 1990 to 1998 (Filonov et al., 2000). In the Latvian epidemic, 80% of patients with diphtheritic polyneuropathy were between the ages of 41 and 60 years (Logina and Donaghy, 1999). In the Russian study of 32 patients, the age range of patients with diphtheritic polyneuropathy was 21–54 years (Piradov et al., 2001). Today, most children in industrial and postindustrial countries receive diphtheria toxoid. Without subsequent booster doses, adults progressively lose immunity. Decreased immunity in the adult population has resulted in the resurgence of diphtheria. Adults vaccinated in childhood do not continue to have sufficient immunity to protect against diphtheria once the infection returns to a community. In the US, 40–50% of adults above the age of 30 years are susceptible to diphtheria (Fontaranosa, 1995). Similar findings were reported from the UK (Maple et al., 1995), while a Danish study (Kjeldsen et al., 1985) showed that 22% of previously vaccinated adults were susceptible.

The incidence of diphtheritic polyneuropathy is directly proportional to the severity of intoxication. Polyneuropathy is considered uncommon in mild diphtheria, but occurs in about 10% of cases of average severity and in up to 75% of severe cases (Holmes, 1997).
In the Latvian study, 15% of patients admitted to hospital with diphtheria developed neurologic complications (Logina and Donaghy, 1999). Diphtheritic polyneuropathy is more likely to occur in patients with severe infection, including those with “bull neck” and toxic shock.

**Pathogenesis and pathology**

Diphtheritic polyneuropathy and cardiomyopathy are caused by a toxic protein secreted by *C. diphtheriae*. The toxin is encoded by the tox bacteriophage gene. Only those *C. diphtheriae* strains harboring this bacteriophage cause polyneuropathy and cardiomyopathy (Pleasure and Messing, 2005). Diphtheria toxin comprises two chains, A and B. The A chain is the catalytic domain. The B chain has two domains – the transmembrane (T) domain and the receptor-binding (I) domain (Ren et al., 1999). The T domain is a ligand for plasma membrane heparin-binding epidermal growth factor (HB-EGF) receptors and plays a role in toxin endocytosis. The I domain penetrates the endosomal membrane and translocates the toxin into the cytosol. In the cytosol, the toxin A chain then irreversibly inhibits protein synthesis by NAD + -dependent ADP ribosylation of elongation factor 2 (Bishai and Murphy, 2008). Toxin-poisoned cells undergo death by apoptosis.

Schwann cells are more susceptible and selectively targeted by diphtheria toxin. They express abundant HB-EGF receptors and are thus more capable of binding diphtheria toxin than most other cell types (Pleasure and Messing, 2005).

Local toxic effects occur by direct spread of the toxin and result in early bulbar dysfunction while generalized polyneuropathy arises from hematogenous dissemination (McAuley et al., 1999). The delay in development of the polyneuropathy as well as the proximal to distal spread relates to the long time for transport of newly synthesized protein down the axons.

Classically, diphtheritic polyneuropathy is considered to be a pure demyelinating disease with sparing of the axons. However, there is increasing suggestion in experimental studies that axonal function is also affected with a loss of sensory neurons and motor axons (Pleasure and Messing, 2005). In a single case report (Solders et al., 1989), sural nerve biopsy showed signs of demyelination with short internodes. The fiber density was slightly reduced. There was no infiltration of inflammatory cells. HLA-DR antigen staining showed expression of the antigen on nonmyelinating Schwann cells and on macrophages. Anterior tibial muscle biopsy showed signs of early neurogenic atrophy with scattered angular atrophic fibers. No signs of inflammation were seen.

**Clinical features**

Diphtheria usually manifests as a pharyngeal, tonsillar, or nasal infection with early local toxic effects that often lead to formation of a characteristic membranous exudate. Cervical lymphadenopathy and soft tissue swelling may lead to the formation of a “bull neck.” This is followed by biphasic, secondary toxicity (early local and late remote).

Typically, a stereotypic pattern of bulbar symptoms occurs 3–6 weeks after initial infection with onset of polyneuropathy at around 8 weeks (McDonald and Kocen, 1991). In 32 Russian patients (Piradov et al., 2001), the latency between the first symptoms of diphtheria and the development of diphtheritic polyneuropathy varied from 18 to 46 (mean, 30 + 8) days. In the Latvian study of 50 patients with diphtheritic polyneuropathy, neurologic symptoms appeared 2–50 (median 10) days after the onset of localized tonsillar and pharyngeal diphtheria (Logina and Donaghy, 1999). Typical initial symptoms include numbness of the tongue and face and dysphonia. Bulbar symptoms include nasal or hoarse voice along with dysphagia and palatal paralysis. These symptoms vary from mild to severe and are seen in almost all patients with diphtheritic polyneuropathy (Logina and Donaghy, 1999; Piradov et al., 2001). Dysphagia may be accompanied by excessive salivation and nasal regurgitation of fluid food or its aspiration into the airways, necessitating the usage of a nasogastric tube for feeding.

Symptoms of bulbar dysfunction recover during weeks 5–10 with appearance of motor weakness worsening during weeks 6–9, reaching a maximum on day 51 + 10 of diphtheritic polyneuropathy (Piradov et al., 2001). This characteristic, biphasic evolution of symptoms has been described by other authors (McDonald and Kocen, 1991; Logina and Donaghy, 1999). Single case reports from the UK (McAuley et al., 1999), France (Creange et al., 1995), and Sweden (Solders et al., 1989) have shown similar patterns of disease.

Other cranial nerves are also involved. Oculomotor impairment, manifested by ptosis, anisocoria, and diplopia, is described with varying frequency: in 84% of patients by Piradov et al. (2001) and 30% in a study by Logina and Donaghy (1999). Facial weakness is also well described.

Limb symptoms typically occur 5–8 weeks after onset of throat diphtheria (Logina and Donaghy, 1999; McAuley et al., 1999; Piradov et al., 2001; Krumina et al., 2005). Thus during the second month of disease, functional recovery of cranial nerves is accompanied by worsening of motor weakness of the trunk and extremities. Proximal quadriaparesis was seen in 60–90% of patients with diphtheritic polyneuropathy.
The severity ranges from mild difficulty in walking to severe weakness and loss of ability to walk unaided. There appears to be an inverse relationship between latency and recovery of motor symptoms – a longer latency corresponds with an earlier regression of limb weakness (Piradov et al., 2001). In addition to motor weakness, sensory disturbance characterized by paresthesia, hypoesthesia, hyperesthesia or a diminished sense of joint position and vibration in distal parts of the extremities is seen in nearly all patients. Sensory ataxia may also be seen in some patients. Deep tendon reflexes are lost.

Autonomic dysfunction is another complication of diphtheria. Circulatory disturbances such as tachycardia, arrhythmias and arterial hypotension are commonly seen; these may be difficult to distinguish from symptoms of diphtheritic myocarditis (Logina and Donaghy, 1999). Bladder dysfunction as well as blurred vision from impaired accommodation and abnormal pupil reactions may occur. Retention of urine requiring persistent catheterization of the bladder develops in one third of cases. Xeroderma and hyperkeratosis were reported in 24 of 32 patients, while hyperemia and hyperhidrosis in the face, neck, and chest were seen in 20 patients (Piradov et al., 2001).

Respiratory muscle weakness is life-threatening and typically occurs in weeks 1–3 and maximizes during weeks 3–4 (Piradov et al., 2001). It necessitates the use of prolonged artificial ventilation. Myocarditis occurs frequently (in almost two-thirds of patients) in patients with diphtheritic polyneuropathy (Logina and Donaghy, 1999); pneumonia is also common.

Laboratory features

Throat cultures provide an accurate means for diagnosis of diphtheria. However, false-negative results may be obtained if there is a delay in processing the specimen (Pleasure and Messing, 2005).

Cerebrospinal fluid (CSF) studies may be normal or show elevated protein (albumin-cytologic dissociation). Occasionally, there may be a lymphocytic pleocytosis (Creange et al., 1995). Piradov et al. (2001) found an elevated CSF pressure in nine of 32 patients.

Nerve conduction studies show slow conduction velocities (sensory and motor), prolonged distal motor latencies, multiple conduction blocks and prolonged F-response latencies (Solders et al., 1989; Logina and Donaghy, 1999). These findings are consistent with pathologic findings of a demyelinating polyneuropathy. Electrophysiologic studies show a maximum impairment at weeks 3–10 and then gradual improvement. Abnormal studies may persist beyond 100 days after the onset of polyneuropathy and occasionally even up to a year later.

Autonomic function tests show an early and prominent impairment of parasympathetic vagal functions (Solders et al., 1989). The R-R variations and heart reaction to the Valsalva maneuver are abnormal and the results of these tests follow clinical recovery.

Treatment

Diphtheritic infection is treated by administration of intravenous penicillin and diphtheritic antitoxin at the time of the initial illness. Alternative treatment options for those who are allergic to penicillin include erythromycin, rifampin and clindamycin. The aim of antibiotic treatment is primarily to prevent transmission to other susceptible contacts (Bishai and Murphy, 2008). Antitoxin administration aims to block cellular binding and uptake of diphtheria toxin. It appears to be effective only when administered promptly in the early course of infection (Logina and Donaghy, 1999; McAuley et al., 1999; Pleasure and Messing, 2005; Bishai and Murphy, 2008). The antitoxin is a horse serum and may cause serum sickness in some individuals. A test dose must be administered to rule out immediate-type hypersensitivity. Those who exhibit hypersensitivity must be desensitized prior to receiving the full therapeutic dose. Glucorticoids may help in reducing the airway obstruction in acute laryngeal diphtheria but have not been shown to reduce the incidence of polyneuropathy (Pleasure and Messing, 2005; Bishai and Murphy, 2008). There is no specific treatment of the neurologic complications other than protection of the airway and physiotherapy (McAuley et al., 1999).

Outcome

Recovery of strength and sensations usually begins 2–3 months after the onset of neuropathic symptoms (Pleasure and Messing, 2005). In the Latvian study (Logina and Donaghy, 1999), the average duration of hospital stay was 34.4 (range 7–101) days. At the time of discharge, 24% of surviving patients were unable to walk independently. At 1 year, all surviving patients were able to walk 10 meters independently. However, two of these patients (6%) were unable to perform manual work. In Russian patients with diphtheritic polyneuropathy, motor symptoms started recovering at the end of month 2 and patients could walk without assistance 2 months later (Piradov et al., 2001).

Mortality from diphtheria increases with the severity of local disease and toxicity produced. The mortality in patients with the toxic form of diphtheria was reported to be 25.7% from Russia (Rakhmanova et al., 1996). Logina and Donaghy reported a mortality of 16% in their study (1999).
PERTUSSIS

Pertussis, or whooping cough, is an acute infectious disease of the respiratory tract caused by Bordetella pertussis or Bordetella parapertussis. These are Gram-negative, pleomorphic, and aerobic bacilli. Use of the pertussis vaccine has greatly reduced the incidence of the disease. In the US, the incidence of pertussis was 8.9 per 100,000 population in 2004 (Cherry, 2006). In the prevaccine era, the majority of cases occurred in children. Widespread vaccination in children has resulted in a shift in the age category with a reservoir of B. pertussis in older individuals. In the US, many cases of pertussis occur in teenagers or adults (Robbins, 1999). Similar findings have been reported from Europe (Schmitt-Grohe et al., 1995; Birkebaek, 1999). The incidence of pertussis in adults is underestimated because the diagnosis is often not considered in adults with cough, who frequently do not present with classic disease (Orenstein, 1999).

Classic disease consists of severe paroxysms of coughing followed by a sudden, massive inspiratory effort, during which a characteristic whoop may occur. Paroxysms may occur several times per hour, during both day and night. Seizures and encephalopathy may occur as a complication. These may be due to cerebral hypoxia related to asphyxia. Tetanic seizures may be associated with severe alkalosis that results from the loss of gastric contents caused by persistent vomiting. Rarely, subarachnoid and intraventricular hemorrhage may occur (Cherry and Heininger, 2009). Neurologic complications occurred in 4% of Swedish patients hospitalized with pertussis (Romanus et al., 1987).

Diagnosis may be established by culturing the organisms on appropriate media, by identifying their presence by polymerase chain reaction (PCR), or by demonstration of specific antibodies. Antibiotics are efficacious in treating pertussis. Erythromycin as well as newer macrolides, such as azithromycin and clarithromycin, are the drugs of choice. Alternatively, trimethoprim-sulfamethoxazole can be used in those who cannot tolerate erythromycin (Cherry and Heininger, 2009).

IMMUNIZATION AGAINST DIPHTHERIA AND PERTUSSIS

Vaccination of children and adequate boosting vaccination of adults is necessary to reduce the incidence of diphtheria. At present diphtheria toxoid vaccine is coadministered with tetanus (with or without acellular pertussis) vaccine. DTaP (full-level diphtheria and tetanus toxoids and acellular pertussis vaccines, adsorbed) is the currently recommended vaccine for children up to the age of 7 years. Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine) is the recommended booster vaccine for older children, adolescents, and adults (Bishai and Murphy, 2008).

Traditionally, there have been concerns regarding the safety of DTP vaccination (diphtheria and tetanus toxoids and whole-cell pertussis vaccine), especially the development of adverse neurologic events (Wilson, 1973). The risk of seizures and other neurologic events following diphtheria-tetanus-pertussis (DTP) immunization for 38,171 children who received 107,154 DTP immunizations in their first 3 years of life was studied (Griffin et al., 1990). The risk of febrile seizures in the 0 to 3 days following DTP immunization was increased. There was no evidence that the risk of afebrile seizures or acute symptomatic seizures was increased. In another large study (Barlow et al., 2001) that assessed the risks of DPT vaccination, 340,386 immunizations were studied. Receipt of DTP vaccine was associated with an increased risk of febrile seizures only on the day of vaccination. The number of febrile seizures attributable to the administration of DTP vaccine was estimated to be 6–9 per 100,000 children. The risk of nonfebrile seizures was not increased. As compared with other children with febrile seizures that were not associated with vaccination, the children who had febrile seizures after vaccination were not found to be at higher risk for subsequent seizures or neurodevelopmental disabilities. Berkovic et al. (2006) studied 14 patients with alleged vaccine encephalopathy in whom the first seizure occurred within 72 hours of vaccination. SCN1A mutations were identified in 11 of 14 patients. The authors postulated that cases of alleged vaccine encephalopathy could in fact be a genetically determined epileptic encephalopathy that arose de novo. Vaccination, however, might trigger earlier onset of Dravet syndrome in children who, because of an SCN1A mutation, are destined to develop the disease (McIntosh et al., 2010). However, vaccination should not be withheld from children with SCN1A mutations because there was no evidence that vaccinations before or after disease onset affect outcome. The consensus is that the risk of vaccine-induced encephalopathy and/or epilepsy, if it exists at all, is extremely low (Shorvon and Berg, 2008).

REFERENCES


