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Chapter 103

Neurologic complications of vaccinations

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INTRODUCTION

Disorders of the nervous system have been linked with vaccines since Pasteur's rabies immunization in 1889 in which a neuroparalytic syndrome was associated with vaccination (Warrell, 1976). Since then, vaccines have been linked to encephalitis, Guillain–Barré syndrome (GBS), seizures, headaches, cranial neuropathies, and demyelinating disorders, to name a few. More recently, a proposed link between autism and vaccination has created a distrust of vaccinations, both in the US and elsewhere, that has limited vaccination efforts. In general, establishing causality is much more difficult than identifying an association. Within the US, there are governmental organizations established to detect potential associations, so that research may be targeted towards understanding these potential causal relationships.

In 1990, the Vaccine Adverse Events Reporting System (VAERS) was established as a means of passive, postmarketing surveillance of adverse health events temporally related to vaccination. VAERS is operated jointly by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). Providers, healthcare workers and the public are encouraged to report to VAERS clinically significant adverse events following vaccination. However, causality cannot be determined solely by reports to VAERS. One of the major limitations to VAERS is the potential propensity towards underreporting; all data are compared against the number of vaccines distributed rather than the number of vaccines administered; and VAERS reports require only a preliminary diagnosis, which may not actually reflect the patient's diagnosis.

The Vaccine Safety Datalink (VSD) is collaborative endeavor between the CDC and eight managed-care organizations with a total of 9.5 million members. VSD utilizes administrative data and electronic medical records to collect information on vaccinations and healthcare encounters to monitor vaccine safety. VSD has the capability to test and strengthen hypotheses generated through VAERS reports. VSD can quickly identify significant adverse events following immunization that may be worrisome enough to consider changing vaccine recommendations. VSD also conducts planned immunization safety studies as well as timely investigations of hypotheses that arise from review of medical literature, changes in immunization schedules, or the introduction of new vaccines. The Clinical Immunization Safety Assessment (CISA) Network is a project between six academic centers in the US which conduct research on adverse events that might be caused by vaccines.

In assessing vaccine safety, it is important to know the background rates of disease in the population in order to identify legitimate safety concerns from events that are temporally associated, but not caused by vaccination. Causality is supported when an adverse event (AE) is reproduced (a positive re-challenge test) upon subsequent exposure to the same vaccine. The Code of Federal Regulations (Regulations) defines serious AEs as those that are reported as resulting in death, life-threatening adverse experience, hospitalization, prolongation of hospitalization, persistent or significant disability, congenital anomaly/birth defect, or any event that, based on appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent these outcomes.

Various mechanisms have been proposed to explain the pathophysiology of neurologic adverse reactions following vaccinations. One potential scenario to explain the development of demyelination in postvaccinal encephalomyelitis is by activation of self-reactive

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Table 103.1

Different types of vaccines with their mechanism of action

Vaccine	Mechanism of action
Whole killed Influenza Pertussis Poliomyelitis Rabies	Vaccines made from whole killed organisms usually produce an antibody response that provides temporary immunity
Live attenuated viruses Influenza (nasal) Measles Mumps Poliomyelitis (oral) Rotavirus (RotaTeq) Rubella Varicella Yellow fever	Live attenuated virus vaccines are intended to trigger the immune system as the natural infection might yet without causing the disease. Once exposed to the antigen, the immune system produces immunity similar to that conferred by the natural disease. Similarly, denatured toxins can produce immune-mediated response immunity without the disease
Conjugate vaccines Hib Meningococcal Pneumococcal conjugate	These vaccines are created by linking weak, polysaccharide antigens to protein carriers. The combination facilitates a more robust immunologic response. This technique is often used with bacterial polysaccharides to prevent invasive bacterial disease
Recombinant vaccines Hepatitis B	These vaccines are developed by inserting genes for the antigen into a vector. Vectors are often viruses with a very low virulence. Recombinant vaccines have a low incidence of adverse events. Hepatitis B is the only recombinant vaccine currently in use in the US

lymphocytes by the vaccine. Autoreactive T cells can be found in blood, thymus, and secondary lymphoid tissues of healthy individuals, but through the action of suppressive cytokines, remain inactive. If a peptide or epitope present in the vaccine shares molecular similarities to self antigens within the host (i.e., myelin basic protein), an autoimmune phenomenon may occur. This mechanism is known as molecular mimicry. Another potential explanation for immune-mediated neurologic complications following vaccinations is by activation of autoreactive immune cells by cytokines released from host cells after virus-mediated cell death.

All vaccines work by triggering the host's immune system. However, the mechanism of action varies by the type of vaccine (Table 103.1). In this chapter we will review the most common neurologic adverse reactions reported after various vaccinations (Table 103.2).

VIRAL VACCINES

Measles, mumps, and rubella

Though individual vaccines for measles, mumps and rubella exist, the majority of children vaccinated against these diseases receive either the MMR vaccine or, more recently, the MMRV. MMR was first developed in the late 1960s. At the time that it was introduced, the annual incidence of measles infection was > 100 000 per year. After the introduction of the vaccine, the incidence of measles infections dropped 100-fold. A second dose of the vaccine was recommended after an increase in number of annual cases in 1990. The second dose was introduced to produce immunity in a small portion of individuals who did not receive immunity from the first dose. More recently, the number of measles infections has been less than 100 per year. The most common neurologic complication of MMR is cerebellar ataxia. Onset usually occurs within 10 days of vaccination. Children less than 2 years old are more affected than other age groups. The overall incidence is less than one case per million vaccines. Each year in the US, nearly 10 million doses of the vaccine are distributed. CDC continues to recommend two doses of MMR vaccine for all children: dose 1 at ages 12–15 months, and dose 2 at ages 4–6 years.

There appears to be an increased risk of febrile seizures 1–2 weeks after immunization with the MMR vaccine. A cohort study of almost 680 000 in the US showed a relative risk of febrile seizure following vaccination of 2.8 (Barlow et al., 2001). The same study showed no increased risk of nonfebrile seizures or neurodevelopmental disability following vaccination. The risk of febrile seizure 1–2 weeks after immunization was higher in children who receive the MMRV compared with children who receive separate injections of MMR and varicella vaccine (Marin et al., 2010). However, the

Table 103.2

Various neurological disorders reported to the Vaccine Adverse Event Reporting System (VAERS)

Vaccine	Various neurological complications reported to VAERS
Viral vaccines	
MMR	Encephalitis, panencephalitis, aseptic meningitis, ADEM, cerebellar ataxia, parkinsonism, sensorineural hearing loss, seizures, mental retardation, autism, GBS
Varicella	Headaches, stroke, aseptic meningitis, encephalitis, cerebellar ataxia, gait disorders, sleep disorders, autism, developmental abnormalities, neuropathies
Smallpox	Headaches, cranial neuropathies, strokes, aseptic meningitis, postvaccinial encephalitis, ADEM, transverse myelitis, multiple sclerosis, poliomyelitis-like syndrome, GBS
Influenza	MS, optic neuritis, CNS demyelinating disease, GBS
Hepatitis B	MS, encephalitis, cerebellar ataxia, strokes, seizures, GBS, transverse myelitis, Bell's palsy, myasthenia gravis, neuropathy
Poliomyelitis (OPV)	VAPP, seizures, encephalitis
Rabies (Semple)	Stroke, meningoencephalitis, ADEM, transverse myelitis, seizures, cranial and peripheral neuropathies, GBS, neuroparalytic disease
HPV	Syncope, dizziness, headaches, GBS
JE	Encephalitis, seizures
YF	Encephalitis, ADEM, acute hemorrhagic fever, seizures, optic neuritis, cranial neuropathies, GBS, CIDP
Bacterial vaccines	
Meningococcal	Encephalitis, meningitis, seizures, AHLE, stroke, demyelinating neuropathy, mononeuritis multiplex
Pneumococcal	Encephalitis, meningitis, TIA, stroke, demyelinating neuropathy
Hib	Seizures, encephalitis, meningitis, stroke, neuropathy
DtaP	Seizures, encephalitis, meningitis, neuropathy, GBS, CIDP
Anthrax	Ulnar neuropathy, ON, GBS
Lyme	Aseptic meningitis, neuropathy, seizures

It is important to emphasize that a causal relationship was not evident in most cases, and some of the disorders listed may reflect an incidental association with the vaccination. MMR, measles-mumps-rubella; ADEM, acute disseminated encephalomyelitis; GBS, Guillain–Barré syndrome; MS, multiple sclerosis; CNS, central nervous system; TIAs, transient ischemic attacks; VAPP, vaccine associated paralytic poliomyelitis; HPV, human papilloma virus; JE, Japanese encephalitis; YFV, yellow fever; CIDP, chronic inflammatory polyneuropathy; AHLE, acute hemorrhagic leukoencephalitis; Hib, *Haemophilus influenzae* type B; DTaP, diphtheria-tetanus-pertussis (acellular); ON, optic neuritis.

overall occurrence of febrile seizure following MMR vaccination is rare: 4–5 cases per 10 000 vaccinations.

In the late 1990s *The Lancet* published an article asserting that MMR vaccination was linked to ileocolonic lymphoid nodular hyperplasia. In the absence of reproducible evidence, this paper has since been retracted. However, the study proposed a mechanism by which nonpermeable peptide could be absorbed enterally. This has fueled an allegation that MMR vaccination can cause autism (Wakefield et al., 1998). This association has been investigated thoroughly, without revealing any scientific support to the hypothesis. Because signs of autism may appear around the same time children receive the MMR vaccine, some parents may worry that the vaccine causes autism. Vaccine safety experts, including experts at CDC and the American Academy of Pediatrics (AAP), agree that MMR vaccine is not responsible for recent increases in the number of children with autism. In 2004, a report by the Institute of Medicine (IOM) concluded that there is no link between autism and MMR vaccine; unfortunately, there are still groups in the US attesting to the validity of this connection (Generation Rescue). Assertions that neuritis, deafness, and encephalitis occur more frequently among recipients of the mumps vaccine have not been proven.

Varicella vaccine

In 1996, the US introduced a program of mass varicella vaccination for children aged 12–18 months (White et al., 1991). The vaccination campaign resulted in a fall in the annual incidence of varicella infection in the US. Some 95% of children immunized will seroconvert after one dose of the vaccine. This live attenuated vaccine is a routine vaccination for children in the US. The varicella vaccine is safe and effective for immunocompetent children, as well as selected immunocompromised children. Discretion is advised with children who are severely

immunocompromised as the benefit of the vaccine may not outweigh the risk.

Neurologic complications following varicella vaccination are extremely rare. Cerebrovascular disease, meningoencephalitis, and cerebellar ataxia have been reported, but no causal link has been identified (Zhou et al., 2003).

Smallpox vaccine

Smallpox is an acute contagious disease caused by variola virus, a member of the orthopoxvirus family. Prior to vaccination against smallpox, it was one of the most devastating diseases known to humanity. Smallpox infection killed approximately 30% of those infected. Through history, it also killed Queen Mary II of England, Emperor Joseph I of Austria, King Luis I of Spain, Tsar Peter II of Russia, Queen Ulrika Elenora of Sweden, and King Louis XV of France.

In addition to pockmarks, deep scars resulting from the infection, many victims of smallpox became blind. In 1798, Edward Jenner demonstrated that inoculation with cowpox could protect against smallpox. However, smallpox disease was not eradicated worldwide until 1978. Vaccination against smallpox had been discontinued for the general population in the US in 1971. Vaccination of healthcare workers was discontinued in 1976 and of US military personnel in 1990. Since that time, no new smallpox infections have been recognized. Vaccination was reinstated for US military personnel and selected healthcare workers in 2002 given the threat of bioterrorism.

Neurologic complications of smallpox vaccination are rare, but severe. Postvaccinal encephalomyelitis, GBS, acute cranial neuropathies, poliomyelitis-like syndrome, and transverse myelitis are among the most commonly reported disorders (Zhou et al., 2003). Postvaccinal encephalitis, the most serious complication, was described in infants, presenting suddenly with encephalopathy and seizures. Recovery is often incomplete, leaving the patient with cerebral impairment and paralysis.

Influenza

Influenza epidemics occur each winter and are a significant cause of morbidity and mortality. On average, more than 200 000 people in the US are hospitalized due to complications of influenza infection. Approximately 36 000 die as a result of influenza infection yearly. The elderly and the young are disproportionately affected. Influenza vaccines must be adjusted annually in response to antigenic drift – the process whereby point mutations arise during viral replication. Each influenza vaccine includes two A viruses and one B virus. The effectiveness of the vaccine depends on the vaccine developers' ability to predict which strains will be circulating during the flu season. When the match of predicted strains and actual season's strains is close, the effectiveness of the vaccine is 70–90%.

Two types of seasonal influenza vaccines are available: trivalent inactivated vaccine (TIV) and live attenuated influenza vaccine (LAIV). The US Food and Drug Administration (FDA) approved the first nasal live virus flu vaccine in 2003. As a live virus vaccine, the immune system is triggered in a manner similar to native infection. In addition to robust immune response from live virus response, other advantages include: ease of administration, subsequent mucosal and systemic immune responses, and long-term memory (Couch, 2004). An adjuvant is required for optimal response.

LAIV is approved for use in healthy people 5–49 years old who are not pregnant. TIV is recommended for children 6 months to 23 months of age and adults older than 65 years. TIV is also recommended for people with chronic disease who are at increased risk of influenza infection.

Several neurologic complications have been linked to the influenza vaccine. Facial palsy is one complication that was historically linked to the nasal influenza vaccine. Facial palsy is a common neurologic disorder with incidence of approximately 20 per 100 000. The etiology of facial palsy is not clear. Following the introduction of newly licensed intranasal influenza vaccine in Switzerland in October 2000, 46 cases of facial palsy were noted among people who received the vaccine. Following this report, the vaccine was removed from the market.

Influenza (trivalent inactivated vaccine)

Perhaps the most notorious neurologic complication of trivalent inactivated vaccine (TIV) influenza vaccination occurred during the 1976–1977 influenza season. That year a vaccine against a swine-origin influenza virus was associated with a small, but statistically significant, increased risk of GBS. The incidence of GBS rose above the background rate of 10 cases per 1 million persons vaccinated (attributable risk: 1 per 100 000 vaccinees, a sevenfold increase in risk). The immunization campaign was discontinued prematurely after this increased incidence was identified. Further analysis identified a likely causal association between TIV and GBS for that seasonal vaccine only. The proposed mechanism was immune system response to *Campylobacter jejuni* antigens present in the vaccine.

There is no evidence to support a proposed link between influenza vaccination and multiple sclerosis relapse (Miller et al., 1997). On the contrary, among patients with relapsing and remitting multiple sclerosis, more exacerbations are seen after influenza illness than after influenza vaccination. Annual influenza vaccination, preferably with inactivated vaccines, should be

offered to all patients with relapsing and remitting multiple sclerosis.

Contraindications to influenza vaccinations include: fever, immune-suppression, or a history of GBS.

Influenza (H1N1)

The FDA licensed the first 2009 influenza A (H1N1) monovalent vaccine in September 2009. Similar to yearly influenza vaccinations, the H1N1 vaccine was available both as a live, attenuated monovalent vaccine (LAMV) for intranasal administration and as a monovalent, inactivated, split-virus or subunit vaccine for injection (MIV). The H1N1 vaccine became available on October 5, 2010. Routine monitoring in the first months following vaccine release showed 82 adverse event reports per 1 million H1N1 vaccine doses, and 47 cases per 1 million seasonal influenza doses. Although the number of adverse event reports was greater than that of the seasonal influenza vaccine, there was no difference in the type or proportion of serious adverse events reported. By November 24, VAERS had received 10 reports of GBS, and two additional cases of possible GBS. Preliminary reports indicate that four of these 12 potential cases of GBS were confirmed by Brighton Collaboration criteria. No cases of GBS were reported in the VSD system during the same time period. VSD detected no increased incidence of demyelinating disease, peripheral nervous system disease, seizure, encephalomyelitis, facial palsy, other cranial nerve disorders, or ataxia during that time period (CDC-2009, 2009).

Hepatitis B vaccine

Infection with hepatitis B virus may be subacute with nonspecific symptoms, clinically apparent with jaundice, or life-threatening with fulminant hepatitis. Vaccination against hepatitis B began with an inactivated plasma-derived vaccine in 1981. Shortly after, the first report of a demyelinating process after hepatitis B vaccination was reported. The patient suffered a case of transient inflammatory polyradiculoneuropathy (Shaw et al., 1988). A series of demyelinating disorders, including relapsing and remitting multiple sclerosis, optic neuritis, transverse myelitis, and GBS, were later described in patients with recent vaccination with hepatitis B.

In 1986, a genetically engineered, recombinant vaccine was developed. Since then, few cases of cerebellar ataxia, demyelinating polyneuropathy, and other neurologic disorders have been reported. In 1988, a case of myasthenia gravis possibly triggered by the administration of hepatitis B vaccine was reported (Biron et al., 1988). However, a causal relationship was never established and this is likely to represent a temporal association only.

Poliovirus vaccine

Poliomyelitis is a viral infection spread by fecal–oral transmission. Polioviruses are enteroviruses, and consist of serotypes 1, 2 and 3. Most individuals (95%) have an asymptomatic infection. Between 1% and 5% may develop neurologic manifestations including aseptic meningitis, sometimes with paresthesias, and paralytic disease (Zhou et al., 2003). Paralytic disease is characterized clinically by rapid onset of asymmetric acute flaccid paralysis with areflexia of the involved limb. Since 1979, the only cases of paralytic polio have occurred as a result of vaccination.

Two vaccines have been developed to prevent polio infection: the inactivated polio vaccine and oral polio vaccine. The inactivated polio vaccine, made of killed poliovirus, is administered subcutaneously or intramuscularly. Seroconversion occurs in almost all vaccines after three doses of the vaccine, with an excellent and long-lasting immune response to all three poliovirus types. However, the inactivated polio vaccine confers little immunity in the intestinal tract, increasing the risk of wild-type poliovirus circulation in the community.

The oral polio vaccine, a live polio vaccine, is taken orally and thus resembles the fecal–oral route of transmission of the virus. By introducing the vaccine in this manner, the oral vaccine produces better local (mucosal) immunity. In addition to superior immunogenicity, the oral polio vaccine has a lower cost and an easier route of administration. The most serious disadvantage is the risk of vaccine-associated paralytic polio. The CDC estimate that there is one case of vaccine-associated paralytic poliomyelitis per 2.5 million doses of oral polio virus vaccine. The risk is highest after the first dose of the vaccine, resulting in one case per 790 000 doses administered (CDC-2006, 2006). Close contacts of vaccinees can also develop vaccine-associated paralytic poliomyelitis with an estimated incidence of 1 case per 6.4 million doses. In developing countries malnutrition, vaccine instability, vaccine formulation, inhibitory substances in the intestine or the presence of other gastrointestinal viruses may interfere with the replication of the attenuated polio vaccine viruses, and the account for a decrease in the effectiveness of the vaccine. The inactivated poliovirus vaccine is used for all routine polio vaccination in the US.

Rabies vaccine

Infection with rabies virus characteristically produces an acute illness with rapidly progressive central nervous system manifestations, including anxiety, dysphagia, and seizures (Pickering et al., 2006). Illness almost invariably progresses to death. Worldwide, rabies causes

more than 50 000 deaths per year. There is no treatment once symptoms have begun. The high mortality associated with rabies infection significantly outweighs the risk of vaccination among exposed individuals.

Pasteur developed the rabies virus vaccine in 1885 by using a suspension of dried spinal cord tissue infected with an attenuated rabies virus. Despite the development of newer and safer vaccines, an attenuated-virus vaccine similar to the one Pasteur developed is still widely used in many parts of the world.

The Semple vaccine is a suspension of phenol or β-propiolactone killed virus in sheep brain. The incidence of neurologic complications with Semple vaccine is approximately one case per 220 vaccinees (Srivastava et al., 2004). Reported reactions include encephalomyelitis, transverse myelitis, acute polyradiculoneuropathy and peripheral neuropathy (Dutta and Dutta, 1994). Neurologic complications following Semple-type vaccine are attributed to myelin basic protein and some of the ganglioside and phospholipid constituents present in the vaccine.

In 1997 the FDA licensed a new rabies vaccine for both pre-exposure and postexposure prophylactic use in humans. This purified child embryo cell culture vaccine has been shown to be safe and effective. Few minor neurologic adverse events have been reported. Given the lethality of the disease, there are no contraindications for postexposure vaccination (Schlenska, 1976).

Human papilloma virus

In 2006, the FDA licensed the quadrivalent human papillomavirus recombinant vaccine. The vaccine is targeted against HPV types 6, 11, 16 and 18. Types 16 and 18 account for 70% of cervical cancer worldwide (Slade et al., 2009). HPV types 6 and 11 are common causes of genital warts. Shortly after the vaccine was approved for use, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination for all girls aged 11–12 years. Within the first $2^1/_2$ years of distribution, VAERS received over 12 000 reports of adverse events, a rate of 53.9 reports per 100 000 doses of vaccine distributed. The most common adverse events reported were syncope, dizziness, and headache. Rare cases of transverse myelitis, GBS, and two cases of amytrophic lateral sclerosis, were reported (Slade et al., 2009). At this time, it does not appear that HPV vaccination was causally associated with any of these cases. Research is ongoing.

Japanese encephalitis

Japanese encephalitis (JE) is a serious lifethreatening viral infection. It is the leading cause of viral encephalitis in Asia with a reported incidence of 50 000 cases per year (Nakayama and Onoda, 2007). Two types of killed JE virus vaccines are commercially available, an inactivated vaccine manufactured in Japan and Korea, and a killed vaccine prepared in China. Also, a live attenuated vaccine has been developed in China with good efficacy. In December 1992, a JE virus inactivated vaccine was licensed for use in the US (JE-VAX). A new, live attenuated vaccine (ChimeriVax-JE) is in early clinical trials and appears to be well tolerated and immunogenic after a single dose. Encephalitis or generalized seizures have been reported after inactivated vaccines, with an estimated incidence of 1 case per 50 000 vaccinees (Marfin et al., 2005). JE immunizations are recommended for all persons living in endemic areas for JE virus, as well as for persons who are traveling to an endemic region during an endemic season. For travelers, the recommended schedule consists of three doses to be completed at least 10 days prior to exposure.

Yellow fever

Yellow fever is an acute viral disease caused by a mosquito-borne flavivirus. It is endemic in at least 40 countries in Africa and South America. Yellow fever infection accounts for 200 000 cases worldwide and 30 000 deaths per year (Marfin et al., 2005). The yellow fever vaccine is a live attenuated virus preparation that confers immunity within 1 week to 95% of vaccines. A single dose provides protection for 10 years, and may provide lifelong immunity. In the US vaccine type 17D-204 is the only commercially available vaccine. Immunization is recommended for all people 9 months or older living in or traveling to endemic areas. Vaccine-associated neurotropic and viscerotropic diseases are rare, but well recognized adverse events (Pickering et al., 2006).

The vaccine-associated neurotropic disease is the most common serious adverse event, especially among children. For this reason, children less than 4 months old are not recommended to receive the vaccine. In a series of 23 cases of encephalitis associated with yellow fever vaccines (strain 17D), 16 cases occurred in children younger than 9 months (McMahon et al., 2007). Analysis of these cases shows that vaccine-associated neurotropic disease can occur up to 30 days after vaccination. Clinically, neurologic adverse events can present as encephalitis, meningoencephalitis, myelitis, acute disseminated encephalomyelitis (Fig. 103.1) (Miravalle et al., 2009), retrobulbar optic neuritis, seizures, cranial neuropathies, GBS, and acute hemorrhagic fever among others.

BACTERIAL VACCINES

Haemophilus influenzae type b (Hib), meningococcal, and pneumococcal vaccines

Hib vaccination confers protection by induction of anticapsular antibodies and immunologic memory. Conjugate Hib vaccines were introduced during the 1990s with an immediate decline in the incidence of Hib. Rare cases

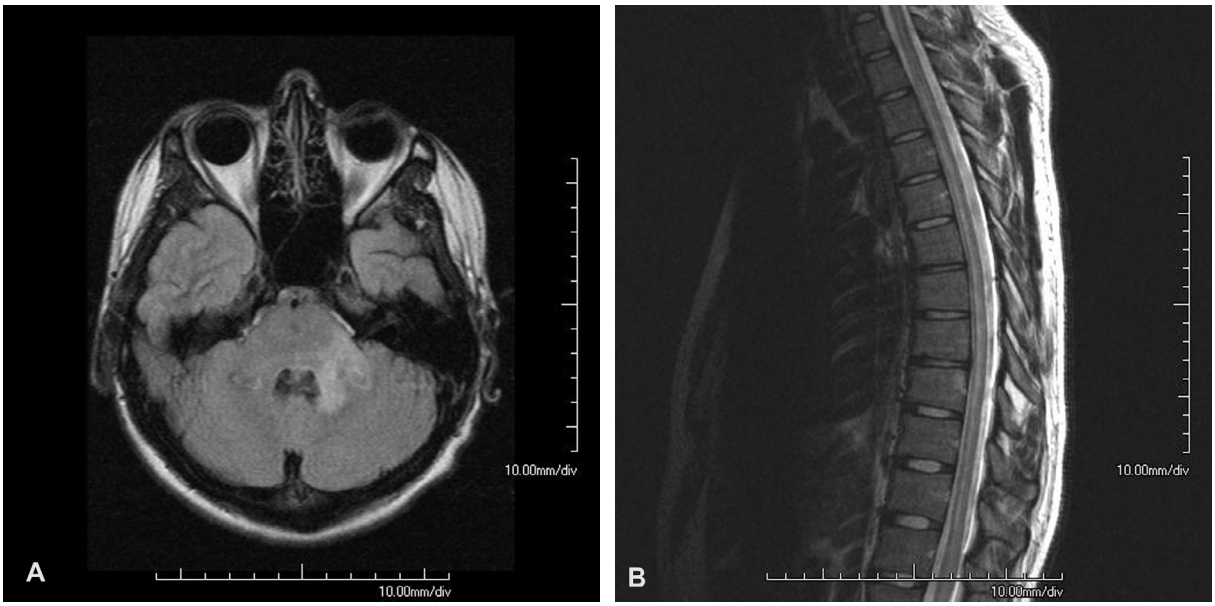

Fig. 103.1. (**A**) Magnetic resonance image (MRI) of the brain showing areas of high signal intensity on fluid attenuation inversion recovery (FLAIR) in the left middle cerebellar penduncle and right dorsal medulla oblongata. (**B**) T2-weighted magnetic resonance image (MRI) shows an extensive multilevel linear area of high signal intensity along the cervicothoracic spinal cord.

of GBS were documented following the administration of conjugated Hib, but there is inadequate evidence to accept or reject a causal relationship (Rosenstein and Feikin, 2004).

The first vaccine to protect against meningococcal meningitis was developed in 1978. It was not until 2000 that the ACIP recommended that students in colleges and universities receive the vaccination. The ACIP later recommended that all children aged 11–12 years, students entering high school, and college students be vaccinated. Eighteen confirmed cases of GBS following meningococcal conjugate immunization were published in 2005 (CDC-2005, 2005). A causal relationship has not been proven (CDC-2005, 2005).

Few cases of seizures, aseptic meningitis, encephalitis and demyelinating polyneuropathy have been reported in association with pneumococcal conjugate and Pneumovax, but no causal relationship can be confirmed in any of those cases (Zhou et al., 2003).

Diphtheria-tetanus-pertussis vaccine

Pertussis immunization originally consisted of inactivated whole cell *Bordetella pertussis*. This was first recommended as a vaccine in 1944 and combined with diphtheria and tetanus toxoids in 1947. Shortly after, Brody and Sorley documented the case of an infant who had episodes of generalized hypotonia and weakness followed by paralysis and decreased level of consciousness shortly after injection of pertussis vaccine (Brody and Sorley, 1947). Subsequently, various cases of similar episodes were recognized as temporally associated with pertussis vaccination. Later, a large retrospective analysis suggested an estimated incidence of seizures of one in 1750 vaccinees (Berg, 1958). Whole cell pertussis contains an endotoxin, which is known to cause fever and localized injection site pain. A more serious condition consisting of seizures, irritability, obtundation, and hypotonia has been rarely reported and given credence by the Institute of Medicine (Bolukbasi and Ozmenoglu, 1999). This so-called hypotonic, hyporesponsive episode (HHE) has been reported in one in 1750 administrations of pertussis immunization (Stratton and Johnston, 1994). Subsequently, whole cell pertussis vaccine has been replaced by the acellular vaccine. The result has been a marked decrease in the incidence of reported severe neurologic reactions. Seizures, which rarely occur following this immunization, are now simply thought to represent febrile convulsions. Other complications of pertussis vaccine have been greatly reduced by the acellular pertussis antigen, but are still rarely reported. If the child does have an encephalopathic reaction with seizures and or alteration of the level of consciousness, no additional pertussis immunization should be given. In particular, caution should be exercised if seizures occur within 3 days of the immunization or if inconsolable crying occurs lasting more than 3 hours. If hypotonia and diminished responsiveness occur within 48 hours, or if a high fever occurs within 48 hours, further exposure to the attenuated pertussis antigen is contraindicated. Furthermore, the American Academy of Pediatrics recommends deferring pertussis

immunization if the child has a history of significant developmental delay, and particularly if an early progressive or degenerative disease is suspected. Other contraindications include an active seizure disorder or conditions known to predispose to epilepsy such as tuberous sclerosis. However, static encephalopathies such as cerebral palsy and a family history of epilepsy are not necessarily a contraindication. Neurologic adverse events following tetanus toxoid have been reported including acute and chronic demyelinating polyradiculoneuropathies. To date, no neurologic adverse reactions have been attributed to diphtheria toxoid (Zhou et al., 2003).

Anthrax

Anthrax is one of the oldest diseases of grazing animals. It is transmitted by spores from *Bacillus anthracis*. The spores are incredibly resilient, reportedly persisting in soil decades after host death. Currently, the only available anthrax vaccine available in the US is BioThrax, prepared from a cell-free culture filtrate. The anthrax vaccine, formerly known as Anthrax Vaccine Adsorbed (AVA), developed in 1970, was offered to individuals felt to be at risk of exposure. Only a minority of those who were offered the vaccine accepted the vaccine secondary to perceived threat of vaccination (Niu et al., 2009). The Anthrax Vaccine Expert Committee (AVEC) reviewed the data from VAERS between March 1988 and January 2007. Their evaluation reported few rare events associated with vaccination. Of the adverse events listed, few were neurologic. The neurologic adverse events included localized edema at the site of injection that caused ulnar nerve impingement resulting in paresthesias. Other neurologic sequelae: optic neuritis, GBS and facial palsy, were not felt to be causally linked. Among the 25 patients who died following AVA immunization (per VAERS reports), three died of amyotrophic lateral sclerosis (ALS). Two of these diagnoses occurred temporally, while the third occurred 7 years later. No causal link has been proposed. Likewise, 11 cases of multiple sclerosis were reported to VAERS. These cases are not thought to be linked to immunization.

Other bacterial vaccines

Cognitive impairment, CIDP, multifocal motor neuropathy, and sensory axonal neuropathy have been described in patients receiving recombinant Lyme vaccine (Latov et al., 2004).

Headaches, transverse myelitis, and seizures have been also reported following typhoid vaccination (Das and Jaykumar, 2007).

Adjuvants

Vaccine adjuvants are sometimes added to improve immune responses to vaccines, although addition of an adjuvant can sometimes increase local side-effects, such as pain at the injection site. Thimerosal (thiomersal) is a preservative that contains ethyl mercury and is used in some vaccines and immunoglobulins.

The antrhrax vaccine (anthrax vaccine adsorbed, AVA) is linked to few medically important adverse events. However, the Anthrax Vaccine Expert Committee (AVEC) found that the aluminum-adjuvanted AVA vaccine administered subcutaneously over the triceps could induce swelling sufficient to pinch the ulnar nerve and cause distal paresthesias (Sever et al., 2004).

CONCLUSION

Prevention of infectious diseases through immunization is one of the greatest public health accomplishments of the past century. In the last decades, new vaccines have become available to prevent various infectious diseases and improved vaccines have been developed. As a result, immunization strategies have changed the epidemiology of various diseases. Indeed, the epidemiology of disease has been markedly altered by the successes of the *Haemophilus influenza* type b, smallpox and polio vaccines. Prior to introduction of the conjugate vaccine, the incidence of Hib meningitis was between 10 000 and 20 000 per year in the US and Canada. Some 3% of those patients died from the infection. Of the survivors, 25% were left with neurologic disability as a result (Wenger, 1998). Polio has been eradicated from North America following vaccination programs. The World Health Organization reports only four countries with endemic polio (WHO). Likewise, vaccination against smallpox was so successful that vaccination ceased worldwide by 1986. Like all therapies, vaccination also carries certain risks. Even though vaccines are tested in clinical trials prior to introduction to the public, clinical studies are generally not large enough to detect the development of rare adverse effects. In recent years numerous controversies and allegations surrounding immunization safety have been reported with significant impact on public health policies and overall public trust. However, the risk of serious events caused by existing vaccines is very small. Neurologic adverse events following immunization may be caused by the active antigen in the vaccine or other constituents, such as adjuvants, or may merely be coincidental. In most cases, the absence of distinguishing clinicopathologic findings and the lack of biologically proven putative association between vaccinations and neurologic injury make it difficult to determine a coincidental or causative relationship. In addition, most of the

evidence incriminating vaccines as a cause of neurologic disorders has been based on case reports. In order to better determine the nature of this relationship, well controlled epidemiologic studies are necessary.

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