The Pathology of Poliomyelitis and the Vaccines and Nonvaccine Therapy

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Abstract. Poliomyelitis is an exclusively human disease that mainly affects children. Clinical features of poliomyelitis can be varied, from mild illness to the most severe paralysis, and the factor why poliomyelitis has different performances in individuals has been proved strongly correlated with membrane protein CD155. The nervous system shows a special protecting phenomenon against the invasion of poliovirus, and the mechanism is not very clear at present. Vaccines are the main means of preventing and controlling polio, and many different vaccines have been invented in the process of fighting polio. Inactivated polio vaccine (IPV) and oral polio vaccine (OPV) are the two main vaccines. IPV is known for its safety while OPV is widely used in developing countries because of its relatively low cost. This usage also leads to some side effects: vaccine-associated paralytic polio (VAPP) and vaccine-derived poliovirus (VDPV). Now, for polio eradication, the elimination of these two diseases has become particularly important. Thus, a new type of vaccine was created: sequential IPV-OPV with the safety of IPV and the low cost of OPV. This paper will talk about the different polio vaccines and their effects. An enormous difference between people who have gotten the vaccine and people who have not got the vaccine. Comparing the two kinds of people, people who get normal poliovirus, and people who get polio virus after taking a vaccine, known as VAPP (vaccine-associated paralytic poliomyelitis), the former cannot get full recovery whole life and the latter has a very low possibility. In conclusion, people should take vaccines if it is affordable for them.

1 Introduction

Poliovirus which causes poliomyelitis is an enterovirus that belongs to the Picornaviridae family [1]. Human is the only natural host for poliovirus [2]. The virus is composed of four proteins and a single-stranded RNA [3]. The transmission of poliovirus follows the fecal-oral route, which mainly affects children [1]. However, infants under 6 months are not symptomatic of poliovirus due to the protection of maternal antibodies [4]. In most cases, poliovirus causes only mild illness [1]. Aseptic meningitis is also found in a small proportion of infections, and in the rarest case paralysis is caused by poliomyelitis [2]. A special sequela which is known as post-polio syndrome can appear decades after initial poliomyelitis and induce further damage to muscles [5]. Past researches have shown that the infection of poliovirus is closely related to membrane protein function as poliovirus receptor (PVR) [2]. Human PVR, or CD155, also plays an important role in the invasion of the central nervous system (CNS), which induces paralysis-polioymelitis [2]. However, CD155 shows no strong relevance to the permeation through the blood-brain barrier (BBB), which causes aseptic meningitis [2]. Due to the application of polio vaccines, wild poliovirus is nearly extinct. Although polio eradication is nearing its end, wild poliovirus (WPV) is still rampant in some parts of the world like Africa, and there are still many developing countries that are not polio-free [6]. The characteristics of these three vaccines will be introduced in detail, and the comparison will be made to show the different application ranges of different vaccines [7]. In this paper, two derivatives of oral polio vaccine (OPV), namely, side effects, will also be referred to. Widespread use of OPV has reduced the global incidence of polio by ≈99.9%. However, the emergence of vaccine-derived poliovirus (VDPV) and vaccine-associated paralytic poliomyelitis (VAPP) is threatening polio eradication plans [8]. This paper will explain the pathogenesis of these two side effects, as well as the method to eliminate the risk——namely the use of sequential IPV-OPV. To eradicate all cases of polio, including VAPP and VDPV, all countries must stop using OPV. But this is not realistic now, and there are many developing countries that cannot afford full IPV. This requires the use of novel OPV (nOPV) to gradually reduce the number of vaccine-induced cases [9]. There different countries in the world, therefore not all countries can afford the vaccine. In addition, the situation of people infected with poliomyelitis is common in the world. There

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are several reasons, the first one is people who are from some poor countries cannot afford the vaccine, second after gotten vaccine, immune system in somebody's body contains some defect, since they infected the polio virus, the third reason is that after people get vaccine, the virus mutates, so their vaccine cannot prevent the mutated virus [10]. Comparing people who get normal poliovirus and people who infected VAPP (vaccine-associated paralytic poliomyelitis), the former seems to have a serious outcome. In conclusion, people should take vaccines before they are infected by the polio virus.

2 The pathogenesis, vaccines and nonvaccine therapy of poliomyelitis

2.1 Pathogenesis

Poliovirus enters the human body by mouth, then attaches to the mucosa and reproduces in various levels of the alimentary tract [1]. Incidental invasion towards lymph nodes is then followed in most cases, though past researches indicated that the virus multiplies in the alimentary tract majorly [1]. This stage can be completely asymptomatic or with very mild symptoms (90-95% of infections) [2, 3]. When the amount of virus in the lymph nodes exceeds the cells' capacity, the virus overflows into the blood, causing viremia in the cases in which poliovirus can multiply in a variety of extraneural tissues [1]. Abortive poliomyelitis (4%-8% of infections), with mild flu-like symptoms as fever or sore throat, is involved in this stage but has no relevance to the central nervous system (CNS) [3, 4]. Viremia can be eliminated due to the appearance of antibodies [2]. These symptoms usually subside within one week [2]. The Circulating poliovirus has two possible routes to enter the CNS subsequently, one is permeation through the blood-brain barrier (BBB) [5]. In this case, aseptic meningitis (0.5%-0.1% of infections) is presented, accompanied by severe muscle spasms of the neck, back, and lower limbs, which follow a brief prodrome like the one in abortive poliomyelitis [2, 11]. The other route, which is the rarest case (less than 1% of infections), is virus transmission via peripheral nerves. The poliovirus may invade sensory peripheral ganglia, lead to further progression within CNS along neural pathways in some situations [1]. Paralysis due to loss of nervous responses in the infected region is produced [2]. In extreme cases, poliomyelitis can be fatal if the brain stem is invaded or if respiratory muscles are infected [2]. A special sequela, Post-polio syndrome (PPS) may appear decades after initial poliomyelitis, causing slowly progressive muscle weakness and muscle atrophy (Fig.1) [12]. In some hypotheses, this deformation is induced by aging and neuron deterioration; another hypothesis suggests PPS is related to the persistence of poliovirus in CNS [12].

![Fig.1 Symptoms corresponding with spread of poliovirus in human body](https://example.com/fig1.png)
2.2 Pathogenesis in molecular dimension

Poliovirus, which causes poliomyelitis, belongs to the Picornaviridae family. Human is the only natural host of poliovirus. The diameter of poliovirus is approximately 31nm, and the virus has a molecular mass of 8.5 x 106 daltons [13]. The virion is made of 60 copies each composed of four proteins—VP1, VP2, VP3, and VP4, and a single-stranded RNA [13]. In human body poliovirus has different affinities to different tissues, this deviation is mainly caused by a specific cell surface molecule function as poliovirus receptor (PVR) [14]. Researches on transgenic mice expressing human PVR also indicated PVR is one of the reasons why poliomyelitis infects human particularly [15]. Human poliovirus receptor, or CD155, is a glycoprotein anchored on the cell membrane with a transmembrane domain, a cytoplasmic domain, and three extracellular immunoglobulin-like domains [14-17]. The Ig-like domain is essential for poliovirus infection by providing a binding site for the virus, showed by molecular genetic analysis [17]. When poliovirus binds to PVR it changes its conformation from 160S particle to 135S and 80S particles [18]. A 135S particle loses VP4 protein, and the 80S particle loses both VP4 protein and the RNA genome [5]. The 135S particle is then involved in the uncoating process and releases the genome that functions as mRNA, which enters ribosome and translates large precursor protein processed into functional viral proteins [5]. However, the permeation across BBB does not correlate with CD155, shown by recent researches [5]. Hence, besides CD155 other host cell molecules must play an important role when poliovirus permeates BBB [5]. In the transport through CNS CD155 is involved. Poliovirus enters CNS via skeletal muscles and is then able to retrogrades through the axon. The transporting velocity is determined to be fast retrograde axonal transport, therefore poliovirus is deduced to be packed in endosomes during transportation through axon for many other substances experiencing fast retrograde transport are usually packed in endosomes [5, 19]. In a possible mechanism for the retrograde transport of poliovirus, the virus is introduced into cells by PVR-mediated endocytosis at synapses without conformational changes, the endosomes enclosed poliovirus are then carried by cytoplasmic dynein retrogradely through the axon to the cell body [5]. Researches also indicated that there is a special anti-poliovirus response in CNS. To cause cytopathic effects in neurons a second infection with progeny poliovirus is necessary [5]. This hypothesis is supported by experiments, which showed after the first infection with virulent poliovirus, the addition of anti-poliovirus serum prevented the death of neural cells productively [5, 20]. This phenomenon, to some extent, may reveal a new treatment for poliomyelitis.

2.3 Polio vaccines

In a world where polio has not been completely eradicated, we cannot afford to let down our guard. The Global Polio Eradication Initiative (GPEI) is now in its final phase; except for several regions, global endemic transmission of wild poliovirus has been stopped. Oral poliovirus vaccine (OPV) has succeeded in eradicating wild poliovirus from most parts of the world. However, the prevalence of vaccine-derived poliovirus (VDPV) and vaccine-associated paralytic polio (VAPP) exposed OPV’s shortcomings, paving the way for the introduction of inactivated poliovirus vaccine (IPV) into the global vaccination program [21]. At the same time, a new form of vaccination has emerged—sequential IPV-OPV. This form may appear as the ultimate vaccination method for developing countries as it is cheaper than all-IPV and contains the same effectiveness as IPV. Depending on the situation, the choice of vaccine varies from region to region, and the required response measures are also different (Fig.2).

Today, IPV vaccine has been fully used in many developed countries, which is an effective vaccine against polio. Several countries have shifted from all OPV to sequential OPV-IPV schedules and all-IPV schedules with elimination of wild polio. IPV contains formaldehyde-killed poliovirus which will generate no risk of neither VAPP nor VDPV. Currently, we use eIPV that contains 40, 8 and 32 D antigen units of type 1, 2 and 3 respectively. Thus, IPV usually refers to eIPV. The optimal storage temperature of the vaccine is 2-8°C and the intramuscular/subcutaneous is 0.5 mL per dose [22]. It is highly immunogenic: In children at 2, 4, and 18 months of age who received three doses of synergistic IPV, 99% to 100% developed three types of serum antibodies against poliovirus. IPV can be administered along with all other childhood vaccines without compromising seroconversion or increasing side effects. The vaccine is generally safe; nevertheless, allergic reactions may be seen in individuals with hypersensitivity to some antimicrobials, because IPV includes tiny amounts of streptomycin, neomycin and polymyxin B. IPV will be absolutely necessary in the post-eradication era when OPV has to stop [22].

The OPV is still used in most developing countries as the main means of combating polio. The live strains contained in OPV replicate in the human gut and are excreted within a few weeks of immunization. In rare cases, this can lead to vaccine-associated paralytic poliomyelitis (VAPP), or to infectious and neurotoxic strains of circulating vaccine-derived poliovirus (cVDPV) [23]. Since 1985, though, OPV has been used under the Universal Immunization Program. Studies have shown low serum conversion rates in infants using OPV. However, OPV wins over IPV as a vaccination strategy because it provides herd immunity. OPV is cheaper, easier to obtain and manage; the following possible dangers are vaccine-associated paralytic polio and vaccine-derived poliovirus with live attenuated polio strains in OPV had emerged [24]. OPV has several serotypes: monovalent OPV (mOPV), bivalent OPV (bOPV), trivalent OPV (tOPV). In the three serotypes, though, they all have probability leading to VAPP or VDPV, tOPV is the safest compare to others. As much as the GPEI would like to obsolete OPV worldwide and promote IPV, OPV cannot be simply obsoleted. Many developing countries cannot afford the economic burden of full IPV vaccination, and IPV doesn’t provide herd immunity like OPV does, which
is a serious disadvantage for populous countries [25].

IPV-OPV may reduce VAPPs compared to OPV, but it does not affect vaccination coverage or safety. Fecal excretion of poliovirus can be increased after OPV challenges certain serotypes of poliovirus. Compared with OPV alone, IPV-OPV, which may have little or no effect on persons with protective humoral responses, may increase neutralizing antibodies and may reduce fecal excretion following oral polio vaccine vaccination with certain serotypes of polio. However, using three doses of IPV as part of the IPV-OPV schedule does not appear to provide a better protective humoral response than two doses of IPV [26]. The dosage and sequence of the two vaccines in sequential IPV-OPV still need further study.

Fig.2 Types and application ideas of polio vaccine

2.4 Derivative diseases

OPV is the most dangerous of all of the polio vaccines, as either mOPV, bOPV or tOPV is likely to cause some vaccine-derived diseases. OPV vaccination is generally not recommended for individuals with weak immune systems because it contains a live virus that can replicate in the body and make people sick.

As mentioned above, OPV virus replicates in the intestines of the vaccinated person. In immunized children, the time for this replication is limited, and the virus excretion period can be 30 to 60 days. During the replication cycle, due to random processes and selection pressures, the OPV virus may mutate gradually, acquire certain neurotoxicity, and may spread in the community. Oral polio vaccine causes rare cases of VAPP, which WHO estimates at 1 case per million people. The risk of VAPP was highest after the first dose and then dropped sharply after the next dose [27].

Despite the effectiveness and benefits of OPV in eradicating wild poliovirus, there are some risks associated with the use of OPV. In polio-free countries, there is a risk of importing vaccine-derived poliovirus (VDPV) that have mutated from polio-associated strains and may resume neurovirulence [28]. During vaccine use, a vaccine-derived poliovirus (VDPV) strain may emerge and spread in underimmunized populations, becoming circulating VDPV (cVDPV) strain and leading to an outbreak of paralytic polio. The GPEI plans to use in the future a new type 2 OPV that has been stabilized to reduce the possibility of neurotoxicity reversal. However, all countries must maintain a high level of population immunity to reduce the risk of cVDPV emergence [29].
2.5 Basic of vaccine

Poliomyelitis vaccine can be divided into two major different types. The vaccine which is used to treat poliomyelitis be divided into oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV). OPV can be accepted in two ways that are injection and oral pills. However, the inactivated poliovirus vaccine (IPV) can only be injected. The human body will produce antibodies after they are injected or had the oral pills of the OPV vaccine. The antibody is produced by the human body is used against the poliovirus. The human would not infect poliomyelitis when they are exposed to causative agents. However, a special situation will be produced in someplace, such as the vaccine-associated paralytic poliomyelitis (VAPP). This special polio would only happen after human took polio vaccine and the virus inside the human body which have not to be eradicated yet and mutated [10]. The overall incidence of vaccine-associated polio was 1 case per 2.6 million doses of vaccine. However, in the OPV series, the relative frequency of paralysis associated with the first dose was 1 case per 520,000 doses and 1 case per 12.3 million doses. Vaccine-associated paralytic polio is very rare and the risk of oral polio vaccine is small [30].

2.6 Treatment after gotten vaccine-associated paralytic poliomyelitis (VAPP)

After people infect vaccine-associated paralytic poliomyelitis (VAPP), the treatment can be divided into three stages. The first stage is called paralysis. Patients who infect vaccine-associated paralytic poliomyelitis (VAPP) need to stay in bed and did the corresponding treatment which focuses on the symptom that appears on patients. Patients should timely take appropriate antipyretic, antimanic, dehydration, and other treatments to deal with the occurrence of high fever, convulsions, respiratory failure, and other serious symptoms. In addition, patients should exercise joints and muscles to avoid malformation of body parts. The next stage is called the recovery stage by individuals which sustain 1 to 2 years. Patients should take considerable pills in this stage and exercised joints and muscles by others, to avoiding sweeney and malformation. The last stage in the treatment of vaccine-associated paralytic poliomyelitis (VAPP) is called the sequelae stage. Occupational therapy and physical therapy should be taken by the patient in this stage. Surgery should be taken by patients that cannot be fully cured by orthotics.

2.7 Infection and recovery of poliomyelitis

Poliomyelitis will be infected by children by contact with the polio virus or contact with the people whose bodies bring polio virus. In 1939, people try to research the way that how did children infect polio virus, scientists chose Jewish children who were lived in Detroit. Thirty-four children were cared for in the family at the time of the outbreak. Fourteen of them were school-age children (5 to 16 years old) who were allowed considerable freedom of movement within the family and in the vicinity. The remaining 20 children were infants and preschoolers, these twenty children were limited in an individual area. During 1939, 5 cases of poliomyelitis occurred in this group, 1 of which died, and the rest were non-paralytic. The children were hospitalized at Herman Keifer Hospital, and all five patients were diagnosed with poliomyelitis based on the typical history, signs and symptoms, as well as the results of spinal fluid tests. The other three children who could not be diagnosed had fevers that lasted between 24 and 48 hours. According to this statistic, the children who have contacted with other people had higher probability to infect poliomyelitis [31]. After infected poliomyelitis, certain parts of the muscles are easier to be paralyzed, such as the deltoid and the anterior tibial muscles. Most paralysis is permanent and cannot be fully cured, in addition, it can be controlled and treated by pills, but children infected with poliomyelitis would still have some negative symptoms after treatment [32].

2.8 Compare treating after non vaccinated people who infect polio virus and vaccinated people

Poliovirus can be transmitted to people through oral-faecal route; therefore, people can use vaccines to prevent polio virus infection. However, there is a low possibility to be infected with poliomyelitis, because the virus can mutate. Vaccines are very useful for prevent virus, and compare with people who have not been vaccinated, vaccination is a wise choice. People who are infected with poliovirus but not vaccinated cannot fully recover from it. So, people should take care of children who have not taken vaccine. If vaccine is affordable for people, they should take vaccine.

3 Conclusion

The main conclusion that can be drawn on the pathogenesis is that the poliovirus enters the human body by the alimentary tract, then enters the blood from the lymph nodes causing viremia. After entering the blood, the virus is able to permeate through BBB, causing aseptic meningitis, or invade neurons from muscles then retrograde through CNS, causing paralysis. Overall, all the infections in the human body are correlated with CD155 protein except permeation through BBB. The CD155 either provides an anchor point for poliovirus to promote uncoating, or makes it possible for poliovirus to be carried by cytoplasmic dynein through axons. Prior to the emergence of inactivated polio vaccine (IPV), sporadic polio outbreaks were reported because of the oral poliovirus vaccine (OPV). This resulted in up to 18,000 cases of paralysis and 3,000 deaths in the United States alone. The data indicate that OPV is indeed dangerous, but compared with OPV, IPV is too expensive to be used widely in globe. Whereupon, sequential IPV-OPV emerged with its valuable features. The public health advantages of this IPV-OPV method of vaccination have been highlighted several times, and it was used in the United States, as well as in Israel and Denmark, with successful results. On this basis, we conclude that IPV-
OPV is a forceful weapon against VAPP and VDPV. Poliomyelitis or its related diseases can happen in both people who have taken the vaccine and people who have not taken the vaccine. However, the possibility of people who have taken the vaccine is really low. In addition, people who are infected with poliovirus before get a polio vaccine cannot get full recovery. Thus, people should take the vaccine if they can afford it.

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