



(MIC 450)

Medical viruses

Diseases caused by viruses

Poliovirus

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1. Introduction:

1.1. History of the disease.

- It is likely that polio has plagued humans for thousands of years. An Egyptian carving from around 1400 BCE depicts a young man with a leg deformity similar to one caused by polio.
- Poliovirus was first isolated in 1909 by Karl Landsteiner and Erwin Popper. In 1981, the poliovirus genome was published by two different teams of researchers: by Vincent Racaniello and David Baltimore at MIT and by Naomi Kitamura and Eckard Wimmer at Stony Brook University
- Because of widespread vaccination, polio was eliminated from the Western Hemisphere in 1994.

1.2. Introduction of the virus.

- **Poliovirus**, the causative agent of poliomyelitis (commonly known as polio), is a human enterovirus and member of the family of Picornaviridae.
- Polio is the common name for poliomyelitis, which comes from the Greek words for grey and marrow, referring to the spinal cord, and the suffix -itis, meaning inflammation. Poliomyelitis, shortened, became polio. For a time, polio was called infantile paralysis, though it did not affect only the young.

1.3. The distribution of this disease.

- Polio reached epidemic proportions in the early 1900s in countries with relatively high standards of living, at a time when other diseases such as diphtheria, typhoid, and tuberculosis were declining. Indeed, many scientists think that advances in hygiene paradoxically led to an increased incidence of polio. The theory is that in the past, infants were exposed to polio, mainly through contaminated water supplies, at a very young age.
- Because of widespread vaccination, polio was eliminated from the Western Hemisphere in 1994. Today, it continues to circulate in a handful of countries, with occasional spread to neighboring countries. (Endemic countries as of 2015 are Afghanistan, Nigeria, and Pakistan.) Vigorous

vaccination programs are being conducted to eliminate these last pockets. Polio vaccination is still recommended worldwide because of the risk of imported cases.

1.4. Epidemic.

- Major polio epidemics were unknown before the 20th century; localized paralytic polio epidemics began to appear in Europe and the United States around 1900. The first report of multiple polio cases was published in 1843 and described an 1841 outbreak in Louisiana. A fifty-year gap occurs before the next U.S. report—a cluster of 26 cases in Boston in 1893. The first recognized U.S. polio epidemic occurred the following year in Vermont with 132 total cases (18 deaths), including several cases in adults. Numerous epidemics of varying magnitude began to appear throughout the country; by 1907 approximately 2,500 cases of poliomyelitis were reported in New York City.
- On Saturday, June 17, 1916 an official announcement of the existence of an epidemic polio infection was made in Brooklyn, New York. That year, there were over 27,000 cases and more than 6,000 deaths due to polio in the United States, with over 2,000 deaths in New York City alone.
- In the United States, the 1952 polio epidemic would be the worst outbreak in the nation's history, and is credited with heightening parents' fears of the disease and focusing public awareness on the need for a vaccine. Of the 57,628 cases reported that year 3,145 died and 21,269 were left with mild to disabling paralysis.

2. Classification of the virus:

2.1. Order : *Picornavirales* .

2.2. Family : *Picornaviridae* .

2.3. Genus : *Enterovirus*

3. Structure and Genome:

3.1. Shape: icosahedral symmetry.

3.2. Size: The viral particle is about 30 nanometres .

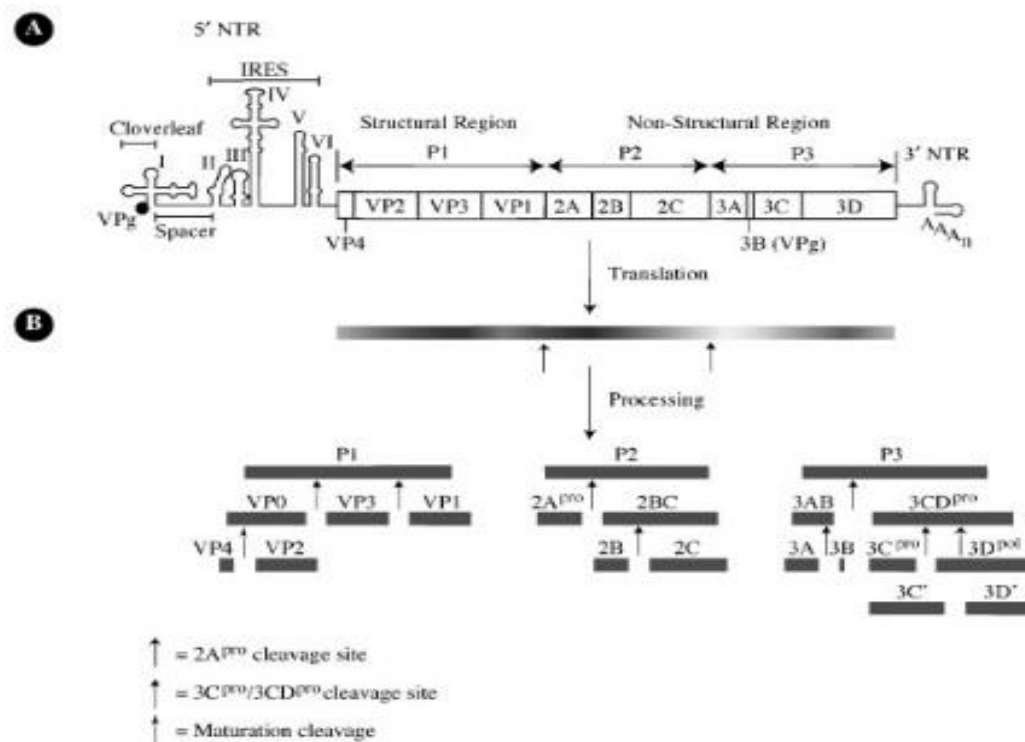
3.3. Enveloped or not: not enveloped .

3.4. Nucleic acid: single-stranded positive-sense RNA genome that is about 7500 nucleotides long

4. Proteins (Virulence Factors):

4.1. Structural proteins and their function.

4.2. Non- Structural proteins.



5. Transmission:

Polio is a highly infectious illness that spreads through contact between people, by nasal and oral secretions, and by contact with contaminated feces. Poliovirus enters the body through the mouth, multiplying along the way to the digestive tract, where it further multiplies.

6. Penetration and the Target Organ.

The virus enters through the mouth and multiplies in the throat and gastrointestinal tract, then moves into the bloodstream and is carried to the central nervous system where it replicates and destroys the motor neuron cells. Motor neurons control the muscles for swallowing, circulation, respiration, and the trunk, arms, and legs.

Attacks the nerve cells of the spinal cord (responsible for the movement of muscle cells)

- Poliovirus infects human cells by binding to an immunoglobulin-like receptor, CD155, (also known as the poliovirus receptor (PVR)) on the cell surface. The precise mechanism poliovirus uses to enter the host cell has not been firmly established. Attached to the host cell membrane, entry of the viral nucleic acid was thought to occur one of two ways: via the formation of a pore in the plasma membrane through which the RNA is then “injected” into the host cell cytoplasm, or that the virus is taken up by receptor-mediated endocytosis. Recent experimental evidence supports the latter hypothesis and suggests that poliovirus binds to CD155 and is taken up via endocytosis. Immediately after internalization of the particle, the viral RNA is released.

7. Replication Cycle (the main site): ****

- Poliovirus is a positive stranded RNA virus. Thus the genome enclosed within the viral particle can be used as messenger RNA and immediately translated by the host cell.
- On entry the virus hijacks the cell's translation machinery, causing inhibition of cellular protein synthesis in favor of virus-specific protein production. Unlike the host cell's mRNAs the 5' end of poliovirus RNA is extremely long—over 700 nucleotides—and highly structured. This region of the viral genome is called internal ribosome entry site (IRES) and it directs translation of the viral RNA. Genetic mutations in this region prevent viral protein production.

- Poliovirus mRNA is translated as one long polypeptide. This polypeptide is then auto-cleaved by internal proteases into approximately 10 individual viral proteins

including :

- 3Dpol, an RNA dependent RNA polymerase whose function is to copy and multiply the viral RNA genome.
- 2Apro and 3Cpro/3CDpro, proteases which cleave the viral polypeptide.
- VPg (3B), a small protein that binds viral RNA and is necessary for synthesis of viral positive and negative strand RNA.
- 2BC, 2B, 2C, 3AB, 3A, 3B proteins which comprise the protein complex needed for virus replication.
- VP0, which is further cleaved into VP2 and VP4, VP1 and VP3 proteins of the viral capsid.

8. Assembly and Egression:

- The assembly of new virus particles, (i.e. the packaging of progeny genome into a capsid which can survive outside the host cell) is not fully understood. Fully assembled poliovirus leaves the confines of its host cell 4 to 6 hours following initiation of infection in cultured mammalian cells .The mechanism of viral release from the cell is unclear, but each dying cell can release up to 10,000 polio virions.
- The proposed steps of assembly include ordered proteolytic cleavages and formation of capsid protein subviral particles prior to RNA encapsidation and maturation of the virion. The three-dimensional structure of poliovirus provided few clues of its interaction, as the encapsidated RNA molecule does not adopt the icosahedral symmetry of the capsid shell. Because the VPg-linked RNA molecules exist in multiple conformations within a crystal lattice of poliovirus virions, structural determinations for the RNA genome and VPg could not be made. It has been reported that portions of the P1 coding region of polio virus contain *cis* elements required for RNA replication and/or encapsidation of the genome. Another report has demonstrated that sequences at the 5' end of the P1 coding region are dispensable for both RNA replication and encapsidation. These studies demonstrated replication and encapsidation of a poliovirus RNA replicon containing a reporter chloramphenicol acetyltransferase (CAT) gene inserted for part of the P1

gene. The methods to analyze the processes of poliovirus capsid assembly and RNA encapsidation include recombinant vaccinia virus vectors. The systems described offer the dual capability of analyzing P1 capsid precursor cleavage and subviral particle formation separately from the encapsidation step.

9. Symptoms:

- In about 95% of all polio cases, the person has no symptoms at all. These are known as asymptomatic cases. The rest of polio cases can be divided into three types: abortive polio, non-paralytic polio, and paralytic polio.
- Abortive polio: In these cases, polio is a mild illness, with viral-like symptoms such as fever, fatigue, headache, sore throat, nausea, and diarrhea.
- Non-paralytic polio: These cases typically involve the symptoms of abortive polio, with additional neurological symptoms, such as sensitivity to light and neck stiffness.
- Paralytic polio: The first signs of paralytic polio, after an initial period of viral-like symptoms, typically begin with loss of superficial reflexes and muscle pain or spasms. Paralysis, usually asymmetric, follows. Fewer than 1%-2% of people who contract polio become paralyzed. In most cases of paralytic polio, the patient recovers completely. However, for a certain number of people, paralysis or muscle weakness remains for life.

10. Diagnosis and Cytopathic effect:

- Poliovirus can be detected in specimens from the throat, and feces (stool), and occasionally cerebrospinal fluid (CSF), by isolating the virus in cell culture or by detecting the virus by polymerase chain reaction (PCR).
- CDC laboratories conduct testing for poliovirus including:
 - 1- Culture
 - 2- Intratypic differentiation
 - 3- Genome sequencing
 - 4- Serology

- Virus Isolation
- Virus isolation in culture is the most sensitive method to diagnose poliovirus infection. Poliovirus is most likely to be isolated from stool specimens. It may also be isolated from pharyngeal swabs. Isolation is less likely from blood or CSF.
- To increase the probability of isolating poliovirus, collect at least **two stool specimens 24 hours apart from patients** with suspected poliomyelitis. These should be collected as early in the course of disease as possible (ideally within 14 days after onset).
- Real-time reverse transcription PCR is used to differentiate possible wild strains from vaccine-like strains ("intratypic differentiation"), using virus isolated in culture as the starting material.
- Partial genome sequencing is used to confirm the poliovirus genotype and determine its likely geographic origin.
- Serologic testing
- Serology may be helpful in supporting the diagnosis of paralytic poliomyelitis, particularly if a patient is known or suspected to not be vaccinated. An acute serum specimen should be obtained as early in the course of disease as possible, and a convalescent specimen should be obtained at least three weeks later.
- CSF analysis
- Detection of poliovirus in CSF is uncommon. CSF usually contains an increased number of leukocytes [from 10 to 200 cells/mm³ (primarily lymphocytes)] and a mildly elevated protein (from 40 to 50 mg/100 ml). These findings are nonspecific and may result from a variety of infectious and noninfectious conditions.

11. Control the virus and Prevention:

- the most effective way to prevent the disease is with polio vaccine

Polio vaccine

- Currently, most children in the United States receive four doses of inactivated poliovirus vaccine (IPV) at the following ages:
 - Two months
 - Four months
 - Between 6 and 18 months
 - Between ages 4 and 6 when children are just entering school
- IPV is 90 percent effective after two shots and 99 percent effective after three. It can't cause polio and is safe for people with weakened immune systems, although it's not certain just how protective the vaccine may be in cases of severe immune deficiency. Common side effects are pain and redness at the injection site.

12.Treatment :

- A. Vaccines
 - Polio Vaccines Oral Polio Vaccine(OPV) Live Attenuated Vaccine Sabin 106 , 105, 105.8 TCID50 per dose Both systemic & local immunity Used for mass campaigns Useful during control of epidemic Cheap & easy to administer
 - Polio Vaccines..2 : Inactivated Polio Vaccine(IPV) Killed Vaccine Salk Only Systemic immunity Not useful for mass campaigns Cannot be administered during epidemics Costly & Administration requires trained manpower
- B. Medication

Because no cure for polio exists, the focus is on increasing comfort, speeding recovery and preventing complications. Supportive treatments include:

- Bed rest
- Pain relievers

- Portable ventilators to assist breathing
- Moderate exercise (physical therapy) to prevent deformity and loss of muscle function
- A nutritious diet

13. Host Immune Defense:

- Immune system is alerted by the lysis of cells infected with polio virus
- Neutrophils, macrophages, and mast cells become active in response
- Neutrophils are responsible only for phagocytosis
- Macrophages phagocytose and simultaneously internalize the antigen for later presentation
- Mast cells de-granulate in response to the cytokines released
- These granules contain pre-formed "packets" of histamine and selectin that signal the endothelial layers of the blood vessels to loosen to allow more cells to enter the area. The selectin slows the white blood cells and pulls them out of the vessel to escalate the immune response. HOWEVER...
- The polio virus inhibits the innate immune response by preventing the cells from releasing adequate cytokines
The Complement Cascade
The second part of the innate immune system
Extremely important in fighting viral infections such as polio
- Since the poliovirus is a cytocidal agent, antibody immune response is the most important among those related to protection; however probably a minimum of helper T cells are required (more than 200 T lymphocytes with phenotype CD4) in order to get a best response. Phagocyte, NK cells and T lymphocytes probably take part in the viral clearance from the central nervous system, also in the host injury mechanisms. Some molecular aspects of the neutralizing antibodies combining site are described too. Activation particularities, of the common mucosal immune system confirm the importance of the secretory immune response in the control of the poliomyelitis.

14. Genetics (Gene Mutation):

Poliovirus lacks the ability to correct its mutations, so its genome evolves at one to two nucleotide substitutions per week. It is always changing.

Polioviruses, as with all RNA viruses, are in a constant process of evolution driven by different mechanisms. With multiple mechanisms for genetic variability, they are successful conformists, adapting to changes in their habitat. The evolution of polioviruses may occur with generation of point mutations followed by genetic drift and selection. The mutation rate of polioviruses based on several studies is approximately 3×10^{-2} mutations/synonymous site/year in the gene encoding viral protein 1. Genetic variation in polioviruses may also be increased by sharing of genetic data of two different poliovirus lineages by means of homologous recombination. According to the current view, recombination is considered usually to occur by strand-switching, but a non-replicative model has also been described. In recombination, polioviruses may either gain a set of advantageous mutations selected and fixed in previous generations of the parental viruses or get rid of deleterious ones.

15. Recent discoveries:

1- Researchers expanding use of poliovirus for cancer treatment

2- Scientists discover way to potentially track and stop polioviruses

Wang, who is a Fralin Life Science-associated faculty member, used brome mosaic virus to study how viral infections start. He found that the brome mosaic virus stimulates synthesis of host lipid cells called phosphatidylcholine at the sites where viral replication occurs, and that by inhibiting its synthesis, the viral replication stopped.

3- Polio Virus May Cure Brain Cancer Thanks To Genetic Re-Engineering

4- Mutated Polio Strain mentions the scientists were able to neutralize the infection using "blood plasma taken from people with healthy immune systems who had been immunized against polio."

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