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Review

Post-poliomyelitis syndrome as a possible viral disease

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SUMMARY

This review summarizes current concepts on post-polio syndrome (PPS), a condition that may arise in polio survivors after partial or complete functional recovery followed by a prolonged interval of stable neurological function. PPS affects 15–20 million people worldwide. Epidemiological data are reported, together with the pathogenic pathways that possibly lead to the progressive degeneration and loss of neuromuscular motor units. As a consequence of PPS, polio survivors experience new weakness, generalized fatigue, atrophy of previously unaffected muscles, and a physical decline that may culminate in the loss of independent life. Emphasis is given to the possible pathogenic role of persistent poliovirus infection and chronic inflammation. These factors could contribute to the neurological and physical decline in polio survivors. A perspective is then given on novel anti-poliovirus compounds and monoclonal antibodies that have been developed to contribute to the final phases of polio eradication. These agents could also be useful for the treatment or prevention of PPS. Some of these compounds/antibodies are in early clinical development. Finally, current clinical trials for PPS are reported. In this area, the intravenous infusion of normal human immunoglobulins appears both feasible and promising.

1. Introduction

Paralytic poliomyelitis is caused by infection with the poliovirus and dates back to the eighteenth Egyptian dynasty (c. 1543–1292 BC), or earlier. Large epidemics occurred in the early nineteenth century, but with the introduction of vaccination, the number of new cases dropped dramatically in the 1960s. Today, paralytic poliomyelitis has been essentially forgotten, both by people and the medical community. Nevertheless, large numbers of individuals who have survived the illness are alive today in the world. Resisting vaccination efforts, scattered poliomyelitis cases continue to surface each year in a few countries. These cases are holding back or hindering the expected goal of polio eradication.[1,2]

Abrupt asymmetrical flaccid paralysis is the clinical manifestation of anterior poliomyelitis, as acute polio may also present with other manifestations. After the acute attack, survivors experience a period of neurological and functional recovery followed by a phase of almost complete stability. During the stability phase, many patients become over-achievers, working hard both physically and emotionally to overcome their disabilities.[3] In 1875, new weakness, muscle atrophy, and fatigue occurring years after poliomyelitis were recognized by the French neurologist Raymond and his famous peer Jean-Martin Charcot.[4] Since the 1970s, a multitude of cases have been published worldwide, and in the 1980s, post-polio syndrome (PPS) was accepted as a new medical condition.[5,6] Whereas the late consequences of polio (i.e., biomechanical decline such as scoliosis, kyphosis, arthrosis, etc.) can manifest for any survivor of polio,[7] PPS (i.e., neurological decline) may develop in 20–75% of polio survivors, 15 to >60 years after acute paralytic or non-paralytic disease.[8–16]

Common manifestations of PPS include central and peripheral fatigue, muscle atrophy and weakness, musculoskeletal pain, and new disabilities that may also affect many other body functions such as respiration, the digestive tract, voiding, and sleep. It is estimated that there are 15–20 million polio survivors worldwide. Medicine has been slow to address the morbidity and cost of chronic disease and the growing number of elderly persons.[17] However, today PPS is recognized as the most prevalent disease of

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anterior horn motor neurons (http://www.post-polio.org). The US Social Security Disability Insurance (SSDI) program first acknowledged the late effects of poliomyelitis in 1987 (http://www.postpolioinfo.com). Subsequently, PPS was recognized by the European Parliament,[18] and a specific code for PPS (G14) was adopted by the International Classification of Diseases 2010.[19] In 2012, the problems of polio survivors were presented at the Commonwealth Parliament of Australia[20] and in the Italian Parliament.

In spite of the numbers of affected patients, the aetiology and pathogenesis of PPS are still unclear and no effective therapy is available.[21] Current treatments are based on a conservative approach consisting of exercise, avoidance of muscular overuse, orthoses, and assistive devices (http://www.post-polio.org; http://www.polioplace.org). Diagnosis is based on the medical history and clinical–instrumental examination, as well as on the exclusion of medical conditions other than polio that could explain the symptoms.[22]

2. Structure and genome of polioviruses

The three poliovirus (PV) types (PV1, 2, 3) belong to Enterovirus group C of the *Picornaviridae* family. Virions are non-enveloped icosahedral particles, about 28 nm in diameter. As shown in Figure 1, the genome consists of a single-stranded, positive-sense RNA of about 7.4 kb, with a 22-aa virus-encoded protein (viral protein genome-linked, VPg) covalently linked to the 5′ end.[23] The 5′ non-translated region (approximately 740 nt) has a complex secondary structure consisting of region 1 (regulatory) and region 2 that represents the internal ribosome entry site (IRES). The single open reading frame encodes a polyprotein of about 2200 amino acids that is processed to yield four different capsid proteins (viral proteins VP1, VP2, VP3, and VP4) and seven non-structural proteins (2A (protease), 2B (endoplasmic reticulum localization, viroporin), 2C (ATPase, helicase), 3A (Golgi localization), 3B (VPg), 3C (major viral protease), and 3D (RNA-dependent RNA polymerase). The 3′ non-translated region contains a variable poly-A tail of approximately 70 nt.

Recently, human enteroviruses have been re-classified, based largely on genome structure (Table 1). Excluding rhinoviruses, the Enterovirus genus contains four species of human pathogen (A, B, C, and D). PVs belong to the C species. Humans are the only natural host of PVs. Many different human cell types express the CD155 poliovirus receptor[24] that is essential for infection, possibly together with a co-receptor. All enteroviruses are quite resistant in the environment. Transmission occurs through the faecal–oral route and the respiratory route.

3. Acute poliovirus infection: poliomyelitis

Poliomyelitis is an acute disease caused by infection with any one of the three PV serotypes. The virus multiplies in the pharynx and intestine for 1 to 3 weeks. In the majority of cases, virus spread is contained by the local immune response. Thus, over 95% of infections are either asymptomatic or characterized by flu-like symptoms. In 5% of cases, a viraemia phase occurs and virus can cross the blood–brain barrier by ways that are possibly independent from the expression of poliovirus receptor (PVR).[24] Upon arrival in the central nervous system (CNS), patients may develop a meningitis-like illness characterized by fever with pharyngitis, myalgia, anorexia, nausea, vomiting, headache, and neck stiffness. The onset of spinal poliomyelitis is associated with myalgia and severe muscle spasms, with the subsequent development of an asymmetrical (predominantly lower limb) flaccid weakness that becomes paretic within a few days.[23] A purely bulbar form with minimal limb involvement may also occur. This form of polio has a particularly high mortality because of vasomotor disturbances and other complications (hypertension, hypotension and circulatory collapse, autonomic dysfunction, dysphagia, dysphonia, and respiratory failure).

In the epidemics of the last century, most paralytic cases were attributed to PV1. Epidemics of polio occurred throughout the USA and Europe, including one severe outbreak from 1943 to 1956 in which 400 000 people were infected, resulting in 22 000 deaths. The introduction of Jonas Salk's inactivated polio vaccine (1955) and Albert Sabin's live oral vaccine (1961) dramatically reduced the number of cases. In 1965, only 61 infections were reported in the USA and by 1991 the disease had been virtually wiped out in the Western Hemisphere. The massive MECACAR immunization program, launched in 1995, started to rapidly clear virus from the 18 countries with residual poliomyelitis, spanning two continents. In most of the world where the four core eradication strategies were introduced, the numbers of both cases of polio-paralyzed children and polio-infected countries began to fall rapidly. The sense that eradication might soon be inevitable was reinforced in 1999 by the global eradication of type 2 wild poliovirus. This suggested that the eradication of the other serotypes would follow quickly in all countries.[25]

New cases of poliomyelitis due to PV1 and PV3 have now been reduced to a few hundred per year. In 2014, cases were found in scattered countries such as Pakistan, Afghanistan, Nigeria, Somalia,

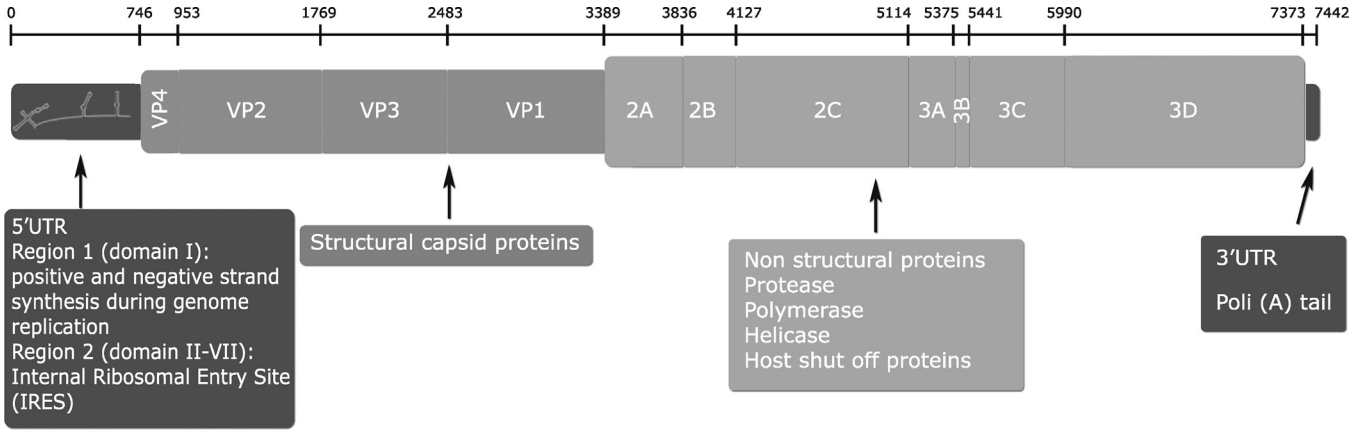

Figure 1. Schematic diagram of the poliovirus genome. Structural and non-structural virus-coded proteins are indicated. The 5′ non-translated genome terminus (5′-UTR) regulates virus replication and plays a fundamental role in the synthesis of viral proteins.