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Rare adverse events associated with oral poliovirus vaccine in Brazil

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Abstract

Oral poliovirus vaccine (OPV) developed by A. Sabin has been effectively used to control poliomyelitis in Brazil, and the last case with the isolation of a wild poliovirus strain occurred in March 1989. Although the vaccine controlled the circulation of wild strains and poliomyelitis cases associated with these strains were not detected during the last eight years, rare cases classified as vaccine-associated paralytic poliomyelitis (VAPP) have been detected. Molecular characterization studies of poliovirus strains isolated from VAPP cases and from healthy contacts have confirmed that the isolates are derived from the Sabin vaccine strains and also detected genomic modifications known or suspected to increase neurovirulence such as mutations and recombination. The molecular characterization of polioviruses isolated during the last eight years from paralysis cases classified as Guillain-Barré (GBS) syndrome and transverse myelitits (TM), and from facial paralysis (FP) cases also confirmed the vaccine origin of the strains and demonstrated mutations known to increase neurovirulence. Analysis of the epidemiologic data of these GBS, TM and FP cases demonstrated that in most of them the last OPV dose was given months or years before the onset of the disease and the isolation of the polioviruses. The temporal association between the isolation of these strains and the GBS, TM and FP suggested that the Sabin vaccine-derived poliovirus strains could also rarely trigger the diseases.

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Introduction

Poliomyelitis, a paralytic and sometimes fatal disease of humans, is caused by poliovirus (1-3). The disease has been effectively controlled in many parts of the world by the use of two vaccines: the inactivated poliovirus vaccine (IPV) developed by Jonas Salk (4) and the oral poliovirus vaccine (OPV) developed by Albert Sabin (1,2,5,6). OPV, the most widely used vaccine, consists of three attenuated poliovirus strains (Sabin 1, 2 and 3), one for each serotype. The three attenuated Sabin vaccine strains were all derived from wild-type isolates by serial passage in monkey tissue *in vitro* and *in vivo* under a variety of conditions, which differed for each of the three serotypes (1,2). Mass immunization campaigns with OPV were a major factor influencing the success of eradication of wild indigenous poliovirus in Brazil and in the Americas. Although OPV is important in the control of poliomyelitis and in the circulation of wild strains, one disadvantage associated with OPV is the rare occurrence (5-8) of vaccine-associated paralyt-

ic poliomyelitis (VAPP) cases. Rare VAPP cases occur mainly with the type 2 and 3 strains and less frequently with the type 1 strain. The larger number of attenuating mutations in the P1/Sabin strain is probably reflected by the higher safety of this strain in comparison to type 2 and 3 strains (8). Knowledge about the molecular basis of attenuation of vaccine strains and the mechanisms of reversion to neurovirulence (1-3,8-11) may allow rational improvement of vaccines and production methods, provide alternative models for vaccine safety tests on transgenic mice and/or molecular approaches (12-15), and avoid expensive safety testing of vaccine pools in primates.

Poliomyelitis in Brazil and other countries

An international effort is underway to eradicate poliomyelitis from the planet by the year 2000 (16). Surveillance for wild poliovirus circulation is crucial to this effort. Today, poliomyelitis is very rare in all developed and many developing countries (17,18). Although the last poliomyelitis case with the isolation of wild indigenous poliovirus in the Americas occurred in Peru in August 1991 (17,19-21), poliomyelitis continues to be a serious threat to children in parts of Asia, Africa and Europe (18,22). Molecular epidemiologic studies have been very important in poliovirus surveillance in several countries (18,22-29), and have demonstrated that although the incidence of cases caused by wild polioviruses showed a major decline in the planet (17,18) with the use of OPV, the circulation of wild strains continues in many regions.

Despite these worldwide impressive gains in the control and reduction of poliomyelitis cases associated with wild polioviruses, rare VAPP cases have been detected in several countries (30-39). Molecular epidemiologic studies have confirmed that the polioviruses isolated from these rare cases are derived from the Sabin vaccine strains, and also detected genomic modifications such as mutations and recombination (38,40-61). Although reverting mutations in attenuating determinants, suppressor mutations, mutations in antigenic sites and genomic recombination have been observed in strains isolated from VAPP cases, the observation of similar genomic modifications in strains isolated from healthy vaccinees (8,9,11,38,43, 44,48-50,53,56,62-69) has supported the view that host factors are also involved in the establishment of the disease. Specific biochemical characteristics of host factor(s) involved in the replication of the virus in human cells may increase the replication level of the virus in certain patients (8). Host factors such as immune deficiency may also be involved in the establishment of the disease in certain cases, and may be related to heritable immunodeficiencies, immunodeficiencies caused by protein-calorie malnutrition, deficiency in vitamin A, or HIV infection (7,33,34,39,70-75). Intramuscular injections within 30 days of exposure to OPV through vaccine or contact with a recent vaccinee might also be a risk factor for VAPP cases (76). Other host factors and other pathological conditions could also be involved.

OPV has also been efficiently used to control poliomyelitis in Brazil and the last case with the isolation of a wild poliovirus strain occurred in March 1989 (77). Molecular epidemiologic studies have been very important in poliovirus surveillance in our country (77-79). Isolation of polioviruses in cell cultures and characterization of the serotype using hyperimmune equine sera (80), molecular hybridization (81), PCR (82) and nucleotide sequencing (23,83) have been important in the characterization of the isolated polioviruses. Although the Sabin vaccine strains have been efficiently used in the control of poliomyelitis in Brazil, rare VAPP cases still occur. Molecular biology studies have confirmed that the polioviruses isolated from these rare cases are derived from

the Sabin vaccine strains (84-87), and have also detected genomic modifications known to increase neurovirulence.

Genomic characterization of polioviruses isolated from vaccine-associated paralytic poliomyelitis cases in Brazil

Polioviruses isolated from fecal samples from VAPP cases in Brazil were characterized as related to the Sabin vaccine strains by molecular hybridization and PCR (77,84-86). Partial sequencing of the genome of some of these strains confirmed the vaccine origin (84-87) and also demonstrated genomic modifications. Most of the strains isolated from VAPP cases presented mutations known to increase the neurovirulence (84,85) and several strains proved to be recombinants (87). Vaccine/vaccine and vaccine/non-vaccine strains were identified among the recombinants isolated (87). Molecular studies of polioviruses isolated from fecal samples and from the central nervous system of VAPP cases in other countries have suggested that not only mutations, but also genomic recombination could increase the neurovirulence of the Sabin vaccine strains and/or provide some advantages for virus replication (38,52,54,57-60). Mutations known to increase neurovirulence and recombination have also been identified in the polioviruses isolated from healthy contacts of VAPP cases in Brazil (84,87). Interestingly, the polioviruses isolated from VAPP cases and from their healthy contacts presented the same serotype, the same nucleotide sequences and the same mutations in the regions analyzed, confirming the transmission of the strains. The isolation of poliovirus strains from VAPP cases and from healthy contacts in Brazil presenting similar genomic modifications (84,87), and known or suspected to increase neurovirulence, supports the idea that host factors are also involved in the establishment of poliomyelitis (8,84). Although some strains isolated from VAPP (84,86) cases maintained important attenuating determinants, one possibility is that other mutations occurred in the partially sequenced genome, which were able to increase neurovirulence and/or provide some advantage for virus multiplication in the patient.

Genomic characterization of polioviruses isolated from Guillain-Barré syndrome and from transverse myelitis cases in Brazil

Some studies in other countries have suggested that paralysis observed during the Guillain-Barré syndrome and transverse myelitis might also be rarely triggered or caused by Sabin vaccine-derived poliovirus strains (88-90). Interestingly, several poliovirus strains were isolated (77) from fecal samples of paralysis cases in Brazil classified as Guillain-Barré syndrome (91) and transverse myelitis. Polioviruses isolated from these cases were characterized as related to the Sabin vaccine strains by molecular hybridization and PCR (77,85,92-94). Partial sequencing of the genome of some of these strains confirmed the vaccine origin and also demonstrated mutations known to increase neurovirulence (85,92). Analysis of the epidemiological data for these cases demonstrated that in most of them the last Sabin vaccine dose was given months or years before the onset of the disease and the isolation of the polioviruses (85,92-94). The temporal association between the isolation of these strains from fecal samples and the Guillain-Barré syndrome or transverse myelitis in Brazil suggested that the Sabin vaccine-derived poliovirus strains could also rarely trigger these diseases. In a recent publication (95) poliovirus type 3 was isolated from the brain tissues of a fatal Guillain-Barré syndrome case observed in another country, and serodifferentiation of this poliovirus within the same type 3 showed a

vaccine-like pattern. Poliovirus was detected in the cytoplasma of brain tissue and also in the intranuclear parts of ganglion and glia cells by an immunofluorescent technique.

Genomic characterization of polioviruses isolated from facial paralysis cases in Brazil

Among the several neurologic syndromes investigated by the Brazilian program for the eradication of poliomyelitis, with the objective of detecting wild poliovirus strains, peripheral facial paralysis was included until 1992 (96). Wild polioviruses were still isolated during the 1987-1989 period from fecal samples of facial paralysis cases (96). The isolation of wild strains from facial paralysis cases suggested that Sabin vaccine-derived poliovirus strains could also rarely cause facial paralysis. The genome of some poliovirus strains isolated from fecal samples of facial paralysis cases and characterized by molecular hybridization and PCR as Sabin vaccine-related strains was partially sequenced (85,92). Nucleotide sequence analysis confirmed the vaccine origin of the isolates and also identified mutations known to increase neurovirulence (85,92). The temporal association between the isolation of these strains and the facial paralysis suggested that the Sabin vaccine strains could also, in rare cases, cause this disease.

Discussion, conclusions and perspectives

Molecular characterization studies of poliovirus strains isolated in Brazil from rare paralytic poliomyelitis cases and also from cases classified as Guillain-Barré syndrome, transverse myelitis and facial paralysis demonstrated that the isolates are derived from the Sabin vaccine strains (77-79,84-87,92-94), and that most of the isolates analyzed present genomic modifications known or suspected to increase neurovirulence (78,79, 84,85,87,92). The temporal association between the isolation of these strains and the Guillain-Barré syndrome, transverse myelitis and facial paralysis in Brazil suggested that these diseases could also be triggered in rare cases by Sabin poliovirus vaccine strains. The isolation of polioviruses derived from the Sabin vaccine strains (and not from wild strains) from rare paralysis cases classified as poliomyelitis, Guillain-Barré syndrome, transverse myelitis and facial paralysis in Brazil during the last 7 years confirms the efficiency of the Sabin vaccine strains in the control of the circulation of wild poliovirus strains, but shows that rare adverse events are associated with the use of the oral poliovirus vaccine.

Since wild poliovirus is still endemic in many regions of the planet (18,22), there is always the threat of importation of these strains from other countries. Although rare adverse events are associated with the use of OPV in Brazil, the circulation of wild strains in other countries demonstrates the importance and the need to maintain immunization against poliomyelitis. Since the Sabin vaccine strains may increase neurovirulence by genomic modifications during multiplication in the vaccinee and after transmission to contacts, there is also always the possibility of the appearance of neurovirulent strains derived from the Sabin vaccine strains (8,9,11,38,42-44,46-60). Thus, these studies demonstrate that immunization is important not only to avoid the possibility of spreading imported wild strains, but also to control and prevent the possible transmission and circulation of Sabin vaccine-derived mutant strains with an increased neurovirulence for humans (84,87).

Studies in other countries have demonstrated the capacity of Sabin vaccine-derived poliovirus strains to cause a persistent infection in human neuroblastoma cells (97); nucleotide sequence analysis demonstrated mutations in these strains (98,99). More recent studies demonstrated that poliovirus

can persistently infect primary cultures of human fetal brain cells (100). Several lines of evidence have suggested that polioviruses and other enteroviruses might cause a persistent infection in humans and chronic diseases of the central nervous system (101-105). The isolation of polioviruses derived from the Sabin vaccine strains from patients presenting paralysis after the onset of motor deficiency and in which the last vaccine dose was given months or years before the onset of disease (84,85,92-94) suggested transmission or a persistent infection. Although most poliovirus infections are silent (106), there is always the possibility of transmission of Sabin vaccine-derived strains to other individuals that may occasionally develop the disease (84). The transmission of Sabin vaccine-derived strains with many genomic modifications was confirmed by nucleotide sequencing of strains isolated from VAPP cases and from healthy contacts (84,87).

It would also be interesting in the future to study the possibility of a persistent infection and excretion of Sabin vaccine-derived strains in Brazilian patients presenting poliomyelitis, post-polio syndrome, Guillain-Barré syndrome, transverse myelitis, and facial paralysis, and also in healthy contacts and healthy vaccinees. Even if persistent infection and excretion of the vaccine strains are rare, they could lead to the excretion of polioviruses for long periods of time and to the possibility of the transmission of highly mutated strains to other individuals. Most polioviruses derived from the Sabin vaccine strains have been isolated from the stool of vaccine-associated cases and of healthy vaccinees (8). It would be interesting to study if genomic modifications able to increase neurovirulence, and detected in Sabin vaccine-derived strains isolated from stool (and/or CNS) also occur during multiplication in the oropharynx of vaccinees. Although different host factors might also be involved in the establishment of the disease, it would be important to evaluate the immune status (71-75,84,95,107) of Brazilian patients presenting VAPP, Guillain-Barré syndrome, transverse myelitis and facial paralysis.

Recent studies in Brazil (108) have indicated the susceptibility of dogs to infection with human enteroviruses, including polioviruses. It would be interesting to infect dogs, or even transgenic mice (109,110) susceptible to polioviruses by the oral route to study the possibility of infection and persistence of these viruses in other animals in nature, and to determine if genomic modifications known to increase neurovirulence also occur during multiplication of the Sabin vaccine strains in these animals, and if these viruses are eventually efficiently excreted.

These studies demonstrate that molecular epidemiologic studies on poliomyelitis and other paralytic diseases possibly also caused by polioviruses are still very important and could contribute to a better understanding of poliovirus biology and the rare adverse events associated with OPV, which could in turn help to eliminate or reduce these rare adverse events.

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