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Seroprevalence of antibodies against the three serotypes of poliovirus and IPV vaccine response in adult solid organ transplant candidates

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ABSTRACT

Objectives: To assess the prevalence of protective antibody titers to polioviruses in adults candidates for solid organ transplant (SOT), and to assess the immunogenic response to inactivated polio vaccine in this population.
Methods: The study included SOT candidates referred to Immunization Reference Centre of Evandro Chagas National Institute of Infectious Diseases from March 2013 to January 2016. It was conducted in 2 phases. The first one, a cross-sectional seroprevalence study, followed by an uncontrolled analysis of vaccine response among patients without protective antibody titers at baseline. Antibody titers to poliomyelitis were determined by microneutralization assay.
Results: Among 206 SOT candidates included, 156 (76%) had protective antibody titers to all poliovirus serotypes (95% CI: 70–81%). Proven history of oral vaccination in childhood was not associated with higher seroprevalence of protective antibody. In 97% of individuals without protective antibody titers at baseline, there was adequate vaccine response with one dose of inactivated polio vaccine.
Conclusions: A relevant proportion of adult candidates for SOT does not have protective titers of antibodies to one or more poliovirus serotype. One dose of inactivated vaccine elicited protective antibody titers in 97% of these subjects and should be routinely prescribed prior to SOT.

1. Introduction

At the beginning of the 20th century, poliomyelitis was an epidemic disease that caused paralysis in many thousands of children, especially in countries with temperate climate, resulting in a public health problem with enormous psychosocial impact. With the advent of specific vaccines, inactivated (1955) and attenuated (1961), the disease has been gradually eliminated in most of the countries [1].

In 1988, following the success of polio control in the Americas, the World Health Organization (WHO) launched the Poliomyelitis Eradication Initiative, recommending the oral attenuated vaccine in the children's basic immunization schedule and in annual campaigns (National Immunization Days – NIDs) [2]. The oral vaccine has favorable characteristics for large-scale use, such as ease of application, low cost and transmission of the vaccine virus to contacts (secondary vaccination) [3,4]. This strategy resulted in a marked fall in the number polio cases in the world (from 350.000 cases in 1988 to 22 in 2017) and in the elimination of poliovirus serotype 2 in 1999 [5,6].

Despite this great progress, the eradication of the disease has not yet been achieved. In the final step of polio eradication, it is essential to maintain adequate immunity in the population even in regions where the disease has already been eliminated. The persistence of endemic areas for wild poliovirus poses a risk of dissemination and reintroduction of the disease in all parts of the world. In 2013, wild poliovirus 1 was isolated from several environment samples in Israel, without the occurrence of polio cases [7–9]. In 2014, wild poliovirus 1 was isolated from sewage samples collected at Viracopos International Airport in Brazil (Campinas, São Paulo), with genetic sequencing close to a strain isolated from a case in Equatorial Guinea [10]. These events show the potential for reintroduction and silent dissemination of the virus.

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In addition, the vaccine-derived poliovirus (VDPV) has the potential for neurovirulence and transmissibility similar to the wild-type virus [11]. The identification of an increasing number of immunodeficient patients with sustained shedding of VDPV for months to decades shows that the risks of using the attenuated vaccine may extend over a prolonged period of time, even after the overall discontinuation of oral vaccine [12]. Therefore, the attenuated vaccine, which was one of the pillars in disease control, should be replaced by inactivated vaccine to reduce the risk of VDPV chronic elimination by immunodeficient subjects, thus contributing to polio eradication [11].

In most cases of immunodeficiency-related vaccine-derived poliovirus (iVDPV), the immunodeficiency has been diagnosed only after the development of paralysis [12]. In addition, approximately 7% of iVDPV cases were infected by vaccinated contacts [13]. This reinforces the need to identify susceptible individuals, especially in groups of immunodeficient patients in regions where the oral vaccine is still used.

Solid organ transplant (SOT) recipients represent a growing population living under perennial immunosuppression. Recommendations for polio vaccination of adult SOT candidates and recipients are not uniform among guidelines from different countries and medical societies. Most of them recommend routine polio vaccination only for children and for adult transplant candidates/recipients belonging to high risk groups, such as travelling to a polio endemic area or with occupational risk of exposure [14–19]. However, data on seroprevalence of protective antibodies among SOT recipients are scarce. In fact, the only study which addressed this issue in adult SOT recipients, found that only 3% of renal transplant recipients had protective titers of antibodies against all three serotypes of polioviruses [20]. Such low levels of protective antibodies could render this growing group of patients vulnerable to reemergence of poliovirus infections and to chronic vaccine derived poliovirus infection. Moreover, hypogammaglobulinemia, which is the most significant risk factor for prolonged elimination of attenuated poliovirus in individuals with primary immunodeficiency [21], has been reported in 16–63% of SOT recipients. These data highlight the need of further studies assessing the seroprevalence of protective antibodies to poliovirus in SOT candidates and recipients in order to guide the preventive strategy in this population, as part of the international efforts to poliomyelitis eradication in the world.

The main objectives of this study were to assess the prevalence of protective antibodies titers to the three serotypes of poliovirus and to determine the IPV (inactivated polio vaccine) response in adult SOT candidates.

2. Methods

2.1. Study design

A cross-sectional study was conducted to determine the prevalence of protective antibodies against poliovirus in adult SOT candidates, followed by a one arm follow-up assessment of vaccine immunogenic response in candidates with low or undetectable initial antibody titers to at least one poliovirus serotype at baseline.

2.2. Population

This study consecutively included SOT candidates, aged 18 years or older, attended at the Reference Center for Special Immunobiologicals (CRIE) of the Evandro Chagas National Institute of Infectious Diseases (INI- Fiocruz) in Rio de Janeiro (Brazil), between March 2013 and January 2016. CRIE is a public reference center of the National Immunization Program that receives patients from public and private institutions for immunizations of special groups.

2.3. Procedures

At the first visit, after obtaining informed consent, a standardized questionnaire with information about clinical, vaccination and family history was filled in. Data collected included age, sex, living in rural area at infancy, OPV vaccination at childhood, number of siblings, contact with polio cases during life, number and age of children, OPV vaccination of children, living with children <5 years of age at the date of the first visit, underlying organ disease, comorbidities such as hepatitis C infection, HIV infection, diabetes mellitus, current use of immunosuppressive drug, hemotransfusion, smoking and, body mass index (BMI). For renal transplant candidates, information about type and duration of renal replacement therapy and use of erythropoietin was also collected. For hepatic transplant candidates, MELD score and Child-Pugh were calculated.

All volunteers, at the first visit, were submitted to blood collection for the following tests: serology for poliovirus, hemogram and albumin. Serologies for hepatitis C and HIV were included in individuals with unknown serological status. In liver transplant candidates, prothrombin time (INR) and serum levels of bilirubin and creatinine were additionally determined.

Patients without protective polio antibody titers received one to three dose of IPV with a minimum interval of 30 days between doses. Immunological response was checked 30 days after each dose of vaccine. The IPV vaccine used in this study was produced by Sanofi Pasteur (Lyon, France) and was distributed by Brazilian Ministry of Health's National Immunization Program for special groups.

2.4. Endpoints and laboratory method

The primary endpoint was seroprevalence of poliovirus protective titers. The secondary endpoint was vaccine response among candidates who at baseline did not have protective titers of antibodies to at least one poliovirus serotype. Both these outcomes were defined by detection of titers $\geq$1:8 of antibodies against all three poliovirus. Antibody titers against poliovirus 1, 2 and 3 were determined by microneutralization test, according to the protocol of the World Health Organization (12), at the Enterovirus Laboratory (WHO Regional Reference Laboratory), at Oswaldo Cruz Institute (Fiocruz, Rio de Janeiro, Brazil). Neutralization titers were expressed as the reciprocal of the highest serum dilution capable of reducing 50% of the cytopathic effect in cells. The sera were serially diluted from 1:8 to 1:512.

2.5. Statistical analysis

Categorical variables were described by their absolute counts and percentages. Numeric variables were described by their median and interquartile range. Prevalence of protective antibodies titers was estimated with its 95% confidence interval (95%CI). The central tendency of the antibody titers to each poliovirus serotype was described by their geometric mean and standard deviation.

The year of birth was categorized according to the historical milestones of polio control in Brazil: 1955, year when immunization with inactivated vaccine began; 1962, year of introduction of oral attenuated vaccine; 1973, year of implementation of the Brazilian National Immunization Program, and 1980, year of start of routine annual national vaccination campaigns.

Data analysis was conducted with R-project (R Foundation) version 3.3.1 (2016) [22].