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ORIGINAL ARTICLE

Low Rates of Poliovirus Antibodies in Primary Immunodeficiency Patients on Regular Intravenous Immunoglobulin Treatment

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Abstract

Purpose Poliovirus has been nearly eliminated as part of a world-wide effort to immunize and contain circulating wild-type polio. Nevertheless, poliovirus has been detected in water supplies and represents a threat to patients with humoral immunodeficiencies where infection can be fatal. To define the risk, we analyzed antibodies to poliovirus 1, 2, and 3 in serum samples collected over a year from patients with primary immunodeficiency diseases (PID) on regular intravenous immunoglobulin (IVIG) replacement.
Methods Twenty-one patients on regular IVIG replacement therapy were evaluated: Twelve patients with common variable immune deficiency (CVID), six with X-linked agammaglobulinemia (XLA), and three with hyper IgM syndrome (HIGM). Over 1 year, four blood samples were collected from each of these patients immediately before immunoglobulin infusion. One sample of IVIG administered to each patient in the month before blood collection was also evaluated. Poliovirus antibodies were quantified by seroneutralization assay.
Results All IVIG samples had detectable antibodies to the three poliovirus serotypes. Despite that, only 52.4, 61.9, and 19.0% of patients showed protective antibody titers for poliovirus 1, 2, and 3, respectively. Only two patients (9.5%) had protective antibodies for the three poliovirus serotypes on all samples. Most patients were therefore susceptible to all three poliovirus serotypes.
Conclusions This study demonstrates the need for ongoing vigilance regarding exposure of patients with PID to poliovirus in the community.

Keywords Primary immunodeficiency diseases · poliovirus antibodies · intravenous immunoglobulin · Global Polio Eradication Initiative · antibody deficiency · common variable immunodeficiency · X-linked agammaglobulinemia · Hyper IgM syndrome

Introduction

As recently as 70 years ago, polio was one of the most feared diseases of childhood. After the introduction of the vaccines, rates of polio fell, however, in 1988 when the Global Polio Eradication effort began, over 1000 children developed paralysis from polio per year. In just the first month of 2018, two cases were reported in Afghanistan and Pakistan, demonstrating the ongoing need for surveillance and outreach efforts directed at vaccination [1].

Patients with PID have increased susceptibility to CNS infections with wild type poliovirus as well as the attenuated vaccine strains [2–8]. This susceptibility has been described primarily in patients with humoral defects. Common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), and hyper IgM syndrome (HIGM) are primary immunodeficiency diseases (PID) that share impairment of antibody

Patrícia M. Fontes is deceased. This paper is dedicated to her memory.

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production where fatal infections with enteroviruses, including poliovirus, have been described [9]. The main therapy for patients with humoral deficiencies is the replacement of antibodies with regular infusion of intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG), which contains diverse antibodies including those for infectious diseases preventable by vaccines [10]. Immunologists have hypothesized that treatment with immunoglobulin replacement has led to decreased incidence of enteroviral infections in patients with PID over time; however, data do not support such a change in incidence [11]. Poliovirus infection in PID patients has not been studied prospectively, but cases still occur [3, 4]. This population is pivotal for poliovirus eradication efforts for two reasons. (1) Patients with PID are susceptible to fatal meningoencephalitis or flaccid paralysis with live attenuated vaccine strains [7]. Thus, these patients are not vaccinated and represent a potential reservoir of non-immune at-risk people. (2) Patients with PID can excrete poliovirus for extremely prolonged periods representing a potential source of wild-type revertants capable of causing infection in the general population [12–16]. Therefore, there is a need for additional information regarding the susceptibility of patients on immunoglobulin replacement to poliovirus.

Immunoglobulin products vary in many aspects that can impact on the quality and quantity of antibodies they contain [17, 18]. We have recently shown that IVIG contains variable levels of antibodies to vaccine-preventable diseases. There is variability in different batches from the same manufacturer due to changes in donors and variability in PID patients and their production and/or catabolism [19, 20].

The Global Polio Eradication Initiative (GPEI) aims for complete eradication of poliomyelitis although there is still work to be done [9]. The end-game will require meticulous attention to potential reservoirs and transmission cycles, settings where patients with PID may be a consideration. To assist in understanding the risks to patients with PID, we defined serum levels of poliovirus types 1, 2, and 3 antibodies in 84 serum samples collected over a year from patients with humoral immunodeficiencies on regular IVIG replacement. We found that limited protection was afforded by IVIG replacement and most patients were susceptible to one or more serotypes.

Methods

Subjects

This was a prospective study approved by the Ethics Committee of the Federal University of São Paulo (protocol number 0480/08), in Sao Paulo, Brazil. Informed consent was obtained from all individual participants included in the study. Twenty-one patients (12 CVID, 6 XLA, and 3 HIGM) on regular IVIG replacement therapy at the Immunologic Outpatient Clinic of the Federal University of Sao Paulo, in Sao Paulo, Brazil, were evaluated. Four samples were collected over a 1-year time span from each of these patients immediately before immunoglobulin infusion, totaling 84 samples. Serum was separated and stored at − 80 °C until testing for total IgG and poliovirus antibody levels. A sample of the IVIG administered to each patient in the month before blood collection was also stored at 4 °C until analysis. All patients had been under IVIG replacement for over a year. IVIG intervals, IVIG dose, and IgG trough levels were assessed.

A control set of samples was used from 41 adult controls who had been immunized for poliovirus during childhood. Clinical and demographic information were collected on each patient using a structured instrument.

Detection of Antibodies

Quantification of poliovirus antibodies was performed using a seroneutralization assay with vaccine poliovirus serotypes instead of wild poliovirus serotypes, as previously described [21]. Results of neutralization with vaccine strains were compared with those with wild strains and sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for the three viral serotypes were calculated. Results showed a very close approximation between the results with the vaccine strain and the gold standard with a sensitivity of 96.7, 100, and 96.4% and a specificity of 71.4, 100, and 78.6% for poliovirus 1, 2, and 3, respectively.

Each serum specimen was tested for all three poliovirus types in triplicate using a microneutralization assay set up at our research laboratory. Serial dilutions of serum (from 1:8 to 1:1024) were incubated with 100 TCID50 of poliovirus types 1, 2, and 3 at 37 °C for 2 h before HEp-2 cells were added to each well.

Serological results were reported as titers of the serum dilution that exhibited 50% inhibition. Seropositivity was defined as a reciprocal titer of at least 1:8 [21].

Statistical Analysis

Categorical variables were analyzed using Chi-squared test. Spearman's rank correlation coefficient was used to verify association between reciprocal poliovirus antibody titers and other variables. Level of significance was set at $p < 0.05$. Statistical analysis was performed using Biostat version 5.0 (Institute Mamirauá, AM, Brazil).

Results

Patient Characteristics

The 21 patients with PID were followed for a median time of 13.9 months (range, 11.5–15.9). The median age of the

patients was 20.7 years (range, 3–42) and 11 (52.4%) were male. IVIG was administered at intervals of 32 days (range, 21–49 days). The median dose of IVIG was 550 mg/kg (range, 340–760), with a median serum trough IgG level of 791 mg/dL (range, 460–1220). Over the study, the IVIG dose remained unchanged for each patient. Most patients received more than one IVIG commercial preparation during the study, as dictated by the government. The IVIG products were as follows: Octagam® (Octapharma Pharmazeutika) in 42/84 (50.0%), Flebogamma 5%® (Grifols) in 23/84 (24.4%), Tegeline® (LFB Biomedicaments) in 8/84 (9.5%), Vigam® (BPL Bio Products Laboratory) in 5/84 (5.9%), Endobulin® (Baxter) 4/84 (4.8%), and Blausiegel ® (Korea Green Cross Corporation) in 2/84 (2.4%) of analyzed samples.

Of the 21 PID patients, 17 (81%) received at least one dose of live polio vaccine before PID diagnosis: six XLA, nine CVID, and two HIGM patients. For six of them, the number of live polio vaccine was described in the patients' files, with a median of 11 doses (range, 2–17). No information on previous live polio vaccine was available from three patients (two CVID and one HIGM). Only one patient did not receive live polio vaccine; after CVID diagnosis, she received inactivated polio vaccine. Of interest, none of the PID patients in the study had adverse events following live polio vaccine.

The median age of the control group was 33.0 years (range, 25 to 39) and 28 (68.3%) were female. Forty individuals reported immunization with oral poliovirus in childhood and one, with inactivated polio vaccine. Among the five controls who kept their first vaccination record card, the median number of poliovirus vaccine doses administered was seven (range, 7–14). The last polio vaccine dose noted on the vaccination cards was 16 years before blood collection for the study protocol.

IVIG provides protection against most vaccine-preventable infections but a study of IVIG-mediated protection for poliovirus has not been previously reported. We examined the proportion of patients with PID who had titers ≥ 1:8 to wild-type poliovirus (Table 1). There was some variability over the 1-year observation period. For poliovirus 1 and 2, the lowest rates of protective titers were 61.9 and 76.2%, respectively, whereas for poliovirus 3, the lowest rate of protective titer was 42.9%. The highest rates of protective titers ranged from 81 to 100%. When we analyzed all patients' data looking for continuous protection over the year, we found the rate of continuously protective antibody titers for poliovirus 1, 2, and 3 was 52.4, 61.9, and 19.0%, respectively. Only two patients (9.5%), one XLA and one CVID, had protective antibody titers for the three serotypes of poliovirus in all four samples collected over the year (Table 1).

We considered whether vaccinated adults, who represent the donor pool for the IVIG products had protective antibody. Among the 41 healthy controls who were tested once, the proportion of individuals with protective poliovirus antibody titers was 87.8% for serotype 1, 91.2% for serotype 2, and 58.5% for serotype 3. When all the three poliovirus serotypes were considered, only 41.5% of healthy controls were immune to all three strains of poliomyelitis (Table 1). The healthy controls had rates of protective antibody on a single time point testings that were comparable to those seen in the patients for a single time point.

We hypothesized that the type of immunodeficiency might impact the rates of protections. When serum samples were grouped according to PID, no differences in frequency of samples with protective poliovirus antibody titers were noted (Table 2). When we examined susceptibility according to serotype, the frequency of susceptibility was higher for serotype 3 when compared to serotypes 1 and 2 (Chi-squared, $p = 0.013$) (Table 1).

There was a weak correlation between total IgG trough levels and polio 2 (Spearman's rank correlation coefficient, $r = 0.265$, $p = 0.022$) and polio 3 (Spearman's rank correlation coefficient, $r = 0.265$, $p = 0.022$) reciprocal antibody titers. No significant correlation was found between total IgG trough levels and polio 1 (Spearman's rank correlation coefficient, $r = 0.192$, $p = 0.099$) reciprocal antibody titers (Fig. 1).

Table 1 Prospective immunological evaluation of patients on regular use of IGIV

Poliovirus serotype		Proportion of samples with poliovirus antibody titers ≥ 1:8				
	Controls	Patients				
	Only sample ($n = 41$) (%)	1st sample ($n = 21$) (%)	2nd sample ($n = 21$) (%)	3rd sample ($n = 21$) (%)	4th sample ($n = 21$) (%)	All 4 samples (%)
1	87.8	95.2	100	61.9	95.2	52.4
2	91.2	90.5	76.2	85.7	100	61.9
3	58.5	42.9	66.7	81.0	81.0	19.0
All tested serotypes	41.5	38.1	52.4	47.6	81.0	9.5

Proportion of samples with protective antibody titers to poliovirus 1, 2, and 3 considering all four samples collected from the 21 PID patients: Chi-squared, $p = 0.013$

Table 2 Frequency of serum samples with poliovirus titers ≥ 1:8 to different poliovirus serotypes according to PID

Poliovirus serotype	XLA (24 samples)	CVI (48 samples)	HIGM (12 samples)	Chi-squared (*p* value)
1	21 (87.5%)	41 (89.6%)	10 (83.3%)	0.860
2	20 (83.3%)	43 (89.6%)	11 (91.7%)	0.682
3	17 (70.8%)	32 (66.7%)	8 (66.7%)	0.934

No significant correlations were found between the time intervals between IVIG administration and polio 1 (Spearman's rank correlation coefficient, $r = -0.122$, $p = 0.269$), polio 2 (Spearman's rank correlation coefficient, $r = -0.155$, $p = 0.159$) or polio 3 (Spearman's rank correlation coefficient, $r = 0.059$, $p = 0.596$) reciprocal antibody titers (Fig. 2).

These data demonstrated that patients with PID might have imperfect protection from wild-type poliovirus or the vaccine strains. We similarly found imperfect protection among healthy controls who are representative of the donor pool for the IVIG products. We therefore tested the antibody levels directly in the IVIG products. Thirty-eight lots from six different commercial IVIG preparations were evaluated. All IVIG samples exhibited positive antibodies for the three poliovirus types. Titers were generally high with 1:64 observed in the majority (Table 3). Therefore, the products themselves have easily detectable levels of antibody to all three serotypes, however, that might not be enough to provide the necessary concentration to maintain poliovirus antibodies until the following IVIG infusion on the majority of occasions.

Discussion

IVIG treatment for patients with primary antibody deficiency represents standard of care and is associated with a reduction in respiratory/severe infections [22, 23]. IVIG is produced from a pool of thousands of donors and it is generally assumed that patients who receive this therapy in recommended doses and intervals are protected from disease caused by common microorganisms, including those preventable by vaccines [19]. Immunoglobulin products can have significant titers to microbes that circulate in the community but are not part of a regular vaccine program such as group B *Streptococcus* [24, 25], West Nile virus [26], RSV [27], and influenza [28]. Yet, titers are known to decline over time after exposure and immunoglobulin products may not have consistently high levels of antibodies to vaccine-preventable disorders [29, 30]. Titers to poliovirus have not been previously examined and the world is poised to achieve a great milestone in public health by eradicating polio forever. Poliovirus serotype 2 has already been eliminated [9]. Achieving this goal will still require intensive efforts as poliovirus can survive in water supplies and patients with PID can excrete virus for prolonged periods, increasing the likelihood of wild-type revertants [31, 32]. Our study has demonstrated that protective titers to poliovirus are found in most patients but that the protection is incomplete and inconsistent from month to month, probably due to the variable-specific antibody kinetics observed in PID patients on IVIG treatment. The rate of susceptibility was more pronounced for serotype 3 despite all IVIG preparations having detectable antibodies to all three serotypes tested in all samples. Different factors might contribute to the poor correlation between total IgG trough levels and poliovirus-specific antibody titers. It is known that IgG subclass half-lives vary, IgG3 being shorter if compared with IgG1, IgG2, and IgG4. If part of specific antibodies is IgG3, they might have a shorter half-life as well.

Two considerations are unique to patients with PID. The first unique consideration is the susceptibility of patients. In our study, many PID patients received oral polio vaccine without sequelae. However, while the frequency of sequelae may be low, the consequences are high with frequent death. Indigenous poliovirus has been eliminated from all but three countries: Afghanistan, Nigeria, and Pakistan, three conflict zones where emerging and resurging infections occur [33–35]. However, all countries remain at risk due to potential importation of wild poliovirus and reversion of oral polio

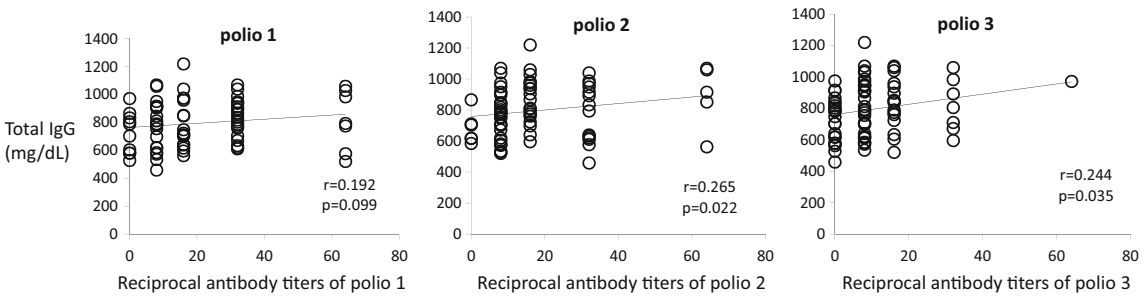

Fig. 1 Correlation between total IgG concentration (mg/dL) and reciprocal titers of polio antibodies 1, 2, and 3

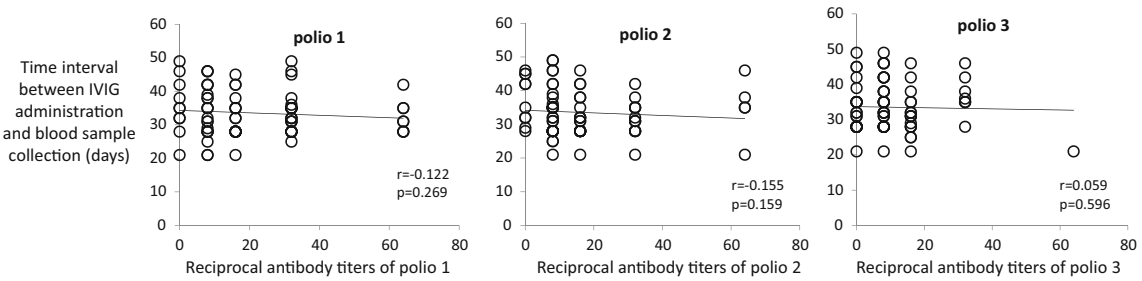

Fig. 2 Correlation between time interval from IVIG administration to blood sample collection in days and reciprocal titers of polio antibodies 1, 2, and 3

vaccine virus [33, 36]. This study demonstrates that patients on IVIG are incompletely protected, a pivotal management issue due to the severity of disease in patients with PID. Moreover, although safe, inactivated poliovirus vaccine (IPV) is of limited efficacy in patients with PID on IVIG/SCID. Flaccid paralysis and mortality are high in patients with PID and polio or vaccine-mediated disease [2–6, 8]. The second consideration is the role of patients with PID in the public health measures directed at control of poliovirus. They represent a risk to the community because patients with PID can have prolonged poliovirus excretion due to impairment in virus replication control, although this phenomenon is infrequent, it represents a key consideration in the battle to eradicate polio [12–14, 16, 37–39]. Prolonged replication may lead to mutations in the vaccine strain, which may acquire increased pathogenicity and ability to survive in the environment. This second consideration is critical for public health measures and has been incorporated into modeling for the final phase of polio eradication [40]. Recently, the Jeffrey Modell Foundation conducted a surveillance study of 608 patients with PID who had all received the oral polio vaccine and 13 (2.1%) of them were identified as excreting poliovirus, of whom 5 (0.8%) were excreting the vaccine-derived poliovirus [41]. Therefore, a complete understanding of the landscape of risk is essential for public health planning.

The highest titer of poliovirus found in IVIG was 1:64 and this was also the highest titer we found in the control group. All controls had been immunized and some received over ten doses of OPV due to regular vaccine administration as part of a campaign for poliovirus in Brazil that lasted over 30 years. We identified variability of antibody concentrations in IVIG preparations. This is expected because the serum antibody levels of the donors will vary over time and according to the precise make-up of the donor pool. The brands of IVIG administered to our patients were not of Latin American origin. Brazil is known for its high coverage rate for polio vaccine [42]. Despite this, fewer than half of our controls had protective antibody levels for all the three polio serotypes. If more than 50% of adults from a country with a highly immunized population do not have antibodies to polio, it is expected that levels in IVIG prepared from donors from countries with even lower coverage rates for polio might not be high enough to provide protective titers at trough levels. As Westernized countries transition to inactivated polio vaccine, there may be less community exposure to the virus and the titers in IVIG may fall.

Table 3 Poliovirus titers in IVIG samples administered to 21 patients on four occasions during the 1-year follow-up

Poliovirus serotype	Number of IVIG samples with different poliovirus antibody titers (%)		
	1:16	1:32	1:64
1	0 (0%)	12 (14.3%)	72 (85.7%)
2	2 (2.4%)	10 (11.9%)	72 (85.7%)
3	2 (2.4%)	8 (9.5%)	74 (88.1%)

Despite high antibody titers for all polio serotypes in all IVIG preparations, a high number of patients were susceptible to all three serotypes on more than one occasion. However, the weak correlations observed between polio antibody titers and total IgG trough levels or the time interval between IVIG administration and blood sample collection do not suggest that adapting dosing intervals or switching to SCIG would make a difference. Similar to our results, a previous study has shown that IgG concentration for other enteroviruses in serum of XLA on IVIG treatment was approximately a tenth of that in the IVIG preparation and some patients showed undetectable serum antibody titers even when these antibodies were present in IVIG preparations [43]. We have also shown variability for pneumococcus serotypes, and measles, varicella, tetanus, and diphtheria antibody levels among different batches of the same IVIG brand [19, 20]. For poliovirus, protection is considered to be provided when measured antibody titers are 1:8 or higher, yet protection is not always predictable based on titer alone, particularly for patients with PID [44].

Patients with PIDD could represent the sentinels in a setting of resurgent polio. Their incomplete protection and high rate of morbidity suggests that they may be the first to exhibit symptoms in an outbreak. Wild poliovirus infection is still present in some parts of the world despite the tremendous efforts that have been made to eradicate this infection [1, 9, 15]. Brazil has a high rate of immigration of refugees from countries where poliovirus has been recently isolated, representing a risk for outbreaks [35, 45].

This study reported a critical finding both from the perspective of patient management and public health policy. It provides critical quantitative information on poliovirus titers in a vulnerable population. Our study does have some limitation. The number of patients was one of the largest studied to date although our sample may not have encompassed all possible diagnoses or ages. Our prospective approach mitigates concerns about cross-sectional bias, however. We also assessed susceptibility to one pathogen, albeit in great detail. Experience with other pathogens should not be extrapolated from this analysis. Finally, the precise protective titer for poliovirus is difficult to know with certainty and will vary depending on exposure route and concentration. Therefore, we utilized the standard definition of protective titer, recognizing the limitation of this standardized approach when it comes to individual patient susceptibility.

In summary, we were able to show that the vast majority of PID patients on IVIG replacement were susceptible to at least one poliovirus serotype over the course of the year. Furthermore, even if protective antibody levels to the three serotypes were maintained throughout the study period, it is uncertain whether IVIG would provide protection at mucosal sites, which are the portal of entry for enteroviruses. These data represent critical information for polio preparedness for any country [46]. Complacency regarding polio is not justified until the last case has been registered.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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