

Accelerated Immunodeficiency-associated Vaccine-derived Poliovirus Serotype 3 Sequence Evolution Rate in an 11-week-old Boy With X-linked Agammaglobulinemia and Perinatal Human Immunodeficiency Virus Exposure

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Primary B-cell immunodeficiencies are risk factors for the generation of vaccine-derived polioviruses. We report immunodeficiency-associated vaccine-derived poliovirus serotype 3 in an 11-week-old boy with X-linked agammaglobulinemia. Unique characteristics of this case include early age of presentation, high viral evolutionary rate, and the child's perinatal exposure to human immunodeficiency virus.

Keywords. oral poliovirus vaccine; acute flaccid paralysis; X-linked agammaglobulinemia; Bruton tyrosine kinase; HIV-exposed but uninfected.

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Oral poliovirus vaccine (OPV) is highly effective in inducing protective immunity, but poliovirus has a high mutation rate due to an error-prone RNA-dependent RNA polymerase [1]. Poliovirus, allowed to replicate unchecked for prolonged periods, will mutate, regain virulence, and become a vaccine-derived poliovirus (VDPV) [2]. Strains are classified as VDPVs when there is ≥1% nucleotide sequence divergence in the major capsid protein, viral protein 1 (VP1), from the parental Sabin reference strain for poliovirus serotypes 1 and 3, and 0.6% nucleotide difference for poliovirus serotype 2 [2]. After immunization with OPV, immunodeficiency-associated VDPV (iVDPV) may occur in individuals with severe humoral immunodeficiency. Absence of antibody production permits uncontrolled viral replication, accumulation of mutations, and reversion to the neurovirulent phenotype [2].

Primary immunodeficiencies (PIDs), like agammaglobulinemia and combined immunodeficiencies, are risk factors for VDPVs, with 3000- to 7000-fold increased risk of disease compared to immunocompetent individuals [3]. Following administration of OPV, immunocompetent children usually shed virus for 3–6 weeks, in contrast, children with B-cell PIDs may shed poliovirus for prolonged periods, often >6 months [4]. Individuals with PIDs can thus serve as reservoirs of VDPV, hampering global poliovirus eradication efforts.

We report a case of iVDPV serotype 3 (iVDPV3) in an 11-week-old boy with X-linked agammaglobulinemia.

CASE PRESENTATION

An 11-week-old infant presented with asymmetrical acute flaccid paralysis (AFP) on 29th December 2017 to Red Cross War Memorial Children's Hospital, Cape Town, South Africa. Reduced muscle tone was noted in his lower limbs. Using the Medical Research Council scale, his muscle power was 0/5 (lower limbs), 3/5 (right upper limb), and 0/5 and 2/5 (proximal and distal left upper limbs, respectively). Deep tendon reflexes were not elicited. There was no bulbar or diaphragmatic involvement. Cerebrospinal fluid analysis showed 1 polymorphonuclear leukocyte/μL, 0 lymphocytes/μL, 113 erythrocytes/μL, raised protein at 1.46 g/L (upper reference value, 0.4 g/L), and negative polymerase chain reaction (PCR) tests for enteroviruses, cytomegaloviruses, and herpesviruses. Findings from spinal magnetic resonance imaging performed 4 days after his presentation were consistent with radiculitis.

The patient's medical history included vaginal delivery at term, birthweight of 3.15 kg, and no immediate postnatal complications. The child was vaccinated in accordance with the Expanded Programme on Immunization in South Africa, including a birth dose of the bivalent oral polio vaccine (bOPV)

on 19 October 2017, and at 6 weeks of age another bOPV dose together with a hexavalent vaccine containing inactivated polio vaccine (IPV) on 22 November 2017. The child had normal growth and development; weighed 7 kg at admission, and was thriving. The infant has a healthy 6-year-old brother.

The mother reported 7 previous first-trimester miscarriages. She was diagnosed with human immunodeficiency virus (HIV) infection during this pregnancy and commenced lifelong antiretroviral therapy. She exclusively breastfed for 3 months before switching to formula feeds. At birth, the infant received zidovudine for 6 weeks and then nevirapine for 12 weeks. He tested negative for HIV via PCR at birth, 9 weeks, 11 weeks, and 9 months of age.

Virus, cultured from the first stool sample was typed by real-time PCR (Poliovirus rRT-PCR ITD/VDPV-V5.0 kits, Centre for Disease Control and Prevention, USA) as poliovirus serotype 3 Sabin-like; however, sequencing of the VP1 region of the virus revealed 11 nucleotide changes consistent with VDPV3 classification. Also, 3 nucleotide changes were identified in the 5' untranslated region, including the neurovirulence-associated mutation T472C [5].

Immunoglobulin (IVIG; 2 g/kg bodyweight), acyclovir, and cefotaxime were administered intravenously during the first 2 days of hospitalization. Nasogastric feeds, physiotherapy, occupational therapy, and speech therapy were initiated. Gradual improvement in his limb movements and head control occurred. After 2 weeks, he was discharged, fully orally fed. Two months after presentation he had residual flaccid paralysis of his right lower limb, which persisted on long-term follow-up.

Immunoglobulins (IgG, IgA, IgM) tested on 22 January 2018 were within reference range as were T-cell parameters; however, there was a marked lack of B lymphocytes (0.1% [normal range, 11%–41%]) and an absolute count of 3 cells/ μ L (reference range, 430–3000 cells/ μ L). The normal IgG concentration was likely due to IVIG administered during admission and maternally derived IgG from transplacental transfer during pregnancy. Long PCR direct sequencing [6] identified a C1684T mutation in the 17th exon of the Bruton tyrosine kinase gene, corresponding to missense mutation R562W [7], and confirmed the diagnosis as X-linked agammaglobulinemia.

Serum from the infant's mother was tested for poliovirus neutralizing antibodies. Antibody titers of ≥ 8 mIU/mL indicate type-specific protection, with the measurable range between 5.7 mIU/mL and 1448 mIU/mL. The infant's mother did not have protective antibody titers for serotype 1 (7 mIU/mL), but had sufficient titers for serotype 3 (18 mIU/mL), albeit low. A booster dose of IPV was subsequently administered to the mother, father, and older sibling.

Stool samples were collected monthly from the infant. Additional samples collected up to 6 months after diagnosis all yielded iVDPV3. The polioviruses showed continuous

accumulation of mutations and new quasispecies (Table 1) despite IVIG replacement.

The infant resided in an informal settlement. Stool samples from 31 close contacts were negative for poliovirus. Vaccination coverage survey was conducted within a 500-m radius of the family abode, including 229 (83%) children aged <5 years with available vaccine information. Polio immunization coverage was 100%, 99.5%, 98.9%, and 74.4% at 6 weeks, 10 weeks, 14 weeks, and 18 months, respectively.

The study received ethics approval from the University of Witwatersrand ethics committee (M1811134). The mother of the patient gave written consent for publication of this study.

DISCUSSION

We report an infant with iVDPV3. Epidemiological data suggest that VDPV arose from the 11-week-old child after OPV administration, as close contacts of the child were all negative for poliovirus. The last case of wild-type poliovirus in South Africa was reported in 1989. In 2011, iVDPV3 was reported in a 10-month-old boy with agammaglobulinemia [8]. Reports of VDPV serotype 3 (VDPV3) are relatively rare. Among global iVDPVs reported from 1962 to 2016, serotype 2 (67%) had the highest prevalence followed by serotype 1 (15%) and serotype 3 (13%) [4]. Since the global switch from trivalent to bivalent OPV in April 2016, the prevalence of iVDPV1 and iVDPV3 may have changed. Both cases from South Africa and a case from Iran [9] were iVDPV3 in children with agammaglobulinemia; lack of humoral immune pressure may allow the evolution of poliovirus serotype 3, which is relatively restricted in an immunocompetent person.

A unique aspect of this case is the young age of the child. In a global systematic review of iVDPV cases from January 1960 to November 2012, the median age of iVDPV detection for 90 children was 1.04 years (interquartile range, 0.67–2.58 years) [10]. Based on the poliovirus molecular evolutionary clock, the rate of nucleotide substitutions is approximately 1%–2% per annum [1]. Since it is almost certain that AFP in the child is the result of OPV, an unusually rapid evolution of this poliovirus of about 2.61%–5.01% per annum occurred (Table 1). A systematic review found evolutionary rates of 0.5%–5.0% per annum, with the highest rates occurring during the initial stages of infection in individuals with iVDPV [10].

This case is novel due to perinatal HIV exposure (HIV-exposed but uninfected). HIV infection or HIV exposure alone does not constitute a risk for iVDPV, as evidenced by the rarity of iVDPV cases in countries like South Africa with a high burden of pediatric HIV infection. Maternal HIV infection reduces transplacental transfer of antibodies from mother to child for a number of vaccine-preventable diseases, including polio [11]. HIV infection also impairs the functional quality of antibodies [12]; even with high maternal antibody levels, maternal HIV

Table 1. Nucleotide and Amino Acid Changes of the Viral Protein 1 Region of Polioviruses Isolated From the Case, Compared With Sabin Poliovirus Type 3 and a Reference Strain of Wild-type Poliovirus Type 3

Table A: 1st quasispecies		Nucleotide (NT) sequence																# of changes	Mutational rate/annum	Days from 1st OPV	Sample collection date
NT Position	46	52	96	101	160	354	372	396	424	477	497	507	510	525	687	694	766				
Wild type 3 (JN812647)	T	C	C	C	G	A	G	C	A	A	A	C	T	C	T	A	G	G			
SABIN 3	T	C	C	C	G	T	A	C	A	C	A	C	C	A	C	A	G	G			
Patient Sample 1	-	A	-	-	A	C	G	T	G	-	G	T	-	G	-	G	A	-			
Patient Sample 2	-	A	-	-	A	C	G	T	G	-	G	T	-	G	-	G	A	-			
Patient Sample 3	-	A	T	-	A	C	G	T	G	T	G	T	T	G	-	G	A	-			
Patient Sample 4	-	A	T	T	A	C	G	T	G	T	G	T	T	G	-	G	A	A/G			
Patient Sample 5	C	-	-	-	A	C	G	T	G	T	G	T	T	G	T	G	A	A			
Nucleotide change	T46C	C52A	C96T	C101T	G160A	T354C	A372G	C396T	A424G	C477T	A497G	C507T	C510T	A525G	C687T	A694G	G766A	G823A			
Table B: 2nd quasispecies		Nucleotide (NT) sequence																# of changes	Mutational rate/annum	Days from 1st OPV	Sample collection date
NT Position	23	108	161	200	261	320	324	393	399	453	497	501	669	679	697	705	732				
Wild type 3 (JN812647)	A	C	T	A	A	G	T	G	A	A	A	G	A	C	G	C	T	G	G	G	
SABIN 3	A	C	C	G	T	G	T	A	C	G	A	A	T	T	G	C	C	G	C	A	
Patient Sample 6	-	-	T	A	C	A	C	G	T	-	G	G	-	C	A	-	T	A	T	G	
Patient Sample 7	-	C/G	T	A	C	A	C	G	T	G/A	A/G	G	-	C	A	T	T	A	T	G	
Patient Sample 8	G	-	T	A	C	A	C	G	T	-	G	G	C	C	A	-	T	A	T	G	
Patient Sample 9	G	-	T	A	C	A	C	G	T	-	G	G	C	C	A	-	T	A	T	G	
Nucleotide change	A23G	C108G	C161T	G200A	T261C	G320A	T324C	A393G	C399T	G453A	A497G	A501G	T669C	T679C	G697A	C705T	C732T	G766A	C771T	A795G	
Table C: 3rd quasispecies		Nucleotide (NT) sequence																# of changes	Mutational rate/annum	Days from 1st OPV	Sample collection date
NT Position	8	36	54	67	87	107	108	131	133	151	166	167	223	226	233	235	244				
Wild type 3 (JN812647)	E	S	V	Q	I	R	I	E	T	Q	K	S	V	S	V	D	V	V	R	V	
SABIN 3	E	S	A	R	I	R	I	E	T	Q	K	S	I	S	V	D	V	V	R	V	
Patient Sample 6	-	-	V	Q	I	H	I	E	T	-	R	S	-	S	I	-	V	I	R	V	
Patient Sample 7	-	S	V	Q	I	H	I	E	T	Q	K/R	S	-	S	I	D	V	I	R	V	
Patient Sample 8	G	-	V	Q	I	H	I	E	T	-	K/R	S	I	S	I	-	V	I	R	V	
Patient Sample 9	G	-	V	Q	I	H	I	E	T	-	K/R	S	I	S	I	-	V	I	R	V	
Amino acid change	E8G		A54V	R67Q		R107H					K166R				V233I			V256I			

The isolated viruses are closely related to Sabin 3 and have been aligned with and compared to both Sabin 3 and WT 3 virus (blue shading). Sequences revealed 2 quasispecies, whose changes are displayed separately (samples 1–5 and samples 6–9). The changes highlighted in gray represent nonsynonymous changes (NT changes that result in an AA change) and those highlighted in blue represent NT or AA changes in the isolate that are the same as in a WT polio 3 isolate (accession number JN812647). A dash (-) represents no change. Mutations are denoted first with the NT/AA present in Sabin 3 reference, the position of the change, and finally the new NT/AA present in the sequenced isolate. The mutational rate per annum was calculated as % divergence × 365 days / days from first OPV dose (% divergence = number of changes × 100 / total number of nucleotides for Sabin 3 [900]).

Abbreviations: AA, amino acid; NT, nucleotide; OPV, oral polio vaccine; WT, wild type.

infection impairs transplacental antibody transfer, leading to reduced poliovirus-specific antibodies in the newborn [11]. Low levels of poliovirus 3 neutralizing antibodies in the child's mother and impaired transplacental transfer may have limited the amount of poliovirus antibodies transferred to the infant, which could have further waned by 11 weeks of age. Despite exclusive breastfeeding, reduced or impaired maternal poliovirus-specific antibodies may have limited the duration of protection, if any, against polioviruses, resulting in the early presentation.

HIV-exposed but uninfected infants have impaired cell-mediated immunity [13]. In this case, limited humoral immunity as well as impaired cell-mediated immunity may have created an environment of minimal restriction on viral replication, thereby allowing a faster evolutionary rate of up to approximately 5% per annum (range, 2.61%–5.01%, Table 1).

Live-attenuated polio vaccine has interrupted transmission of wild-type poliovirus in most countries globally, except for Afghanistan, Pakistan, and Nigeria [2]. Individuals with PIDs

are a threat to global polio eradication, as they can provide a reservoir for neurovirulent viruses. Early diagnosis of PID is beneficial to allow early treatment and avoid prolonged viral shedding in these individuals. Availability of antiviral drugs such as pocapavir [2], a capsid inhibitor, could potentially reduce the duration of viral shedding in individuals with PIDs. As the last case of wild-type poliovirus 3 was observed in 2012 [2], consideration should be given toward hastening global withdrawal of Sabin serotype 3 from OPV. Although not widely researched, administering IPV before OPV may reduce the risk of VDPVs, even in children with PIDs [2]. Both South African cases of iVDPV were detected through systems for AFP surveillance, highlighting the need for continued diligence in poliovirus surveillance to achieve global polio eradication.

Notes

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