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Original Article

Incidence of Poliovirus Infection in Patients with Severe Combined Immunodeficiency (SCID)

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Abstract

Background: Severe combined immunodeficiency (SCID) is a group of disorders with impairment in function of T, B and sometimes NK cells that could lead to high susceptibility to infectious diseases and premature death. Live-attenuated vaccines are contraindicated in SCID patients. However, in regions without screening programs for SCID, oral polio vaccine (OPV) could lead to vaccine-derived polioviruses (VDPVs) which are reverted to the neurovirulent virus types and could cause outbreaks of vaccine-associated paralytic poliovirus (VAPP) in communities with inadequate vaccine coverage.

Method: 20 SCID patients registered in Iranian national registry for Primary immunodeficiency (PID) disorders were tested for polio virus stool shedding. The demographic data, clinical presentation, polio test results, laboratory data and whole exome sequencing (WES) of the patients were available.

Results: Among the 20 SCID patients enrolled in the study, 6 patients tested positive for immunodeficiency-related VDPVs (iVDPV) shedding. Four patients (20%) had iVDPV type 2, one patient (5%) had iVDPV type 1 and one patient (5%) had iVDPV type 3.

Conclusion: Due to the high possibility of asymptomatic and long-term iVDPV shedding in SCID patients, the enhancement of screening of PID patients for poliovirus and iVDPV excretion is strongly needed.

Keywords: Polio; SCID; Primary Immunodeficiency; Oral Polio Vaccine

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Introduction

Primary immunodeficiency (PID) disorders or inborn errors of immunity are conditions caused by monogenic mutations that result in increased susceptibility to infection, autoimmunity, allergy or malignancy (1). Severe combined immunodeficiency (SCID) is a heterogeneous group of disorders characterized by impairment in function of T, B and sometimes NK cells that could lead to death in the early years of life, due to the high susceptibility to infectious diseases (2). Newborn screening in 11 programs in the United States reported the incidence of SCID to be 1 in 58,000 infants (95% CI, 1 in 46,000 to 1 in 80,000) (3). Although the incidence of SCID is much higher in countries with high rates of consanguineous marriage, due to the lack of screening programs, the exact incidence could not be determined. According to national PID registry of Iran, the incidence of PID is estimated to be 0.21 cases in 1000 births, and SCID is reported to be the most frequent specific disorder (21.1%) (4, 5).

Live-attenuated vaccines are contraindicated in SCID patients. However, in regions without screening programs for SCID, oral polio vaccine (OPV) (6, 7), rotavirus (8, 9), varicella, measles-mumps-rubella (MMR) (10) and Bacille Calmette-Guerin (BCG) (11, 12), vaccinations could lead to disseminated infection in these patients. Although the polio vaccine schedule in the United States shifted to all-inactivated poliovirus vaccine (IPV) schedule in 2000 (13), OPV is still being used in developing countries due to its lower cost, spread of vaccine virus to other contacts leading to herd immunity and ease of administration. The vaccine-derived polioviruses (VDPVs) developed from OPV viruses that are reverted to the neurovirulent types, could lead to outbreaks of vaccine-associated paralytic poliovirus (VAPP) in communities with inadequate vaccine coverage (14). Moreover, PID patients who receive OPV, excrete the virus for a longer time and are at higher risk of carrying immunodeficiency-related VDPVs (iVDPV) (15). It is necessary for PID patients to receive IPV in place of OPV in their vaccine schedule, except in severe PID cases that vaccination is not recommended and is unlikely to be advantageous (16).

It has been reported that the rate of asymptomatic virus shedding in patients with SCID is higher as compared to other types of PID (17). Therefore, in the present study, we aimed to report the polio test results and estimate the incidence rate of polio virus shedding in patients with SCID in Iran.

Methods

Among patients with SCID registered in Iranian national registry for PIDs under the supervision of the Research Center for Immunodeficiencies (18), a total of 20 patients who were tested for poliovirus stool shedding were included in the present study. In Iran's National Polio Labratorary, the stool specimens were inoculated with L20B (mouse cell line expressing the human receptor for poliovirus) and RD cells (derived from human rhabdomyosarcmoa) and the vaccine-related polioviruses were identified using RT-PCR, in accordance with WHO protocol (19). It should be mentioned that all the demographic data, consanguinity status, clinical presentation, polio test results, laboratory data and whole exome sequencing (WES) of the patients were available. Laboratory data included complete blood count, serum immunoglobulin levels and lymphocyte immunophenotyping. Consent from the parents of patients were obtained beforehand.

Statistical analyses were performed using the SPSS software package, version 22 (SPSS Inc., Chicago, IL, USA). Values were presented as frequency, percentage, mean ± SD and median (IQR).

Results

A total of 20 SCID patients, including 10 males and 10 females, with a median (IQR) age of 1 (0.65-1.9) year old were enrolled in the study. Among these patients, 6 patients (30%) tested positive for iVDPVs. Polio results were as follows: four patients (20%) had iVDPV type 2, one patient (5%) had iVDPV type 1 and one patient (5%) had iVDPV type 3 (**Figure 1**).

The demographic data, clinical presentation and polio test result of the selected patients are presented in **Table 1**. Polio positive SCID patients (42.9% female, 57.1% male) had a mean (SD) age of 1.26 (±0.53) year old. The median (IQR) age at the onset of symptoms and at the time of diagnosis were 2 (0-6) and 6 (2-8) months, respectively. The mean (SD) diagnostic delay was

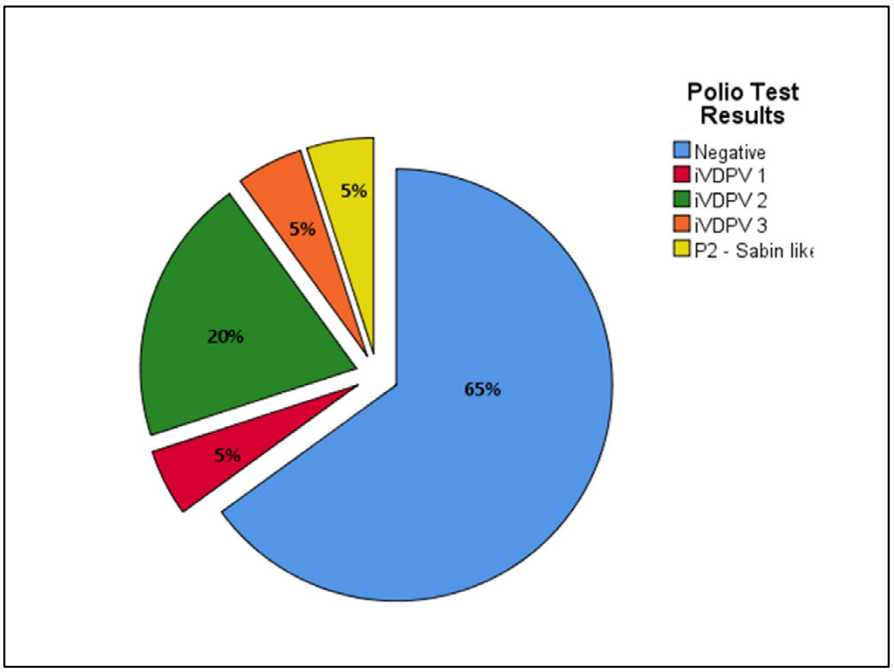

Figure 1. Polio test results of 20 tested SCID patients.

Table 1. Demographic data, clinical presentation, and Polio type of SCID patients with positive Polio stool shedding.

Patient Number	Sex	Age (year)	Age of Onset (month)	Age of Diagnosis (month)	Dead/Alive	First Clinical presentation	Other Clinical Presentations	Polio Type
1	Male	1	6	8	NA	BCGosis	Pneumonia, Skin Infection	iVDPV 1
2	Male	1.5	2	3	Dead	Oral Candidiasis	FTT, Skin Infection, UTI, Hepatomegaly	iVDPV 2
3	Female	2	6	8	Alive	Diarrhea	Fever, UTI	iVDPV 2
4	Female	1	6	11	Dead	Diarrhea	Oral Candidiasis, FTT	iVDPV 2
5	Female	1.6	1	6	NA	BCGosis	Rash	iVDPV 2
6	Male	NA	0	2	NA	Diarrhea	Pneumonia	iVDPV 3
7	Male	0.5	0	0	Dead	BCGosis	Pneumonia, Oral Candidiasis, Rash, Fever, Hepatomegaly, splenomegaly	P2-Sabin like

NA, not available; FTT, failure to thrive; UTI, urinary tract infection.

2.43 (±1.9) months. In addition, 85.7% of patients had consanguineous parents and 14.3% had positive family history. At the time of study, 42.9% of patients were deceased, 14.3% were alive and 42.9% of patients had missing data in this regard. The first clinical presentation of 4 patients (57.1%) was BCGosis. As the first clinical manifestation showed, the other two and one patients had diarrhea and oral candidiasis, respectively. The frequency of clinical presentations is shown in **Figure 2**.

The WES results demonstrated the causative mutated genes for SCID in the selected patients. The identified gene mutations include *CD3D*, *DCLREC1* and *JAK3*, each in one patient, and ADA and *IL2RG*, each in two patients. The genetic results and immunologic data of the patients are presented in **Table 2**.

Discussion

During OPV replication after administration, frequently a small number of substitutions could revert, conferring to the attenuated phenotype. However, in immunocompromised patients, the genetic divergence of Sabin strains to neurovirulent poliovirus and formation of VDPVs could occur, which is threatening for eradication program of Poliovirus. VDPV isolates differ from Sabin strains by 1-15% of VP1 nucleotides. The long-term excretion of VDPVs in PID patients is a concerning matter that could lead to prolonged virus replication, increased risk

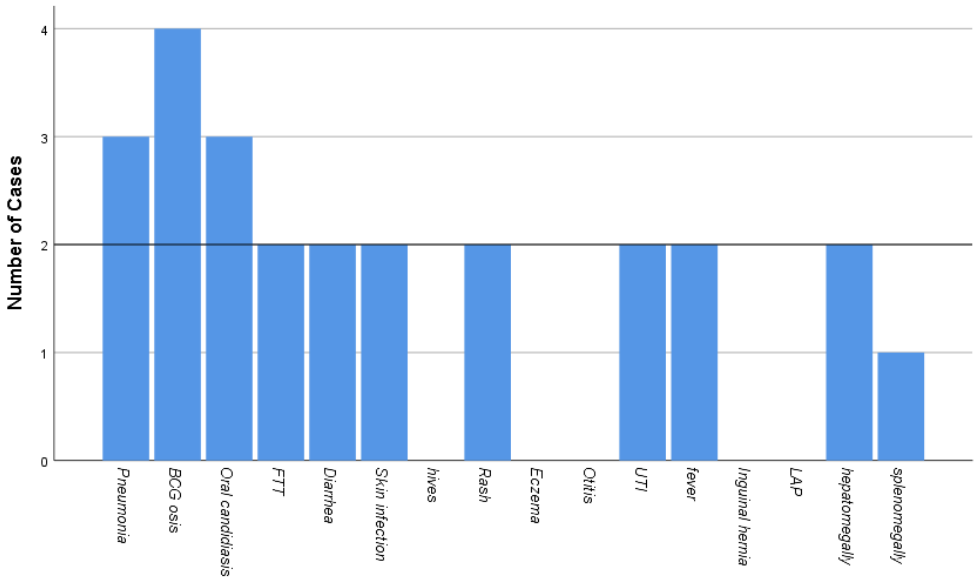

Figure 2. The frequency of clinical presentations among SCID patients with positive Polio stool shedding. FTT, failure to thrive; UTI, urinary tract infection; LAP, lymphadenopathy.

Table 2. The genetic results and immunologic data of SCID patients with positive Polio stool shedding.

Patient Number	CD3, %	CD4, %	CD8, %	CD16-56, %	CD19, %	IgG, mg/dl	IgM, mg/dl	IgA, mg/dl	IgE, mg/dl	Phenotype	Genotype	Gene Mutation	Mutation Type
1	20.48	10.32	0.09	70.53	0.01	NA	NA	NA	NA	T-B+NK-	T-B+NK-	*IL2RG*	c.AGAGGTT60caGTGTTT;Del CA CAG>--G
2	13.98	7.70	1.70	27.30	1.60	NA	NA	NA	NA	T-B-NK+	T-B-NK-	*ADA*	c.G415T,GAG>TAG
3	56.67	13.17	39.86	6.93	30.63	14	20	4	0	T-B-NK-	T-B-NK-	*ADA*	c.556G>A
4	5.80	3.90	2.30	81.00	0.20	815	118	666	13.5	T-B+NK-	T-B+NK+	*CD3D*	c.247G>T
5	42.20	37.06	5.32	15.86	0.50	39	20	13	81	T-B+NK-	T-B+NK-	*IL2RG*	c.850G>T
6	26.00	15.00	10.00	4.00	63.00	73	18	0	5	T-B-NK+	T-B-NK+	*DCLRE1C*	c.41 G>T
7	76.16	2.20	79.95	NA	4.09	56	39	9	0	T-B+NK-	T-B+NK-	*JAK3*	c.2164G>A

of VAPP and reintroducing polioviruses into the community (15). This study reported that among 20 SCID patients who were tested for poliovirus stool shedding, 6 (30%) patients tested positive for iVDPVs and one (5%) patient had P2 Sabin-like stool shedding. It was previously demonstrated that SCID patients had a higher risk of persistent infection with less likelihood of iVDPV clearance among other PIDs (20). It is hypothesized that the long-term virus shedding in CID patients could be attributed to the role of cellular immunity in clearance of poliovirus infection (13, 20-22). In Iran, 23 iVDPV patients were identified during 1995-2019, and 7 (30%) patients never experienced VAPP. Furthermore, SCID patients had the highest risk for asymptomatic infection (28.6%) as compared to other PIDs. The rate of iVDPV infection among adaptive PID patients who did not experience paralysis was reported to be 3.1% (17). However, Aghamohammadi et al in a study on 635 PID patients from 13 OPV-using countries reported that only 5 (0.8%) patients excreted iVDPV in their stool, among which 3 patients had SCID (23).

The most common detected iVDPV serotype in the present study was iVDPV2 which consisted 66.6% of positive cases. This was similar to previous studies on PID patients in Iran (17), OPV-using countries (23), and a systematic review conducted for cases during 1962 to 2016 (20), which reported 69%, 80% and 69.3% of cases to excrete iVDPV2. However, trivalent OPV vaccination schedule was switched to bivalent since 2016 which led to the reduction of iVDPV2 emergence (24).

Under-vaccinated communities are at higher risk of poliovirus break-out from iVDPV transmission to contacts which threatens the Global

Polio Eradication Initiative (15, 22). In contrast to developing countries, high-income countries have replaced OPV with IPV which resulted in a dramatic decrease in incidence of paralytic polio (25). There has been reports that PID patients with iVDPV infection could benefit from hematopoietic stem cell transplantation (HSCT) and it could lead to the clearance of infection (26). Moreover, PID patients who are not suitable candidates for HSCT could benefit from novel antiviral drugs, including Pocapavir and V-7404 (27).

The enhancement of screening of PID patients for poliovirus and iVDPV excretion is strongly recommended. Since SCID patients are prone to long-term iVDPV infection, implementing screening programs for surveillance of iVDPV infections and treating the high risk patients with antiviral agents are of great importance for poliovirus eradication. In addition, neonatal screening for PIDs is the best strategy for prevention of OPV exposure and could lead to reduction of iVDPV infection and VAPP.

Conclusion

Live-attenuated vaccines including OPVs are contraindicated in SCID patients. SCID patients who receive OPV could develop iVDPV over replication of virus. Long-term viral shedding in SCID patients with iVDPV could threaten the eradication program of poliovirus. Therefore, the efforts to replace OPV with IPV, screen newborns for PID before vaccination and screen PID patients for poliovirus shedding should be strengthened.

Conflict of Interest

All the authors declared no conflict of interest.

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References

1. Bousfiha A, Jeddane L, Picard C, Al-Herz W, Ailal F, Chatila T, et al. Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification. J Clin Immunol. 2020;40(1):66-81.
2. Chinn I K,Shearer W T. Severe Combined Immunodeficiency Disorders. Immunol Allergy Clin North Am. 2015;35(4):671-94.
3. Kwan A, Abraham R S, Currier R, Brower A, Andruszewski K, Abbott J K, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. JAMA. 2014;312(7):729-38.
4. Abolhassani H, Kiaee F, Tavakol M, Chavoshzadeh Z, Mahdaviani S A, Momen T, et al. Fourth Update on the Iranian National Registry of Primary Immunodeficiencies: Integration of Molecular Diagnosis. J Clin Immunol. 2018;38(7):816-32.
5. Aghamohammadi A, Mohammadinejad P, Abolhassani H, Mirminachi B, Movahedi M, Gharagozlou M, et al. Primary immunodeficiency disorders in Iran: update and new insights from the third report of the national registry. J Clin Immunol. 2014;34(4):478-90.
6. Heiman S, Weil M, Shulman L M, Simon A J, Lev A, Somech R, et al. Co-appearance of OPV and BCG vaccine-derived complications in two infants with severe combined immunodeficiency. Immunol Res. 2018;66(3):437-43.
7. Shaghaghi M, Parvaneh N, Ostad-Rahimi P, Fathi S M, Shahmahmoodi S, Abolhassani H, et al. Combined immunodeficiency presenting with vaccine-associated paralytic poliomyelitis: a case report and narrative review of literature. Immunol Invest. 2014;43(3):292-8.
8. Patel N C, Hertel P M, Estes M K, de la Morena M, Petru A M, Noroski L M, et al. Vaccine-acquired rotavirus in infants with severe combined immunodeficiency. N Engl J Med. 2010;362(4):314-9.
9. Bakare N, Menschik D, Tiernan R, Hua W,Martin D. Severe combined immunodeficiency (SCID) and rotavirus vaccination: reports to the Vaccine Adverse Events Reporting System (VAERS). Vaccine. 2010;28(40):6609-12.
10. Bayer D K, Martinez C A, Sorte H S, Forbes L R, Demmler-Harrison G J, Hanson I C, et al. Vaccine-associated varicella and rubella infections in severe combined immunodeficiency with isolated CD4 lymphocytopenia and mutations in IL7R detected by tandem whole exome sequencing and chromosomal microarray. Clin Exp Immunol. 2014;178(3):459-69.
11. Sadeghi-Shabestari M,Rezaei N. Disseminated bacille Calmette-Guerin in Iranian children with severe combined immunodeficiency. Int J Infect Dis. 2009;13(6):e420-3.
12. Marciano B E, Huang C Y, Joshi G, Rezaei N, Carvalho B C, Allwood Z, et al. BCG vaccination in

patients with severe combined immunodeficiency: complications, risks, and vaccination policies. J Allergy Clin Immunol. 2014;133(4):1134-41.
13. Ni L, Seward J F, Santibanez T A, Pallansch M A, Kew O M, Prevots D R, et al. Vaccine policy changes and epidemiology of poliomyelitis in the United States. Jama. 2004;292(14):1696-701.
14. Alleman M M, Jorba J, Greene S A, Diop O M, Iber J, Tallis G, et al. Update on vaccine-derived poliovirus outbreaks—worldwide, July 2019–February 2020. MMWR 2020;69(16):489.
15. Kew O M, Sutter R W, de Gourville E M, Dowdle W R,Pallansch M A. Vaccine-derived polioviruses and the endgame strategy for global polio eradication. Annu Rev Microbiol. 2005;59:587-635.
16. Sobh A,Bonilla F A. Vaccination in Primary Immunodeficiency Disorders. J Allergy Clin Immunol Pract. 2016;4(6):1066-75.
17. Shaghaghi M, Shahmahmoodi S, Nili A, Abolhassani H, Madani S P, Nejati A, et al. Vaccine-Derived Poliovirus Infection among Patients with Primary Immunodeficiency and Effect of Patient Screening on Disease Outcomes, Iran. Emerg Infect Dis. 2019;25(11):2005-12.
18. Shahbazi Z, Yazdani R, Shahkarami S, Shahbazi S, Hamid M, Sadeghi-Shabestari M, et al. Genetic mutations and immunological features of severe combined immunodeficiency patients in Iran. Immunol Lett. 2019;216:70-78.
19. Organization W H. Polio laboratory manual. World Health Organization; 2004.
20. Shaghaghi M, Soleyman-Jahi S, Abolhassani H, Yazdani R, Azizi G, Rezaei N, et al. New insights into physiopathology of immunodeficiency-associated vaccine-derived poliovirus infection; systematic review of over 5 decades of data. Vaccine. 2018;36(13):1711-19.
21. Lopez C, Biggar W D, Park B H,Good R A. Nonparalytic poliovirus infections in patients with severe combined immunodeficiency disease. J Pediatr. 1974;84(4):497-502.
22. Shaghaghi M, Shahmahmoodi S, Abolhassani H, Soleyman-Jahi S, Parvaneh L, Mahmoudi S, et al. Vaccine-derived polioviruses and children with primary immunodeficiency, Iran, 1995–2014. Emerg Infect Dis. 2016;22(10):1712.
23. Aghamohammadi A, Abolhassani H, Kutukculer N, Wassilak S G, Pallansch M A, Kluglein S, et al. Patients with Primary Immunodeficiencies Are a Reservoir of Poliovirus and a Risk to Polio Eradication. Front Immunol. 2017;8(685):685.
24. Organization W H,Initiative G P E. Polio endgame strategy 2019-2023: eradication, integration, certification and containment. World Health Organization; 2019.
25. Schonberger L B, Sullivan-Bolyai J Z,Bryan J A. Poliomyelitis in the United States. Adv Neurol. 1978;19:217-27.
26. Shaghaghi M, Irannejad M, Abolhassani H, Shahmahmoodi S, Hamidieh A A, Soleyman-Jahi S, et al. Clearing Vaccine-Derived Poliovirus Infection Following Hematopoietic Stem Cell Transplantation: a Case Report and Review of Literature. J Clin Immunol. 2018;38(5):610-16.
27. McKinlay M A, Collett M S, Hincks J R, Oberste M S, Pallansch M A, Okayasu H, et al. Progress in the development of poliovirus antiviral agents and their essential role in reducing risks that threaten eradication. J Infect Dis. 2014;210(suppl_1):S447-S53.