Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

New insights into physiopathology of immunodeficiency-associated vaccine-derived poliovirus infection; systematic review of over 5 decades of data

Mohammadreza Shaghaghi [a,b,1], Saeed Soleyman-jahi [a,c,1], Hassan Abolhassani [a,d], Reza Yazdani [a], Gholamreza Azizi [e], Nima Rezaei [a,b,f], Mohamed-Ridha Barbouche [g], Mark A. McKinlay [h], Asghar Aghamohammadi [a,*]

[a] Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Science, Tehran, Iran
[b] Network of Immunology in Infections, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran
[c] Cancer Immunology Project (CIP), Universal Scientific Education and Research Network (USERN), Tehran, Iran
[d] Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden
[e] Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran
[f] Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[g] Department of Immunology, Institut Pasteur de Tunis and University Tunis El-Manar, Tunis, Tunisia
[h] Center for Vaccine Equity, Task Force for Global Health, Atlanta, GA, United States

ARTICLE INFO

Article history:
Received 7 December 2017
Received in revised form 26 January 2018
Accepted 15 February 2018
Available online xxxx

Keywords:
Primary immunodeficiency
Paralysis
Poliomyelitis
Oral poliovirus vaccine
Vaccine-derived poliovirus
Mutation

ABSTRACT

Widespread administration of oral poliovirus vaccine (OPV) has decreased global incidence of poliomyelitis by ≈99.9%. However, the emergence of vaccine-derived polioviruses (VDPVs) is threatening polio-eradication program. Primary immunodeficiency (PID) patients are at higher risks of vaccine-associated paralytic poliomyelitis (VAPP) and prolonged excretion of immunodeficiency-associated VDPV (iVDPV).

We searched Embase, Medline, Science direct, Scopus, Web of Science, and CDC and WHO databases by 30 September 2016, for all reports of iVDPV cases. Patient-level data were extracted form eligible studies. Data on immunization coverage and income-level of countries were extracted from WHO/UNICEF and the WORLD BANK databases, respectively. We assessed bivariate associations between immunological, clinical, and virological parameters, and exploited multivariable modeling to identify independent determinants of poliovirus evolution and patients' outcomes. Study protocol was registered with PROSPERO (CRD42016052931).

4329 duplicate-removed titles were screened. A total of 107 iVDPV cases were identified from 68 eligible articles. The majority of cases were from higher income countries with high polio-immunization coverage. 74 (69.81%) patients developed VAPP. Combined immunodeficiency patients showed lower rates of VAPP ($p < .001$) and infection clearance ($p = .02$), compared to humoral immunodeficiency patients. The rate of poliovirus genomic evolution was higher at early stages of replication, decreasing over time until reaching a steady state. Independent of replication duration, higher extent ($p = .04$) and rates ($p = .03$) of genome divergence contributed to a less likelihood of virus clearance. PID type ($p < .001$), VAPP occurrence ($p = .008$), and income-level of country ($p = .04$) independently influenced patients' survival.

With the use of OPV, new iVDPVs will emerge independent of the rate of immunization coverage. Inherent features of PIDs contribute to the clinical course of iVDPV infection and virus evolution. This finding could shed further light on poliomyelitis pathogenesis and iVDPV evolution pattern. It also has implications for public health, the polio eradication effort and the development of effective antiviral interventions.

* Corresponding author at: Research Center for Immunodeficiencies, Children's Medical Center Hospital, 62 Qarib St., Keshavarz Blvd., Tehran 14194, Iran.
E-mail address: aghamohammadi@tums.ac.ir (A. Aghamohammadi).
[1] These authors contributed equally to this article.

https://doi.org/10.1016/j.vaccine.2018.02.059
0264-410X/

Contents

1. Introduction

Since the foundation of Global Polio Eradication Initiative, billions of oral poliovirus vaccine (OPV) doses have been administered as the mainstay of polio-eradication strategy due to lower cost, ease of administration, and the ability to induce intestinal immunity and passively immunize contacts in areas of poor sanitation. This has led to ≈99.9% decreased in annual incidence of wild-type poliomyelitis from 350,000 cases in 1988 to 35 cases in 2016. However, emergence of neurovirulent vaccine-derived polioviruses (VDPVs) has raised concerns regarding continued OPV use [1–3].

Normally, attenuated viruses replicate in the gastrointestinal (GI) tract of OPV recipients for a short period and disappear in 2–6 weeks after OPV exposure [4]. In rare situations, particularly in immunocompromised patients, vaccine-polioviruses are not cleared from GI tract and continue to replicate for prolonged durations. The unstable genome of OPV strains is susceptible to spontaneous mutations, occurring to ∼1–2% of nucleotides in viral protein 1 (VP1) region per each year of replication. Revertant substitutions in modified genes of OPV strains, in very rare instances (1 in every 2.7 million doses) recover neurovirulent potential resulting in vaccine-associated paralytic poliomyelitis (VAPP) [2,5–7]. VDPVs are defined as poliovirus serotypes 1&3 with >1%, and serotype 2 with >0.6% divergence in VP1 coding region from the parental OPV strains [8].

Primary immunodeficiency (PID) patient are at ∼3000-fold increased risk of VAPP, and may chronically excrete immunodeficiency-associated VDPVs (iVDPVs) in stool. iVDPV emergence is a major challenge for the polio-eradication program. Vaccine viruses may also continue replication by infecting several healthy hosts, through person to person transmission in under-immunized communities, and attain genetic drift to meet the definition of circulating-VDPVs [2]. Ambiguous VDPVs are isolates from either immunocompetent individuals or the environmental samples, without any evidence of community circulation [2]. In addition to the risk that all 3 VDPV categories pose to the current eradication efforts, a silent excretion of divergent viruses by PID patients presents a long-term risk of polio-outbreak after OPV cessation [2,5,8,9]. A literature review on this topic is provided in Supplementary Background.

Despite the passage of more than 54 years from identifying the first iVDPV patient in 1962, most of our understandings about different aspects of iVDPV infection have come from case studies, each presenting a limited number of patients. Previous review studies provided valuable findings regarding the epidemiological aspects of the infection. However, they lacked in-depth analysis of clinical and immunological parameters [10,11]. We conducted this systematic review of iVDPV cases and analyzed the associations between clinical, immunological and virological variables to identify factors which determine presentations and outcomes of these patients, as well as the pattern of iVDPV genomic evolution.

2. Methods

This systematic review has been registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID = CRD42016052931). We conducted a systematic search of CDC and WHO websites and electronic databases: Embase, Medline, Science direct, Scopus, and Web of Science till 30 September 2016, to find articles describing at least 1 immunodeficient patients who shed VDPV. We designed a sensitive search strategy using the key words "poliomyelitis", "oral poliovirus vaccine", "vaccine-derived poliovirus", "immunodeficiency", and their related terms. No restrictions were considered for study design and publication time. Articles in English and French were included. Study selection and quality assessment were performed by 2 reviewers. The quality of articles was not a matter of exclusion and was used when there was an inconsistency in results between papers, with the highest quality paper being used when different articles referred to the same cases.

Two reviewers independently extracted patient-level data in terms of epidemiological data, patients' characteristics, and features of iVDPV infection. Possible discrepancies were resolved by consensus or consulting a third reviewer.

Data on polio-immunization coverage and income-level of countries were extracted from WHO [12] and the World-Bank [13] databases, respectively. When available, the interval between presumed infective OPV dose and the latest positive stool specimen was calculated to estimate total virus replication time. Otherwise, results of phylogenetic analysis of poliovirus RNA reported by original case-studies were considered for this estimation. This was in line with the most recent strategy used by CDC/WHO to estimate this duration [11,14]. We defined "iVDPV detection speed" as an index of how quickly excretion was documented, which was calculated as the duration of virus shedding under observation divided by the total virus replication time. "Virus evolution rate" was defined as the maximum percent VP1 divergence divided by the total virus replication time. PIDs were categorized into 2 groups of predominantly antibody deficiencies (PADs) and combined immunodeficiencies (CIDs) based on International Union of Immunological Societies (IUIS) classification [15]. After summarizing the descriptive results, bi-variate and multivariable analyses

Please cite this article in press as: Shaghaghi M et al. New insights into physiopathology of immunodeficiency-associated vaccine-derived poliovirus infection; systematic review of over 5 decades of data. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.02.059