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Adverse events following immunization in patients with primary immunodeficiencies

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ABSTRACT

Background: Adverse events following immunization (AEFI) requires special consideration in patients with primary immunodeficiency diseases (PID) because they may represent a "red flag" for the initial diagnosis and may cause disease complications. Therefore, the definition of appropriate vaccination schemes is a major issue in PID. The aim of this study is to describe the AEFI in a cohort of PID patients.
Methods: Medical records from 379 PID patients were included. AEFI severity was classified according to the WHO 1999 guidelines. Causality was assessed using the Clinical Immunization Safety Assessment (CISA) 2009 criteria.
Results: Evidence of AEFI was found in 26 medical records and represented a total of 29 reactions. Most of the AEFI were observed in patients with idiopathic hypogammaglobulinemia (IHG), chronic granulomatous disease (CGD) and severe combined immunodeficiency (SCID), representing 10, 4 and 4 cases, respectively. A total of 21 reactions were associated with replicative vaccines, 7 of which were serious cases related to Bacille Calmette-Guérin (BCG). BCG was also the vaccine more often associated with definitive AEFI in PID. In addition to BCG-related complications, seizures were the most serious AEFI among PID patients.
Conclusions: Our study included a large cohort of PID patients and confirmed an increased risk of serious AEFI in these populations. The design and implementation of neonatal screening strategies for the early detection of congenital lymphopenias and other PID are urgently needed to avoid serious complications of the BCG vaccine usually applied immediately after birth. Our findings also support the use of the acellular pertussis vaccine to minimize the appearance of seizures in PID patients vaccinated with diphtheria, pertussis and tetanus (DPT).

1. Introduction

Q2 Primary immunodeficiency diseases (PID) are heterogeneous genetic disorders that variably affect the immune system. Patients commonly exhibit increased susceptibility to recurrent or opportunistic infections, although autoimmunity and cancer are also frequently observed [1]. Increased susceptibility to infections may also manifest as adverse events to vaccines, especially those containing live microorganisms.

An adverse event following immunization (AEFI) is defined as any event after immunization believed to be caused by the administration of a vaccine [2]. AEFI may be caused by the inherent properties of a vaccine, errors in the preparation process, handling or administration, coincidental events not attributed to the vaccine or application reactions precipitated by anxiety or pain after injection [2]. However, for most of the AEFI, little information is available that helps determine the cause–effect relationship [3].

AEFI demands special consideration in PID because they can represent the first manifestation of these diseases, in many cases resulting in the "red flag" for the initial diagnosis [4–6]. Lymphadenitis, seizures, paralysis, failure to thrive, dissemination of a vaccine strain to other organs and death have been reported after vaccination in PID patients. Several reports describe several AEFI following Bacille Calmette-Guérin (BCG) vaccination in severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), interferon-gamma receptor 1- and ZAP-70-deficiency [4–14]. Moreover, a comprehensive review of the published mycobacterial complications in patients with CGD revealed that 45/72 (62.5%) are BCG-related [11]. Specifically for SCID, a multicenter retrospective study has recently reported 51%

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Table 1
Characteristics of the 379 patients included in this study.

Major PID groups[a]	*n*
Combined immunodeficiencies	27
Severe combined immunodeficiency	19
Other cellular deficiencies[1]	8
Combined immunodeficiencies with associated or syndromic features	39
Wiskott–Aldrich syndrome	7
Ataxia-telangiectasia	6
DiGeorge syndrome	15
Hyper-IgE syndromes	11
Predominantly antibody deficiencies	274
Agammaglobulinemia	17
Common variable immunodeficiency	24
Partial[2] or Selective IgA deficiency	52
Specific antibody deficiency	11
Transient hypogammaglobulinemia	28
Idyopatic hypogammaglobulinemia	139
Other[3]	3
Diseases of immune dysregulation	6
Chediak–Higashi syndrome	5
Autoimmune lymphoproliferative syndrome	1
Congenital defects of phagocyte number, function, or both	19
Chronic granulomatous disease	14
Other[4]	5
Defects in innate immunityChronic mucocutaneous candidiasis	7
Autoinflammatory disordersPeriodic fever, adenopathy, pharingitis and Afthae-PFAPA[5]	6
Complement deficienciesC1INH deficiency	1
Total	379

[a] As proposed by Bousfiha et al., [1].
[1] One case with congenital medullary aplasia and 7 cases of unspecified cellular immunodeficiencies.
[2] Partial IgAD refers to detectable but decreased IgA levels that are more than 2 standard deviations below normal age-adjusted means.
[3] The other cases in the group with predominantly antibody deficiencies included two cases of IgG subclass deficiency and one case with Good syndrome.
[4] Other congenital defects of the phagocyte number included two cases of congenital neutrophenia, two cases of Shwachman–Diamond syndrome and one unspecified defect in the phagocytes.
[5] Although is not included as a PID by Bousfiha et al., [1], PFAPA is one of the most common autoinflammatory conditions.

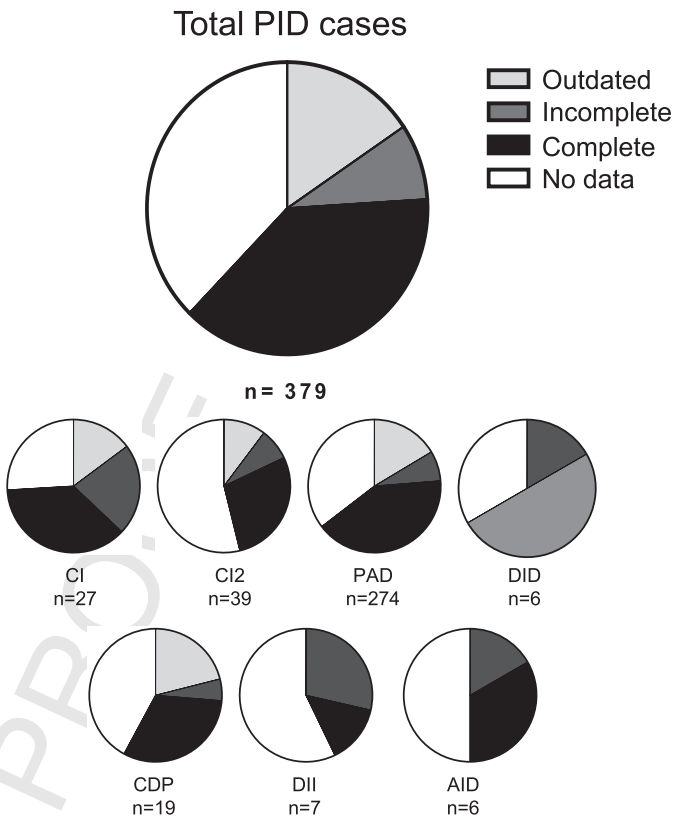

Fig. 1. Vaccination categories in the whole PID group as a whole and in every major subgroup are included here. Vaccination schedules were classified according to the quality of the information found, considering in every case the vaccines that should have been administered according to date of birth and age at the time of this study. PID: primary immunodeficiencies, CI: combined deficiencies, CI2: combined deficiencies with associated or syndromic features, PAD: predominantly antibody deficiencies, DID: diseases of immune disregulation, CDP: congenital defects of phagocytes, DII: defects in innate immunity and AID: autoinflammatory diseases. Complement deficiencies included only one case with no data about the vaccination status.

of complications in 349 patients exposed to BCG, with an overall increase in the risk of localized or disseminated reactions of 400 and 33,000, respectively compared to the normal population. This study also reported a 2.03-fold increase in BCG complications among SCID patients receiving BCG before the first month of age compared to those vaccinated later in life [15].

General guidelines in PID recommend maintaining a vaccination schedule similar to that used for healthy individuals and to perform serum antibody measurements to assess the vaccine response efficacy. However, depending on the type of immune defect, individual recommendations exist for each type of vaccine [16–19]. Overall, the administration of live vaccines is contraindicated in patients with severe antibody deficiencies such as agammaglobulinemia and also in SCID patients. However, vaccines with inactivated microorganisms are a safe option for these patients, although the immune responses may not be appropriate.

In Colombia, the real incidence of AEFI is unknown because only severe reactions are reported to the healthcare system, resulting in underreporting of mild and moderate reactions. Additionally, there are limitations to the comprehensive follow up to assess causality, as shown in the national AEFI report in 2012 [20]. More importantly, the BCG vaccine might be causing serious AEFI in PID patients with cellular deficiencies in Colombia, because it is administered at birth before newborns screening programs for severe congenital lymphopenias are implemented.

The aim of this study is to describe AEFI in a cohort of patients with PID to improve vaccination policies in this population. These data also encourage the active search for AEFI and its comprehensive follow up in order to establish an earlier diagnosis of PID allowing a more favorable outcome and prognosis for patients.

2. Methods

We included 379 medical records from the database of the Group of PID (GPID) at the University of Antioquia in Medellín, Colombia. Taking into account the extended immunization program (EIP) covered by the Ministry of Social Protection from Colombia, [21] the vaccination certificates were classified into three categories: complete if the patient has received all vaccination doses recommended for infancy; incomplete if any of the vaccination doses recommended by age were missing; or outdated if patient information about vaccination existed but was not updated according to age. Changes in the EIP introduced in Colombia in 2002 were considered depending on the patient's date of birth [22]. The AEFI severity was classified according to the WHO 1999 guidelines as common, minor or rare and more serious vaccine reactions [2]. AEFI are considered serious when they result in death, are life-threatening, require in-patient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability/incapacity, or induce a congenital anomaly/birth defect [2]. An assessment of causality was performed by a consensus of experts following the CISA-2009 criteria [2,23].

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