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CLINICAL CASE

Hypotonic-Hyporesponsive Episode after immunization with whole-cell pertussis combination vaccine. Clinical Case Report

Episodio Hipotonía-Hiporreactividad posterior a la inmunización con vacuna combinada con pertussis de células enteras. Reporte de un caso

Juliana Velasco[a], David A. Montero[b], Miguel Guzmán[a]

[a]Pediatric Emergency Service, Hospital University of Chile "Dr. José Joaquín Aguirre", Santiago, Chile.
[b]Microbiology and Mycology Program, Faculty of Medicine, University of Chile, Santiago, Chile.

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Abstract

Introduction: Hypotonic-Hyporesponsive Episode (HHE) is an adverse event after vaccination, mainly associated with whole-cell pertussis vaccines. It is characterized by a sudden onset of muscle flaccidity, reduced response to stimuli and pallor or cyanosis. Although the HHE is infrequent, it is considered a severe adverse event. **Objective:** To report a case of HHE following the administration of the whole-cell pertussis combination vaccine (DTwP-HB-Hib), which is included in National Immunization Program (PNI) of Chile, and to contributing to the knowledge of this adverse event in the country. **Case report:** A 6-month-old infant, 3 hours post-vaccination with the third dose of DTwP-HB-Hib vaccine, presented a decreased level of consciousness that was interpreted as atonic seizure but finally considered as EHH. The infant progressed favorably after 2 hours of clinical observation and was discharged 24 hours later. Parents were suggested to continue the immunization schedule of the infant with acellular pertussis vaccines as a preventive measure. **Conclusions:** The lack of knowledge about the EHH may discourage childhood immunization. Therefore, it is important for the medical staff to inform parents of the patients about this benign, self-limited and non-recurrent adverse event. In these cases, it is recommended to continue the immunization schedule of the infant with acellular pertussis vaccines.

Keywords:
Hypotonic-Hyporesponsive Episode,
Vaccine-associated adverse events,
Whole-cell pertussis combination vaccine,
(DTwP-HB-Hib)

Correspondence:
Dr. Miguel Guzmán
mguzmann@hcuch.cl

Introduction

Whooping cough, also known as pertussis, is an acute infection of the respiratory tract that is characterized by the presence of a paroxysmal cough for at least two weeks, respiratory stridor or posttussive vomiting[1]. The main etiological agent is the *Bordetella pertussis*, although other species of Bordetella, such as *B. parapertussis*, *B. bronchiseptica* and *B. holmesii* have also been associated with sporadic cases and outbreaks of this disease[2,3].

The first vaccines for whooping cough were approved in the United States, 1914, and were formed of *B. pertussis* inactivated whole-cells (wP) by heat and/or chemical agents. Then, in the 1940s, wP formulations were ~~in~~ included in combined vaccines that contained tetanus (T) and diphtheria toxoids (D)[4]. Notably, DTwP combined vaccines showed to be highly immunogenic and protective against *B. pertussis*, however, the pertussis component was associated, commonly, with adverse effects such as irritability, fever and erythema, and less frequently, seizures and hypotonic-hyporesponsive episodes (HHE)[5]. The HHE is a severe adverse effect that is characterized by the clinical triad of sudden muscle flaccidity, a lower response to stimulus and a change in the skin coloration (paleness or cyanosis)[6].

Despite of the massive vaccination of the population with DTwP Vaccines the occurrence of whooping cough plunged[7,8], concern about adverse effects led to developing acellular anti-pertussis vaccines (aP) composed of one or more purified antigens (pertussis toxin, filamentous hemagglutinin, pertactin and fimbriae) in the 1970s and 1980s. DTaP vaccines were less reactogenic than vaccines with wP and they are, currently, included in the vaccination programs of many developed countries[9,10]. In fact, the rates of incidence of HHE after the administration of DTaP vaccines (from 4 to 140 episodes per 100,000 children) are lower than DTwP vaccines (from 36 to 250 episodes per 100,000 children)[6]. However, despite the availability of anti-pertussis vaccines and the wide vaccination coverage, it has been reported that in some countries, including Chile, there has been an increase in the incidence and mortality due to whooping cough, especially in children under 6 months[2,7,11-13]. Even though that the reasons for the re-emergence of the disease are complex and can vary in each country, the short duration of the protection and the probable lower impact of the aP vaccines on the infection and transmission seem to have an important role[14], which is currently a topic of study and discussion[15,16]. In this epidemiological scenario, whooping cough remains a public health problem and one of the most common vaccine-preventable diseases, both in developed and developing western countries[8,17].

The vaccination for pertussis started, in Chile (1955), with a combined vaccine of wP and diphtheria (DP). Significantly, as in other countries, the introduction and massive administration of anti-pertussis vaccines led to a significant reduction in the incidence of whooping cough, in comparison with the pre-vaccination period. Later, between 1975 and 2006 a DTwP vaccine was administered and in 2007, the National Immunization Program (NIP) included the combined DTwP-HB-Hib vaccine[8]. After the change of immunization schedule of anti-pertussis vaccination in 2012, the current NIP administrates three dosis DTwP-HB-Hib vaccine at 2nd, 4th, 6th months with the first booster injection at the 18th month and two additional booster injections of acellular anti-pertussis vaccine with reduced-antigen content (Tdpa), which ~~were~~ are administrated to scholars of primary education (first and fourth of basic elementary education)[18,19].

After the change of immunization schedule of anti-pertussis vaccination in 2012, the current NIP administrates three dosis DTwP-HB-Hib vaccine at 2nd, 4th, 6th months with the first booster injection at the 18th month and two additional booster injections of acellular anti-pertussis vaccine with reduced-antigen content (Tdpa), which are administrated to scholars of primary education (first and fourth of basic elementary education)[18,19]. In addition, as of May 2017 premature newborn younger than 37 weeks of gestation must receive a vaccination schedule at the 2nd, 4th, 6th and 18th month with a hexavalent combined vaccine (diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio and *Haemophilus influenzae* type ~~B~~ b)[20].

On the other hand, regarding the safety of the vaccines for whooping cough available in Chile, there is only one study carried out by Abarca et al[21], where the adverse effects of two formulations DTwP used as a booster during 2005 were evaluated. In this study, the most common adverse effect was high fever, while more severe adverse effects such as HHE and encephalopathy were not present.

In addition, it is important to mention that in the country, every adverse event following immunization (AEFI) must be notified to the Pharmacovigilance Sub-Department of the Public Health Institute (SDFV) by an AEFI questionnaire. The notification can be made by an assistance center, emergency services or immunization clinics. Later, the SDFV, the NIP and the Regional Ministerial Secretary of Health (SEREMI) carry out the evaluation, research, and tracking of the notified AEFI[22].

The objective of this study is to report a case of HHE after the administration of the pentavalent combined vaccine with diphtheria, tetanus, acellular pertussis, hepatitis B and Haemophilus influenzae type B (DTwP-HB-Hib) which is included in the NIP of Chi-

le, in order to spread this infrequent complication of benign evolution, auto-limited and non-recurrent.

Clinical Case

A 6-month old infant, with a history of allergies to cow's milk protein and a vaccination schedule up-to-date according to the NIP schedule (without evidence of previous adverse effects). After 3 hours of the administration of the third dose of DTwP-HB-Hib, the patient assisted to **Pediatric Emergency Service,** due to a medical symptom: sudden loss of consciousness for less than 1 minute, hyporeactivity, muscle flaccidity, general paleness and perioral cyanosis. The parents also reported clonic movements and eye deviation.

At the moment of admission to the emergency service, the patient had skin paleness, slight cyanotic tone on the lips, and coldness in the extremities with good reactivity and vigorous cry. The patient was also afebrile, hemodynamically stable, without respiratory distress and hypoglycemia. In the face of a possible case of seizures, samples for a blood count, biochemical profile, venous blood gases, plasma electrolytes, C-reactive protein and hepatic profile were required. After 30 minutes of monitoring, the patient recovered the skin tone with warm extremities, a firm pulse and a normal capillary nail refill test.

Two hours after the admission, there was no clinical deterioration, the infant showed a recovery of the muscular tone, normal reactivity to stimulus and a better tissue perfusion, with a normal physical and neurological exam.

The HHE diagnosis was considered, due to the normal results of the clinical tests and electroencephalogram, and the record of the patient vaccinated with a combined vaccine DTwP-H B-Hib.

The patient was discharged after 24 hours of monitoring. The family was notified of the boosters with an acellular anti-pertussis vaccine as a preventive measure. The immunization clinic, where the infant received the vaccine, was notified of the HHE, who later reported the case to the SDFV through an AEFI questionnaire. Lastly, in the first and sixth month after the discharge, the patient was monitored via phone, the family reported that the infant did not show any sequelae related to HHE.

Discussion

Despite the unquestionable success of the vaccination, the safety of vaccines is an issue of public interest that is becoming increasingly important[23]. Thus, the monitoring and identifications of adverse effects supposedly attributable to vaccination must be a priority in the public health of each country.

HHEs are infrequent adverse reactions after infant vaccinations, mostly associated with whole-cell anti-pertussis vaccines. However, there are some reports of HHE due to acellular anti-pertussis vaccines[23], diphtheria, tetanus, hepatitis B, polio and Haemophilus influenzae type b[24]. In general, the major incidence of these episodes can be observed after the administration of the first dose of vaccine and the time range, in which the symptoms show up, goes from the administration to 48 hours. Additionally, it is an auto-limited event that does not leave sequelae on a long-term basis. The HHE phathophysiological mechanism has not been established yet, but it is probable that many factors contribute to it, such as idiosyncratic/immunological from the children and inherent to the vaccine.

On the other hand, it is important to point out that the diagnosis of this clinical condition is difficult because: (i) its short duration, most of the times ~~we base~~ based on the description of the parents, (ii) a possible confusion with other similar clinical symptoms and (iii) the lack of laboratory tests that confirm this condition. In addition, it has been reported, historically, in the literature as shock, fainting or syndromes similar to fainting, consequently, the various descriptions of the condition have complicated interpretation and comparison of reports about its occurrence and consequences[6,24,26]. Therefore, to facilitate an early diagnosis of HHE and its notifications, it is important that the doctor and the sanitary staff are familiarized with a standard description of of this AEFI[6].

In this sense, the definition established by the Work Group for HHE from the "Brighton Collaboration"[6] has been the first international effort to elaborate a global consensus about this clinical condition, which is now used in many countries[24-26]. Since the clinical triad of hypotonicity, hyporeactivity and cyanosis is not always present in the HHE, the definition given by the "Brighton Collaboration" includes the level of diagnostic certainty according to the presence or absence of these clinical symptoms (Table 1). Also, during the differential diagnose the vasovagal syncope and atonic seizures of short duration must be considered. The vasovagal syncope is defined by the same clinical-triad, but it appears in a different age group (children older than 10 years), while atonic seizures are characterized more by hypotonicity than hyporeactivity, and there is no cyanosis. It must be rejected if the symptoms are caused by intoxication, septicemia or if the patient is just sleeping[6].

Thus, considering the HHE definition by the "Brighton Collaboration", this report corresponds to an HHE case with level 1 of diagnostic certainty. Authors consider that the classifications of these ad-

Table 1. Definition of HHE with levels of diagnostic certainty established by the "Brighton Collaboration"

Level	Present symtoms[a]	Absence o unknown symtoms
1	Hypotonia Hyporeactivity Pallor or cyanosis	None
2	Hyporeactivity Pallor or cyanosis	Muscle tone unknown
	Hyporeactivity Hypotonia	Skin color unknown
3	Hyporeactivity Pallor or cyanosis	Normal muscle tone
	Hypotonia Pallor or cyanosis	Level of responsiveness unknown

[a]Sudden onset of: Hypotonia (muscle flaccidity), Hiporeactivity (decrease or absence of response) and changes in skin color (pallor or cyanosis). Besides, there may be fever in up to one third of cases of HYPOTONIC-HYPORESPONSIVE EPISODE (HHE).

verse effects and the proper notification to the corresponding authorities (SDFV) significantly contribute to the vigilance of the safety of authorized vaccines. These notifications also contribute to the execution of epidemiologic studies that can be a guide in policy-making by authorities of public health.

Conclusion

A classic HHE case is reported, with the classic triad of hypotonicity, hyporeactivity, and cyanosis due to a vaccine combined with wP. It is essential that the pediatrician and the medical staff educate families about HHE since these events might discourage infant vaccination, especially taking into account the emergence of anti-vaccination movements that discuss this topic in mass media without the proper scientific support. During the orientations, the topic to be discussed is that it is an entity of benign evolution, auto-limited and non-recurrent, thus the vaccination on children schedule can be continued by administrating formulations that contain acellular anti-pertussis components as precaution measures.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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