Hypotonic hyporesponsive episode and the 13-valent pneumococcal vaccine

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Hypotensive-hyporesponsive episodes are rare events after immunizations performed for diphtheria, tetanus, *Haemophilus influenzae* type b and hepatitis B virus vaccines, but most of the reported episodes have been associated with pertussis-containing vaccines. We report the case of a 3-month-old girl, previously healthy otherwise, presenting with the unusual event of a hypotonic- hyporesponsive episode after vaccination with the 13-valent pneumococcal vaccine. Diagnosis was established after a thorough evaluation of the patient and by exclusion of other clinical conditions.

Key words: vaccine, adverse reactions, child, pneumococcal conjugate vaccine, hypotonia

Hypotensive-hyporesponsive episode is described as a sudden reduction in muscle tone, with hyporesponsiveness and skin pallor or cyanosis within 48 hours after immunization in children age <10 years, lasting for 1 min to 48 hours[1]. We describe the case of a 3-month-old female who presented with a hypotonic-hyporesponsive episode after vaccination with the 13-valent pneumococcal vaccine.

Case Report

The current case concerns a 3-month-old Caucasian female born at the 39th week of gestation by normal vaginal delivery with a birth weight of 3.24 kg. The perinatal period was unremarkable and the neonate was discharged home after 3 days of hospitalization. At presentation, her weight was 5900 g (75th percentile), length 61 cm (75th percentile) and head circumference 40 cm (75th percentile). The patient on the day of admission received the 13-valent pneumococcal vaccine. Eight hours after the vaccination the patient developed a fever up to 38.2° C (skin temperature), as measured by the parents, and 10 hours after the vaccination hypotonia, hyporesponsiveness and skin pallor of 1 min duration were manifested, as witnessed and described by her parents at their home.

Personal history revealed that the patient had had a similar episode 1 month ago, at the age of 2 months, also in the home setting and witnessed only by the parents, after the first immunization with the DTaP–IPV–Hib vaccine, which was not further investigated. At that time the parents were advised to continue vaccination as scheduled without any changes. The rest of the patient's history was unremarkable.

The patient was immediately transferred to the emergency department after the episode, where she appeared fully aroused with appropriate color and tone. No local reaction was noted at the vaccine administration site. Temperature was 36.8° C, blood pressure 89/56 mmHg, pulse rate 135/min, Sat O_2 99% at room air. White cell blood count was 19.100/μL, Ne 55%, Ly 34%, Hct 35.3%, Hb 11.8 g/dl, PLT 409,000/μl, C-reactive protein 5 mg/L. Glucose, blood urea nitrogen, creatinine, serum electrolytes, urine analysis and lumbar puncture results (2 cells/hpf, glucose 52 mg/dl, protein 21 mg/dl with negative gram stain test), urine and serum amino acids and urine organic acids were within normal limits. Blood, urine and CSF cultures were sterile. Cardiovascular assessment with electrocardiogram and echo was unremarkable except from a patent foramen ovale revealed by the cardiac ultrasound. Brain ultrasound scan was unremarkable. Developmental assessment

revealed an infant who had developed a social smile and was able to follow moving objects and lift her head when supine to 45°. The patient did not receive any treatment and was discharged from the hospital two days after admission. An electroencephalogram performed one month later was normal. The parents were advised to continue further scheduled vaccinations under the supervision of a pediatrician, preferably in a hospital setting.

We lost follow-up of the patient for more than a year, until she returned for a regular visit at age 19 months. At that time she presented in excellent condition, having had regular follow-up appointments with her primary care pediatrician. She had grown well: her weight was 10 kg (25th percentile), height 85 cm (75th percentile) and head circumference 47 cm (50th percentile). She was able to speak using 10 words, obey commands and repeat words. Her development following the episode has been normal; according to her records, she has been meeting all of the developmental milestones for her age. She was sitting without support at the age of 7 months and has been walking since 12 months. Her body growth was in the 25th-50th percentile range for weight, 50th-75th percentile for height and 25th-50th percentile for head circumference. No major illnesses, hospitalizations, surgeries or chronic diseases were reported. At age 13 months the patient had received the hexavalent (DTaP-Hib-IPV-HBV) vaccine and, during the same visit, the 13-valent pneumococcal vaccine without any adverse events; at age 19 months she received the MMR-V vaccine. The reason for the delay and lack of compliance with the regular immunization program was the parents' fear of a relapse event, although the family was advised by both the primary care pediatrician (repeatedly) and our service to continue vaccination according to the national immunization program.

Discussion

Hypotensive-hyporesponsive episode (HHE) has been reported after diphtheria, tetanus, *Haemophilus influenzae* type b and Hepatitis B vaccines, but most of the reported episodes have been associated with the pertussis vaccine[2]. Episodes have also been reported after MMR, varicella, HBV, HAV, IPV, OPV and DT[2]. The risk of HHE after administration of the whole-cell pertussis vaccine is estimated at 1:1000 to 1:6000, but has decreased since the introduction of acellular pertussis vaccines[3]. HHE should be distinguished from many clinical conditions occurring post-vaccination, such as syncopal episode related to vaccine stress, insufficient ejection fraction on the ground of heart disease, cyanotic or pallid breath-holding spells, the post-ictal state that follows non-observed seizures, atonic convulsions, deep sleep, narcolepsy-cataplexy, anaphylaxis, intoxication or endocrine or metabolic disorders[1]. The recurrence rate of HHE after pertussis revaccination is low, and HHE should be considered as a precaution in relation to but not a contraindication for future vaccinations[4,5]. Full recovery of patients after the episodes has been reported in all cases so far, and long-term outcome is excellent. A case control study in the Netherlands of 101 children with HHE revealed low rates of episode recurrence and normal growth and development up to the age of 18 months[6]. A Swedish cohort also revealed normal development of affected children up to the same age[7].

In our case, laboratory and clinical investigation revealed no apparent reason for the HHE episode due to the usual causes mentioned above. Therefore, it was attributed to the 13-valent pneumococcal vaccine. The first episode, which according to the personal history was observed after the administration of the DTaP–IPV–Hib vaccination, could also be attributed to the vaccination; however no investigation was performed at that time in order to fully support this position.

Regarding the administration of the 13-valent pneumococcal vaccine at different times than the DTaP-IPV-Hib vaccine, the initiation of the 13-valent pneumococcal vaccine administration is, according to the national immunization schedule, recommended in the 2nd month of life and then at 2-month intervals for the next 2 injections, concomitantly with the DTaP-IPV-Hib vaccines. Nevertheless, private practitioners sometimes choose to administer the pneumococcal vaccine separately, in the 3rd, 5th and 7th months of life. This is in order to avoid giving the second injection on the same day, thereby avoiding possible additional adverse side effects due to the simultaneous administration of different antigens and

possible anxiety for the family—practice which contradicts the official recommendations.)

Furthermore, the increased WBC count and the C-reactive protein increase could possibly be attributed to a mild concomitant viral infection; however, there were no clinical signs to support this, and even if so, the presence of HHE could not be accounted for. There is no current evidence that immunization with the 13-valent pneumococcal vaccine can increase WBC count and C-reactive protein levels. Nonetheless, there is published evidence that immunizations can increase the values of C-reactive protein and WBC count [8, 9], so the increase of those laboratory values in our case could be attributed to the immunization itself.

HHE is a benign, self-limited syndrome. It is difficult to establish a casual relationship between the administration of the vaccine and the unusual event since the latter can be attributed to multiple clinical conditions. The case described here is extremely rare because the patient presented with a recurrent episode following the immunization program, and the current episode could be attributed to the administration of the 13–valent pneumococcal vaccine since it was the only antigen provided. Up to now, no case of HHE has been reported in the literature after administration of the 13-valent pneumococcal vaccine.

REFERENCES

1. Braun MM, Terracciano G, Salive ME, et al. Report of a US public health service workshop on hypotonic-hyporesponsive episode (HHE) after pertussis immunization. Pediatrics 1998; 102: E52.
2. DuVernoy TS, Braun MM. Hypotonic-hyporesponsive episodes reported to the Vaccine Adverse Event Reporting System (VAERS), 1996-1998. Pediatrics 2000; 106: E52.
3. Le Saux N, Barrowman NJ, Moore DL, Whiting S, Scheifele D, Halperin S. Decrease in hospital admissions for febrile seizures and reports of hypotonic-hyporesponsive episodes presenting to hospital emergency departments since switching to acellular pertussis vaccine in Canada: a report from IMPACT. Pediatrics 2003; 112: E348.
4. Goodwin H, Nash M, Gold M, Heath TC, Burgess MA. Vaccination of children following a previous hypotonic-hyporesponsive episode. J Paediatr Child Health 1999; 35: 549-552.
5. General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011; 60: 1-64.
6. Vermeer-de Bondt PE, Labadie J, Rumke HC. Rate of recurrent collapse after vaccination with whole cell pertussis vaccine: follow up study. BMJ 1998; 316: 902-903.
7. Heijbel H, Ciofi degli Atti M, Harzer E, et al. Hypotonic hyporesponsive episodes in eight pertussis vaccine studies. Dev Biol Stand 1997; 89: 101-103.
8. Pourcyrous M, Korones SB, Crouse D, Bada HS. Interleukin-6, C-reactive protein, and abnormal cardiorespiratory responses to immunization in premature infants. Pediatrics 1998; 101: E3.
9. Pourcyrous M, Korones SB, Arheart KL, Bada HS. Primary immunization of premature infants with gestational age <35 weeks: cardiorespiratory complications and C-reactive protein responses associated with administration of single and multiple separate vaccines simultaneously. J Pediatr 2007; 151: 167-172.