LEADING ARTICLE

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Hypotonic-Hyporesponsive Episodes Following Pertussis Vaccination

A Cause for Concern?

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Abstract

Vaccine safety has become a major community concern and of particular importance for parents, vaccine recipients and vaccine providers. A hypotonic-hyporesponsive episode (HHE) is a sudden and unexpected episode of loss of tone, unresponsiveness and colour change which uncommonly affects infants and children after vaccination. Although any vaccine may be associated with this adverse event, HHE usually follows administration of a pertussis containing vaccine. There has been renewed interest in this adverse event in the light of community concerns regarding vaccine safety. The focus of this interest has been to formulate an acceptable case definition, to document possible risk factors and to better define the outcome of HHE. In addition, studies have documented the outcome of revaccination of children who have had an HHE. Although much remains to be learnt about HHE it would appear that there are no long-term sequelae and that children who have had an HHE can be revaccinated. Parents should be provided with the available information such that they can make an assessment of the risks and benefits of pertussis vaccination. The benefits of pertussis vaccination still outweigh the risk and universal childhood pertussis vaccination should continue to be advocated.

The past two centuries have demonstrated that vaccines are effective and that immunisation strategies have resulted in significant health benefits most notably the eradication of small pox and the elimination of polio and measles from many continents. Although vaccine efficacy remains important vaccine safety is now the major concern of parents and vaccine recipients.[1] The reasons for this include a fall in vaccine preventable disease, a low community tolerance of adverse vaccine reactions, changes to consent procedures and the availability and rapid dissemination of information. These should be viewed as positive developments in the field of vaccination. However, there are significant challenges in maintaining community confidence in vaccine safety which once lost may lead to a decrease in vaccine coverage and a resurgence of vaccine preventable disease.[2] Recent strategies have been to develop safer vaccines, to ensure that adequate clinical safety trials have been performed prior to vaccine licensure and to enhance the post-marketing surveillance of vaccine adverse events. The effective communication of knowledge about the risks and benefits of vaccination both to vaccinees and/or to their parents and the wider community is also important. Those individuals who do experience an adverse event following immunisation should be appropriately managed.

Given this background it is timely to review HHE. In 1991, the review by the Institute of Medicine concluded that there was sufficient evidence available to establish a causal relationship between whole cell pertussis vaccine and HHE.[3] However, HHE has also been documented to occur after other vaccines, including diphtheria, tetanus, *Haemophilus influenzae* type B and hepatitis B.[4,5] Since every child who receives a vaccine is at risk of this uncommon event it is important for vaccine providers and health professionals to have some knowledge of HHE. This review will highlight the current knowledge of HHE after a pertussis vaccine.

1. Definition

Until recently there has been no generally accepted definition of HHE. This has resulted in confusion and hampered further research into the condition. A recent US Food and Drug Administration sponsored work shop has proposed a case definition (table I).[5] Importantly both hypotonia and hyporesponsiveness are always required to meet this case definition. Lack of colour change excludes the diagnosis if this is commented on by an observer but not if the observer cannot recall whether colour change occurred. HHE should be the term used to replace those events which were previously described as shock or collapse provided the proposed case definition is met.

It is recognised that this case definition is broad in terms of the age range and onset of HHE symptoms.[5] However, a broader definition aims to be sensitive in terms of surveillance and to allow for later analysis of cases to arrive at a more specific case definition.

2. Incidence, Morbidity and Mortality

There is a wide variation in the reported incidence of HHE following pertussis vaccination.[6-9] This reflects the variability in case definitions and case ascertainment rather than inherent properties of different pertussis vaccines. However, based on clinical trials and passive surveillance data, the reported rate of HHE following a whole cell pertussis vaccine is higher than that following an acellular pertussis vaccine.[6,7,9-11] The reported rates (per 100 000 doses) following a whole cell pertussis vaccine may vary from 57 to 250 episodes. In contrast, the reported rates following acellular pertussis vaccines vary from 4 to 140 episodes.

Table I. Proposed case definition for hypotonic-hyporesponsive episodes (HHE)[5]

An event of sudden onset occurring within 48 hours of immunisation with the duration of the episode ranging from 1 minute to 48 hours, in children younger than 10 years of age
All of the following must be present:
limpness or hypotonia
reduced responsiveness or hyporesponsiveness
pallor or cyanosis or failure of the observer to recall skin colouration
HHE is not considered to have occurred if there is a known cause of these signs, if urticaria is present during the event, if normal skin colouration is observed throughout the episode, or the child is simply sleeping.

There is a paucity of data concerning the morbidity from HHE. A review of Canadian tertiary care hospitals has shown that HHE accounts for a hospitalisation rate of less than 5 cases per 100 000 admissions.[12] Of those children who are hospitalised, the majority (60%) were hospitalised for less than 24 hours. There is no current evidence to suggest that HHE is associated with any long-term morbidity or mortality.

3. Pathogenesis

The pathogenesis of HHE is unknown and has been poorly studied given the constraints of investigating a condition which is rare and only results in transient symptoms. Cardiovascular, neurological, metabolic, and allergic or immunological mechanisms have been postulated.[5] Any postulated mechanism would need to explain the increased risk following a whole cell pertussis vaccine (as opposed to acellular pertussis and other vaccines), the reduced occurrence with increasing age and/or increasing doses and the apparent idiosyncratic nature of the reaction.

Patients with HHE have a leucocytosis due to a neutrophilia but this also occurs in vaccinated infants who have not had an HHE.[13,14] Pertussis immunisation in mice may cause hyperinsulinaemia

and hypoglycaemia resulting from pertussis toxin exposure. This has been proposed as a mechanism for convulsions and HHE post immunisation.[15,16] However, studies of children within 48 hours of experiencing an HHE have not shown any significant changes in insulin or glucose levels, nor any evidence of lymphocytosis promoting factor (pertussis toxin) compared with a group of children experiencing febrile convulsions unrelated to immunisation.[16] The biological properties of diphtheria-pertussis-tetanus (DPT) vaccines have been studied in relation to adverse events.[17,18] These have found a positive association between vaccine endotoxin content and fever and local reactions. The number of cases of HHE, in these studies, have been insufficient to draw similar conclusions.[17,18]

The pathogenesis of HHE is likely to be multifactorial and may result from factors both idiosyncratic to the child as well as inherent in the vaccine.

4. Risk Factors, Clinical Presentation and Management

Case-control studies have failed to demonstrate any risk factors for HHE. Review of passive reports to the Vaccine Adverse Event Reporting System (VAERS), in the US, has demonstrated a slight female predominance of 53%.[18] HHE occurs more commonly after the primary schedule and usually after the first dose.[4,12,19] Typically the median time to the onset of symptoms is between 3 and 4 hours but cases have been reported to occur immediately and up until 48 hours post vaccination.[4,12,19,20] Interestingly, of the cases whose onset is less than 5 minutes, only 8.5% were younger than 24 months of age as compared with 66.7% of those older than 24 months.[20] The presentation of HHE is usually unexpected and sudden with the reported symptoms of colour change (pallor or cyanosis), unresponsiveness and floppiness. Fever may occur in up to one third of cases.[19,20] The median duration of symptoms is between 10 and 30 minutes but parents may report the time to full recovery as being up to 10 days.[19]

Once an HHE is recognised the immediate management of HHE should provide supportive care for the child and reassurance for the parents. Hospital data from a small case series have documented that blood pressure and blood glucose are normal at the time of presentation.[12] Hence, despite HHE sometimes being called 'collapse or shock', there is no evidence to support the requirement for fluid resuscitation because of cardiovascular compromise. Importantly, other conditions should be excluded and these include an ictal (particularly atonic seizures) or postictal state, rare cardiovascular anomalies which may result in reduced cardiac output, (arrhythmia, congenital cardiac disease), anaphylaxis, and in older children a vaso-vagal or breath holding episodes. At the time of the event, or following the event, parents should be provided with an explanation of the condition and a plan to review the child in order to document full recovery

Table II. Studies determining the outcome of hypotonic-hyporesponsive episodes (HHE)

Study	Case ascertainment	No.of children with HHE evaluated	Follow-up period	Method of assessment	Outcome
Baraff et al.[21]	Prospective clinical trial	6	6 to 7 years	Neurological examination and psychometric testing	Normal performance IQ and low verbal IQ – explained by number of hispanic and bilingual children
Gold et al.[12]	Hospital admissions	10	Mean 26.5mo; range 4 to 52mo	Parental report	100% parental report of normal development
DuVernoy & Braun[20]	Passive surveillance (VAERS)	215	NS	Telephone questionnaire of parents	98.6% parental report of full recovery
Vermeer-de Bondt et al.[22]	Enhanced passive surveillance	101	NS	Child health information	No developmental problems reported

NS = not stated; **VAERS** = Vaccine Adverse Event Reporting System.

and discuss the implications for further vaccination.

5. Long-Term Outcome

No long-term sequelae have been associated with HHE. A number of studies have reported on the follow up of HHE cases;[12,20-22] however, these studies have relied on parental reporting rather than formal neurodevelopmental testing with the exception of the study by Baraff et al.[21] (table II). In this study, 6 children with HHE underwent a neurological review and psychometric evaluation 6 to 7 years after the episode. All children had normal performance IQ scores but low verbal IQ scores. The later finding was explained by the proportion of Hispanic and bilingual children in the sample. The conclusion of the study was that there was nothing to indicate that any of these children had any evidence of serious neurological damage associated with the HHE.

Clearly, further studies are required regarding any long term sequelae and studies will need to be carefully designed to select appropriate controls and eliminate any biases. At least two follow-up studies in progress and these have selected cases from a passive surveillance system and a large clinical trial.[5] In time it is hoped that the results of these studies will become available.

6. Revaccination with a Pertussis Containing Vaccine

HHE is regarded by many providers as a contraindication to revaccination with a pertussis vaccine. Understandably parents and vaccine providers have been reluctant to administer further pertussis containing vaccines and this has been reflected in the immunisation recommendations of many countries. In many communities the risk of acquiring pertussis remains substantial. This has led to difficulties in obtaining valid consent from parents since the risk of recurrence of an HHE is unknown. Fortunately, recent studies have documented the outcome of revaccination in a number of children with HHE (table III).[19,21-25] In a Dutch study, 84 children who had an HHE following a whole cell pertussis vaccine tolerated revaccination with further doses of whole cell pertussis vaccine.[22] Similar findings occurred in an Australian study that involved 68 children who presented with HHE following administration of a whole cell vaccine and who were subsequently administered an acellular pertussis vaccine.[23] Recurrence of an HHE has been documented after whole cell vaccination in two children both of whom had an HHE after a whole cell vaccine.[24,25] One of these children was attending a special immunisation clinic and the other was part of an Italian pertussis vaccine clinical trial.

Although the number of children who have been revaccinated with pertussis vaccine has been relatively small these preliminary results have been encouraging and they suggest that the rate of recurrence is not high. Current published data show that no child who has had an HHE following vaccination with a whole cell vaccine, and has then received an acellular pertussis vaccine has had a recur-

Table III. Revaccination of children with pertussis vaccine following a hypotonic-hyporesponsive episode (HHE)

Study	Case ascertainment	No. of children with HHE	No. of children revaccinated with a pertussis vaccine	Follow-up period	Outcome of revaccination
Andrews et al.[25]	Special immunisation clinic	5	NS	Variable	1 recurrence
Vermeer-de Bondt et al.[22]	Enhanced passive surveillance	105	84 children (236 doses)	NS	No recurrence
Gold et al.[23]a	Special immunisation clinic	81	68 children (68 doses)	24 and 72 hours and 7 days	No recurrence
Tozi et al.[24]	Prospective clinical trial	12	NS	48 hours	1 recurrence

a Patients in this study were included in the study by Goodwin.[9]

NS = not stated.

rence of HHE. However, further studies are required to confirm these findings. It is less clear whether children who experience an HHE after acellular pertussis vaccine are likely to experience a recurrence after further doses of acellular vaccine. Many health authorities now advocate revaccination in children who have experienced an HHE after a pertussis vaccine.[26-28]

Vaccine providers should be able to provide parents with this information concerning the possible risk of recurrence of HHE. Revaccination under medical supervision, such as a special immunisation service, has been an effective way of ensuring that such children are revaccinated.[23] For most parents the presenting episode has been a frightening experience and they are motivated to have their children revaccinated provided that their child is observed post immunisation and has immediate access to care should the episode recur.

7. Conclusions

Much remains to be learnt about HHE and this will be a challenge given that the condition is rare and symptoms transient. However, a uniform and accepted case definition combined with good adverse event surveillance may allow for further case-control studies to be performed. The imperative will be to identify possible risk factors and define the pathogenesis and outcome of the condition. As for all vaccines any recommendations for its use requires a careful consideration of the risks and benefits of a particular vaccine for a specific child within a defined community. Concern about HHE will rightly persist until all of the questions concerning HHE have been answered. Although the current knowledge of HHE is deficient, the benefits of pertussis vaccination still outweigh any possible adverse effects of the vaccine and universal pertussis vaccination should continue to be advocated for all children.

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