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ORIGINAL ARTICLES

Lack of Evidence for a Causal Relationship Between Hypoxic-Ischemic Encephalopathy and Subdural Hemorrhage in Fetal Life, Infancy, and Early Childhood

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ABSTRACT

It has been asserted that hypoxic-ischemic encephalopathy (HIE) with cerebral swelling in the absence of marked trauma may be responsible for subural hemorrhage in the young. As this may have considerable implications in determining both the mechanism of death and the degree of force required to cause injury in certain cases of inflicted head injury in infancy, clarification is required. A retrospective study of 82 fetuses, infants, and toddlers with proven HIE and no trauma was undertaken from forensic institutes in Australia, the United Kingdom, Germany, Denmark, and the United States. The age range was 35 weeks gestation to 3 years, with a male to female ratio of 2:1. All cases had histologically confirmed HIE. Causes of the hypoxic episodes were temporarily resuscitated sudden infant death syndrome with delayed death (N = 30), drowning (N = 12), accidental asphyxia (N = 10), intrauterine/delivery asphyxia (N = 8), congenital disease (N = 6), aspiration of food/gastric contents (N = 4), inflicted asphyxia (N = 3), epilepsy (N = 1), dehydration (N = 1), drug toxicity (N = 1), complications of prematurity (N = 1), and complications of anesthesia (N = 1). The initiating event was not determined in 4 instances. In no case was there macroscopic evidence of subdural hemorrhage. In this study no support could be given to the hypothesis that HIE in the young in the absence of trauma causes subdural hemorrhage.

Key words: hypoxic-ischemic encephalopathy, non-accidental head injury, shaken infant syndrome, subdural hemorrhage.

INTRODUCTION

The Shaken Infant Syndrome (also known as nonaccidental head injury), is a term that has been used for a situation where an infant has been gripped firmly by an adult and shaken backwards and forwards in a violent manner, resulting in significant brain damage and/or death [1,2]. Conflicting opinions have been expressed as to the alleged manifestations of shaking and whether

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the features could be due to impact rather than to shaking alone [3–11]. In recent years it has been hypothesized by Geddes et al that the neuropathological findings that have been cited as evidence of traumatic diffuse axonal injury in shaking may have instead been caused by hypoxia with brain swelling secondary to brainstem injury [12,13]. Following this proposal, the same investigators hypothesized that subdural and retinal hemorrhages found in cases of alleged shaking could also be due to hypoxia with cerebral edema and raised central venous pressure and not to trauma [14,15]. To help clarify this issue, the following multi-institute study was undertaken to examine the neuropathological findings in a series of fetuses, infants, and toddlers with confirmed hypoxic brain damage. As the eyes were not always examined, no comment could be made on the likelihood of retinal hemorrhage being present or absent.

MATERIALS AND METHODS

The files of the Forensic Science SA and Womens and Childrens Hospital, Adelaide, South Australia, Australia, were searched over a 17-year period from 1989 to 2005 for cases of brain death from hypoxic-ischemic encephalopathy (HIE) due to short-term survival following an anoxic episode. Similar cases were identified by searching the files from the Department of Legal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, during a 4-year period from 2000 to 2003; the Department of Forensic Medicine, University of Aarhus, Aarhus, Denmark, over a 9-year period from 1997 to 2005; and the San Diego SIDS/SUDC Research Project in the Rady Children's Hospital, Department of Pathology, San Diego, California, USA, for a 12-year period from 1991 to 2002. Further cases were contributed from one pathologist's (GR) case records.

All cases had been subject to full medicolegal investigation and evaluation. Autopsies were done by trained pediatric and forensic pathologists. The case details were examined, the autopsy findings summarized, and the neuropathology reports reviewed. There were no cases of cranial trauma, and cases with vascular malformations, established sepsis, or other possible causes of disseminated intravascular coagulation were excluded.

Table 1. Causes of hypoxic episodes in 82 infant deaths

Temporarily resuscitated SIDS	30
Drowning	12
Accidental asphyxia[a]	10
Intrauterine/delivery asphyxia	8
Congenital disease[b]	6
Undetermined	4
Aspiration of food/gastric contents	4
Inflicted asphyxia[c]	3
Dehydration	1
Drug toxicity	1
Post epilepsy	1
Complications of prematurity	1
Complication of anesthesia	1

SIDS indicates sudden infant death syndrome.
[a]Choking on food, hanging, positional asphyxia, wedging.
[b]Congenital cardiovascular disease, gastroschisis, multiple congenital anomalies.
[c]Suffocation, strangulation.

RESULTS

A total of 82 cases were accessioned. The male to female ratio was 55:27, with an age range of 35 weeks gestation to 3 years. All had histologic evidence of HIE, including neuronal nuclear pyknosis and cytoplasmic eosinophilia. Causes of the hypoxic episodes are summarized in Table 1.

In every case there was evidence of diffuse HIE with cerebral edema, neuronal eosinophilia, and neuronal loss in the longer surviving cases. There was no case with macroscopic evidence of subdural hemorrhage. Intradural hemorrhage had not been noted macroscopically, and the duras had not been routinely examined microscopically for this.

DISCUSSION

In 2003 Geddes et al proposed a "unified hypothesis" in which they suggested that subdural and retinal hemorrhages found in shaken infants were due to hypoxia with brain swelling and not necessarily to marked trauma [14]. However, only 1 case (a premature infant with *Enterobacter* sepsis secondary to severe chorioamnionitis) manifested a macroscopically observable subdural hemorrhage, microscopy revealed intradural and not subdural hemorrhage, and ocular examinations were not performed on any of the 50 infants and fetuses studied. Despite these features, however, the hypothesis has been widely cited in courts, along with the proposal that the degree of force necessary to produce the findings in shaking cases was not

necessarily "considerable" [14]. However, this opinion has been challenged [4], and the basis for the hypothesis has been criticized for "serious flaws in methodology" [16]. In a judgement of a Court of Appeal dealing with a series of cases of shaking and inflicted head injury in infants in the United Kingdom, the validity of the hypothesis was also called into question [17,18]. This issue obviously requires urgent clarification given the level of disagreement that exists.

The purpose of the present study was, therefore, not to discuss the manifestations and biomechanics of inflicted craniocerebral trauma in infants, but to help provide evidence either for or against the hypothesis that cerebral hypoxia with cerebral swelling causes subdural hemorrhage in the young. To test this, a retrospective multicenter study was undertaken in forensic institutes in 5 countries. This involved detailed gross and microscopic neuropathological study of 82 fetuses, infants, and children 3 years of age or less who survived for variable time periods after documented hypoxic episodes. There was no history or clinicopathological evidence of trauma in any case, and there were no significant underlying diseases present that might confound neuropathological interpretation. If hypoxic brain damage is a cause of subdural hemorrhage in the young, as has been asserted, then it would not be unreasonable to expect that at least some in this series would have this finding; but there were none. This is perhaps not surprising, as subdural hemorrhage is not usually cited as a manifestation of HIE. These results would accord with the statement in the judgement of the Court of Appeal (paragraph 69) that "the unified hypothesis can no longer be regarded as a credible or alternative cause of the triad of injuries" (that is, encephalopathy, subdural hemorrhage, and retinal hemorrhage) [17].

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