Acta Neuropathol (1998) 95 : 625–631

REGULAR PAPER

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Axonal injury and the neuropathology of shaken baby syndrome

Received: 20 October 1997 / Accepted 19 November 1997

Abstract We examined an autopsy series of 14 children with shaken baby syndrome (SBS) who lacked skull fracture. Evidence of axonal injury was sought using immunohistochemical stains for neurofilament, 68-kDa neurofilament and β-amyloid precursor protein (βAPP). βAPP-positive axons were present in the cerebral white matter of all cases of SBS but were also present in 6 of 7 children dying of non-traumatic hypoxic ischemic encephalopathy (HIE). Swollen axons were present in 11 of 14 cases of SBS and in 6 of 7 cases of HIE. βAPP-positive axons were present in both groups in the midbrain and medulla. The cervical spinal cord in SBS contained βAPP-positive axons in 7 of 11 cases; 5 of 7 contained swollen axons within the white matter tracts; in 2 immunoreactivity was localized to spinal nerve roots; in all 7 there was a predilection for staining at the glial head of the nerve root. Among cases of HIE, none showed abnormal axons or βAPP-positive reactivity in the cervical cord white matter. We conclude that cerebral axonal injury is common in SBS, and may be due in part to hypoxic/ischemic injury. Cervical cord injury is also common, and cannot be attributed to HIE. These findings corroborate suggestions that flexion-extension injury about the cervical spinal column may be important in the pathogenesis of SBS.

Key words Shaken baby syndrome · Shaken infant · Axonal injury · β-Amyloid precursor protein

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Introduction

In the early 1970s, Caffey published a series of articles [2, 3] to popularize and support the hypothesis that violent shaking of infants was sufficient to cause them severe neurological damage [8]. Since that time, the syndrome he described as "shaken infant whiplash syndrome" (also known as the shaken baby syndrome, SBS) has been the subject of extensive ophthalmological [14], neurological [10, 12], and forensic investigation [6]. Clinically, the syndrome presents as a seemingly inexplicable, catastrophic decline in an infant's neurological status, often in a familial or social setting suspicious for child abuse [2, 3, 5, 9, 12]. Clinical investigation usually reveals minimal or no evidence of blunt head trauma, but acute subdural and/or subarachnoid hemorrhages are present, often accompanied by cerebral edema; retinal hemorrhages are common [2, 3, 6, 9, 12, 15].

It has long been considered that shaking of the infant produced flexion/extension injury of the weakly supported infant neck, and acceleration/deceleration of the infant brain with resultant tearing of vessels and intracranial hemorrhage [3, 8, 14]. Some authors have proposed that acceleration-induced shearing injury to axons (diffuse axonal injury, DAI) might contribute to the neurological collapse of these infants [5] and, on the basis of biomechanical models and animal experiments, have concluded that the angular accelerations produced by shaking are too low to produce either intracranial hemorrhage or DAI.

Reports of pathological investigations have been predominantly confined to descriptions of gross changes present at autopsy [5, 9, 10, 14] and published accounts of the histological examination of the injured brains are uncommon. A single series, using silver impregnation methods, has demonstrated evidence of axonal injury in the white matter of children with non-accidental trauma, but only in children with either skull fracture or frank white matter lacerations [4, 20]. The presence of a skull fracture might imply that any injury sustained is more reasonably assigned to blunt impact than to shaking [5], but not all

clinically "shaken" infants have skull fracture [1, 6, 8, 9]. Similarly, white matter lacerations are well reported in SBS, but are relatively uncommon [4, 11]. It remains to be established whether most children with "pure" shaking-type injury (i.e., without skull fracture) suffer from DAI, as some authors have proposed.

Because of the relative paucity of systematic neuropathological studies, we undertook to study axonal injury in SBS. The study of axonal injury in infants presents some difficulties. Firstly, survival time in fatal cases following presentation is usually short, and the morphological hallmark of axonal injury, the swollen axon, may take from 12 to 48 h to develop [7]. Secondly, the infantile axon can be difficult to stain using traditional silver impregnation methods [20]. Within the last 5 years, a variety of monoclonal antibodies have come into routine use for the staining of the axonal cytoskeleton [4]. In addition, several reports have noted that damaged axons rapidly (within 2 h of insult) become strongly reactive with antibodies β-amyloid precursor protein (βAPP) [18, 19]. However, βAPP positivity can be induced by a variety of insults including hypoxic/ischemic injury [15, 18, 19]. Other studies have shown increased expression of 68-kDa isoforms of neurofilament 6 h after injury [7]. In this study, we examined the frequency and distribution of axonal injury in the brains of children with SBS using immunohistochemical staining for neurofilament and βAPP and compared it to that found in children dying of nontraumatic hypoxic ischemic encephalopathy (HIE) and to histologically normal, age-matched controls.

Materials and methods

We searched the forensic autopsy records at our institution over the last 15 years in conjunction with the files of the office of the Chief Coroner of Ontario to identify cases of fatal SBS. In every case included there was either a witnessed or confessed episode of shaking prior to presentation, or a coroners verdict of child abuse. All children presented with sudden neurological deterioration and clinical evidence of raised intracranial pressure. At autopsy, each case had subdural or subarachnoid hemorrhages, with or without retinal hemorrhage. Cases with either skull fracture, cervical fracture or a history of blunt head trauma were excluded. Chart review was undertaken to determine the results of neuroimaging studies and the time elapsed between presentation and clinical brain death. For the purposes of this study, brain death was assumed when there was loss of cranial nerve and brain stem functions and the child was ventilator dependant. In all cases in this series, once these criteria were met, subsequent EEG and/or cerebral perfusion studies confirmed brain death. Further clinical and medicolegal data were also retrieved from the records of the office of the chief coroner of Ontario.

To asses the potential contribution of hypoxic ischemic insults to axonal injury, we identified seven age-matched children who briefly survived an ultimately fatal, atraumatic episode of HIE to the CNS. Five of these were resuscitated after near drowning in bathtubs or swimming pools. One was nearly suffocated by thin plastic sheeting and one was resuscitated after an episode of overlying. None bore any marks of injury. A second control group of six children who died suddenly of acute asphyxia and who had normal brains at autopsy were also identified. Two of these drowned in a bathtub or pool, two died of positional asphyxia after their heads became wedged between either cot bars or between a mattress and the wall, one died of accidental hanging, and one was found dead after overlying by parents. All of these children were found without vital signs; none showed evidence of trauma, retinal hemorrhages or intracranial hemorrhage. In one case extensive resuscitative efforts were undertaken and there was mild cerebral edema at autopsy.

At our institution, the forensic autopsy routinely involves the detailed recording of any facial or external scalp injury. In addition, the scalp is reflected and examined for contusion or hemorrhage. Autopsy records were retrospectively reviewed for each patient, and the presence or absence of any facial or scalp contusion, abrasion, ecchymosis or hematoma was recorded. The brain and entire spinal cord were removed from each patient and immersion fixed in buffered formalin. Brains and spinal cords were sectioned and tissue blocks were submitted and paraffin embedded according to standard protocols.

From each case of SBS, HIE and normal control brain, all routine histological sections of brain and spinal cord were reviewed and archived paraffin-embedded blocks of sections of corpus callosum, internal capsule, midbrain, medulla and cervical spinal cord were retrieved where available. Staining with antibodies to βAPP (Boehringer Manheim, 22C11 1:200), neurofilament "cocktail" (a monoclonal antibody directed against high and low molecular weight neurofilament subsets, Sanbio 2F11, 1:200) and 68-kDa neurofilament (Zymed DA2, prediluted) was performed on sections from each block after overnight incubation at 4°C following microwave-induced thermal epitope retrieval. Immunoreactivity was localized using the avidin-biotin peroxidase (Elite Vectastain) method with diaminobenzidine as the chromogen. In addition, sections from each block were stained with gold-toned modified Bielchowsky silver stain counterstained with Luol-fast blue (LFB).

All histological sections from infants with SBS, HIE and normal controls were evaluated by a neuropathologist blinded to the clinical history and diagnosis of each case. The order in which cases were reviewed was randomized. Sections stained for βAPP were assessed for the presence or absence of positively staining axons; within sections of corpus callosum and internal capsule, they were recorded as occurring either singly or in aggregates. Positively staining axons often appear in clusters or aggregates, and if such an aggregate was visible at × 25 magnification and had a density of greater than 10 axons per high power field, then aggregates were scored as present. The density of aggregates in white matter was scored semi-quantitatively as absent = 0, occasional = 1, frequent = 2, and numerous or confluent = 3. Similarly the presence or absence of single positively staining axons outside of aggregates was graded as 0 = absent, 1 = occasional, 2 = frequent and 3 = numerous. Swollen axons were also recorded as being present or absent. Axons were only judged to be swollen if a distinct fusiform profile was present with an axon of normal caliber extending from both ends, or if unequivocal retraction balls were present. Sections stained with Bielchowsky/LFB, neurofilament and low molecular weight neurofilament were also scored for the presence or absence of tortuous or swollen axons.

Results

The clinical features of the 14 cases of SBS are summarized in Table 1. As in other series, the time between presentation and brain death was short (median time 13.5 h, range 0–96 h) and all but one of the patients were under 2 years of age (range 1–27 months, median age 5 months). The age span of both control groups was similar: those patients dying with HIE ranged in age from 1 to 24 months of age (median age 12 months), and those with sudden asphyxial death ranged from 4 to 22 months (median age 11 months). The group dying of HIE survived slightly longer after clinical presentation than the SBS group (median time to brain death 32 h, range 10–120 h), although all but one were dead within 48 h. In this series of patients

Table 1 Summary of clinical features in 14 cases of SBS. All neuroimaging was performed by computed tomography scanning with the exception of patient 2 who had a head ultrasound scan. (*SBS* shaken baby syndrome, *SAH* subarachnoid hemorrhage, *SDH* subdural hematoma)

Patient no.	Age (months)	Gender	Imaging	Time to brain death (h)
1	4	M	? SAH, edema	12
2	2	M	Edema	0
3	6	M	Old SDH	0
4	1	M	Edema	9
5	2.5	M		19
6	27	M	Edema	1
7	10	F	SDH	2
8	5	M		1
9	21	F	Edema	9
10	21	M	SAH	19
11	16	F	Edema	92
12	11	M	SAH, edema	16
13	5	M		5
14	0.5	F	SDH, edema	15

with SBS, there is a 2.5:1 male:female predominance. One child (case 1) had Down's syndrome and congenital heart disease, but the post-mortem findings were not in any way discordant with the remainder of this series.

Criminal convictions were obtained in nine of the cases of SBS. In at least another two cases conviction could not be obtained because exclusive opportunity could not be established. In one case there was no criminal conviction, but an out of court settlement was reached in the ensuing civil suit. In another case unusually vigorous shaking by paramedic personnel was witnessed, in an effort to revive an infant who was said to have "choked" and stopped breathing.

All cases of SBS had either subarachnoid or subdural hemorrhages; these were uniformly thin and were often, but not inevitably, bilateral. In 7 of the 12 cases with subdural hematomas, the hematomas were extensive, covering most of one or both cerebral convexities, but only one exerted significant mass effect. Of the 14 children, 8 also had retinal hemorrhages. The presence or absence of craniofacial bruising did not affect the length of time between presentation and brain death (Kruskal-Wallis one way analysis of variance, $\chi^2 = 1.98$, $df = 1$, $P = 0.159$), but the absence of such injuries was correlated with a younger age (Kruskal-Wallis one way analysis of variance, $\chi^2 = 5.179$, $df = 1$, $P = 0.023$) similar to other series [10]. The presence or absence of bruising did not affect the pattern or frequency of intracranial hemorrhage or of retinal hemorrhage (Table 2).

Imaging by computed tomography or ultrasound established the presence of acute intracranial hemorrhage in only 6 of the 11 patients examined, even though all patients with SBS had subarachnoid and/or subdural hemorrhages. Most intracranial hemorrhages were thin and forced against the dura by cerebral edema, which might make them difficult to detect by imaging.

Evidence of cerebral edema was ubiquitous at autopsy. Of the 14 patients with SBS, 12 suffered transtentorial and/or tonsillar herniation. In the remaining 2, the ventricles were small, the gyral pattern was flattened and the brain weights were increased. The occipital hemorrhagic infarction seen in one patient was accompanied by transtentorial herniation and was probably a consequence of posterior cerebral artery occlusion. Duret hemorrhages were not seen. Petechial hemorrhage within white matter

Table 2 Summary of neuropathological findings in 14 cases of SBS. Letters in superscript letters give the location of the hemorrhages [^{b} bilateral, ^{c} cerebellum, ^{f} frontal, ^{t} temporal, ^{p} parietal, ^{o} occipital, ^{bas} basal, ^{orb} orbital, ^{sc} spinal cord, ^{h} hemispheric (extending over more than half of the cerebral convexity)]

Patient no.	Facial or scalp trauma	SAH	SDH	Retinal hemorrhage	HIE	Other	Cerebral βAPP$^+$ axons	Spinal βAPP$^+$ axons
1	–	+^{sc}	+^{o}	+	–	Occipital infarct	+	+
2	–	+$^{sc, t}$	+$^{b, h}$	–	+		+	
3	–	+$^{m, c}$	+$^{b, o, p}$	+	+		+	–
4	–	+$^{b, bas}$	–	+	+		+	
5	–	+$^{b, h}$	+^{h}	–	+	Parieto-occipital laceration	+	–
6	+	+^{m}	+$^{b, h}$	+	+		+	+
7	+	+^{sc}	+$^{b, p, o}$	+	+		+	–
8	+	+^{f}	–	–	+		+	+
9	+	+$^{b, h, c, s c}$	+$^{m, b, h}$	–	+	Frontal contusion	+	–
10	+	+^{m}	+$^{b, h}$	+	+		+	+
11	+	–	+$^{b, h, c}$	+	+	Corpus callosum laceration	+	+
12	+	+^{f}	+$^{b, f}$	+	–		+	+
13	+	+$^{b, h, c, s}$	+^{h}	+	–		+	+
14	+	+$^{p, o, c}$	+$^{f, p, o}$	–	+		+	

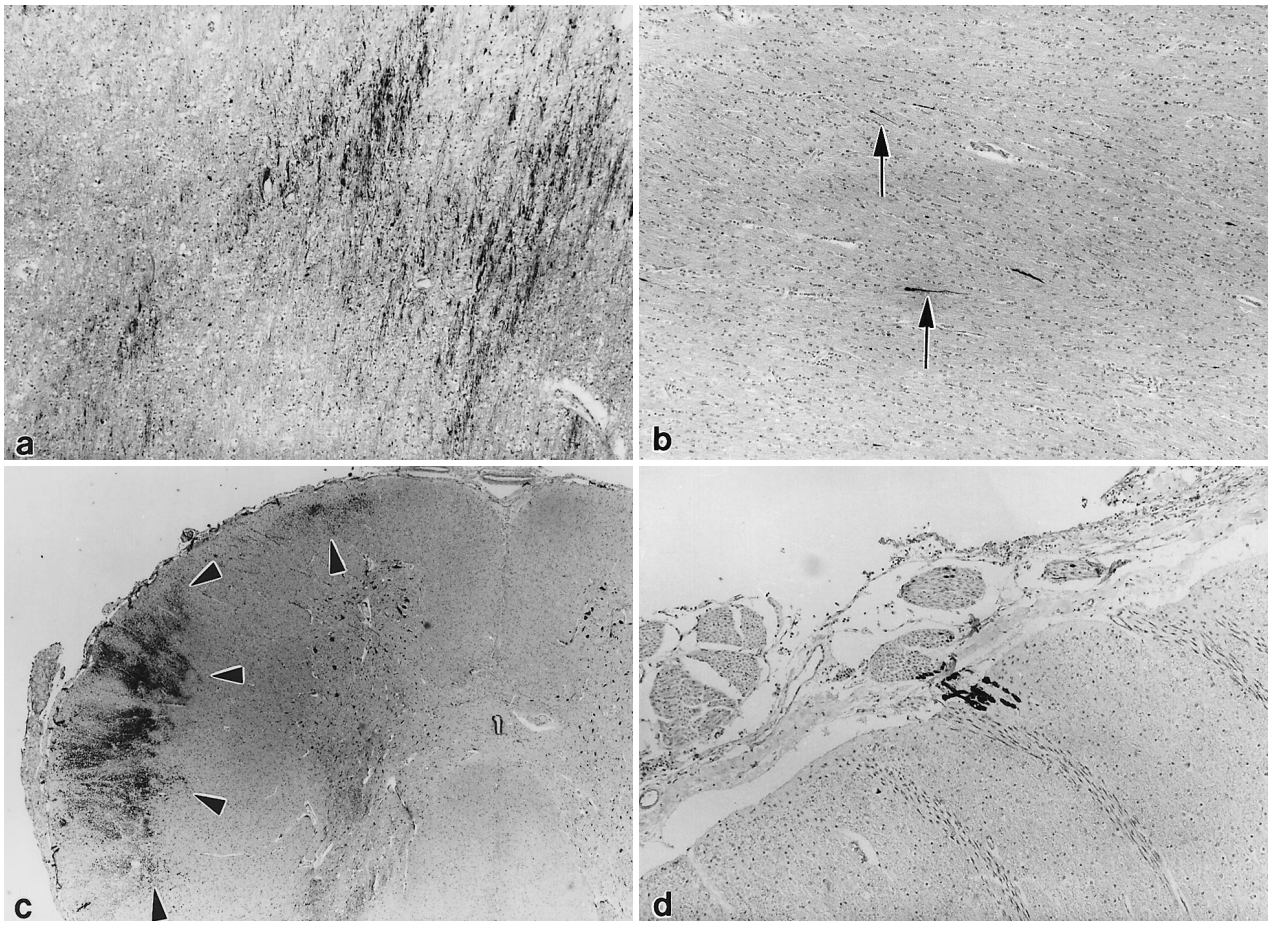

Fig. 1 a–d Photomicrograph of tissue sections stained with antibodies to βAPP. **a** Clusters or aggregates of positive axons in internal capsule from a case of SBS. **b** Isolated, swollen βAPP-positive axons *(arrows)* from the internal capsule of a case of HIE. **c** Section of spinal cord with *arrowheads* indicating areas containing numerous positive axons in the lateral and anterior columns. *d* Ventral nerve root exit zone of same case with SBS, showing distinctly positive axons, many near the glial head of the nerve root (*βAPP* β-amyloid precursor protein, *SBS* shaken baby syndrome, *HIE* hypoxic ischemic encephalopathy). **a** × 100; **b**, **d** × 250; **c** × 25

tracts was noted in 2 cases, accompanying gross white matter lacerations. Hemorrhage or necrosis in the dorsolateral quadrant of the midbrain were not seen.

Of the cases of SBS 9 had sections of corpus callosum available for study, 14 had blocks of internal capsule, 9 of midbrain, 14 of medulla, and 11 of cervical spinal cord. Of the 7 cases of HIE, 7 had blocks of corpus callosum, 6 of internal capsule, 6 of midbrain, 7 of medulla and 7 of cervical spinal cord. Of the 6 normal controls, 4 had blocks of corpus callosum, 6 of internal capsule, 5 of midbrain, 4 of medulla and 5 of cervical spinal cord.

In all 14 cases of SBS, axons expressing βAPP were present in sections of either corpus callosum or internal capsule (Fig. 1 a, b). Positively staining axons were present in 9/9 sections of corpus callosum, and swollen axons were present in 8/9. βAPP-positive axons were present in 12/14 sections of internal capsule, and swollen axons were seen in 11 cases. In only 3/14 cases were swollen axons absent from all sections; these were children who experienced brain death 0, 5 and 15 h after presentation. The presence or absence of craniofacial bruising did not affect the density of either aggregates or singly scattered βAPP-positive axons in either the corpus callosum or the internal capsule (Kruskal-Wallis one way analysis of variance, $\chi^2 < 2.0$, $df = 1$, $P > 0.15$ for both locations and estimates of βAPP-positive axon densities at each location).

Children with HIE also had a high prevalence of swollen axons within their cerebral white matter, with 6 of 7 cases showing swollen, βAPP-positive axons in both the internal capsule and corpus callosum. No infarctions were present in any of the cases of HIE. Among cases of SBS and HIE, the frequency of aggregates of positive axons and singly swollen axons was similar (Fig. 2), although confluent aggregates of positive axons were only seen in cases of SBS. Among normal controls, the internal capsule of one case contained showed scattered βAPP-positive swollen axons; this was from a victim of bathtub drowning who had undergone vigorous resuscitative efforts and who had mild cerebral edema at autopsy.

Sections of midbrain showed a similar prevalence of βAPP-positive axons; among cases of SBS, βAPP-positive axons were present in 5 of 9 cases. Positively staining axons were most frequent in the cerebral peduncles and superior cerebellar peduncles (4 of 9 cases each) as well

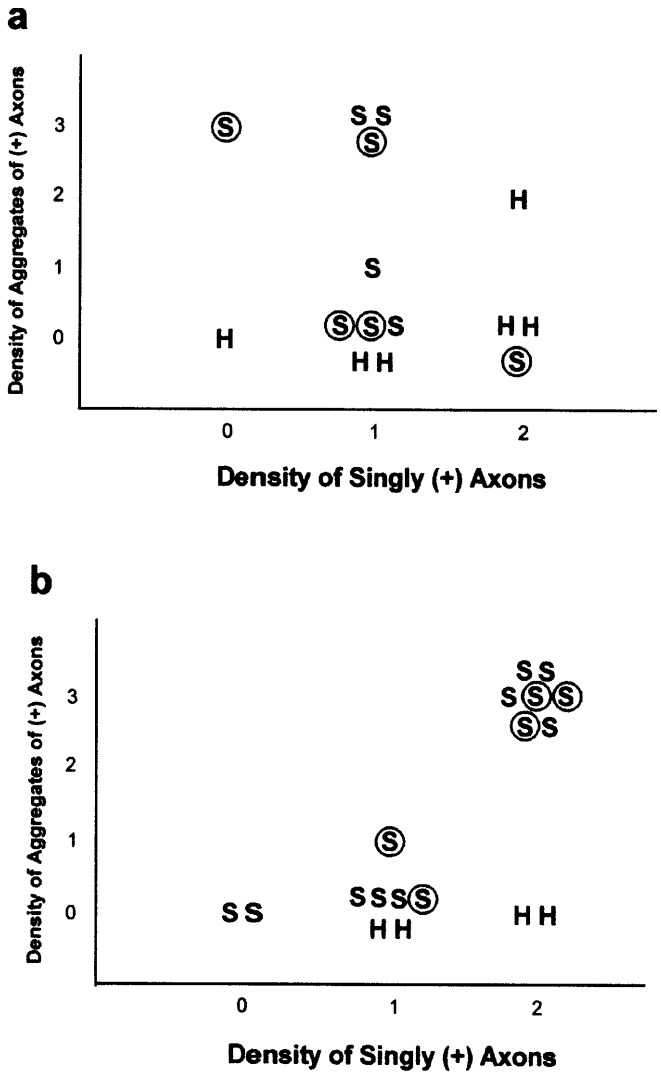

Fig. 2 The density of aggregates of βAPP-positive axons plotted against the density of singly scattered βAPP-positive axons in sections of (**a**) corpus callosum and (**b**) internal capsule (*S* cases of SBS, *H* cases of HIE, *circled S* case of SBS without craniofacial bruising). Although confluent aggregates of axons were only found in cases of SBS, the estimates of the density of either aggregates or singly scatterd axons did not differ statistically between cases of SBS and HIE (Mann Whitney U test, $P > 0.06$ for each estimate of density in both corpus callosum and internal capsule)

as the third cranial nerve exit zone and the midbrain tegmentum (3 of 9 cases each). Among cases of HIE, 2 of 6 cases showed positively staining axons, again predominantly in the cerebral and superior cerebellar peduncles, as well as within the substantia nigra.

Within the medulla, βAPP-positive axons were seen in 10 of 14 cases of SBS, and were most frequently seen in the amiculum olivae (6/10), the decussation of the medial lemniscus (5/10), the tract of the 12th cranial nerve (4/10) and the dorsal spinocerebellar tract (4/10). The spinal trigeminal tract, reticular formation and inferior cerebellar peduncle also contained positively staining axons in a minority of cases (3/10 cases each). Among cases of HIE, 3 out of 7 cases contained βAPP-positive axons; this proportion is not significantly different from that seen in SBS (Fisher's exact test, $P > 0.1$). In cases of HIE, however, positively staining axons did not tend to be as frequent, and were present in the tractus cuneatus and gracilis (2/7) as well as within the amiculum olivae and tract of the 12th cranial nerve (1/7 cases each).

Among cases of SBS, 7/11 cases contained βAPP-positive axons within sections of cervical spinal cord. In all 7 cases, there was staining of the spinal nerve roots, with a distinct predilection for the glial head (Fig. 1c, d). In 5 of these 7 cases there was marked, predominantly peripheral staining of white matter tracts accompanied by axonal swelling. By contrast, none of the 7 cases of HIE had βAPP-positive axons in the cervical cord. This difference in prevalence is statistically significant (Fisher's exact, $P = 0.015$). The sections of cervical cord stained for βAPP were then independently assessed by a second neuropathologist, who was also blinded to the clinical history of all cases and who did not know the outcome of the initial assessment. On review, the same results were found, with the exception of a single focus of axonal positivity in one nerve root of one of the control cases. That section came from a child who suffered an episode of near drowning in her bathtub; the remainder of the case was unremarkable. None of the sections of midbrain, medulla or cervical cord from normal control cases showed any βAPP-positive axons.

Examination of sections stained with antibodies to neurofilament subsets or with modified Bielchowsky preparations did not contribute significant additional information to βAPP immunohistochemical stains; if swollen βAPP-positive axons were numerous, swollen axons could be readily identified on H&E- or H&E/LFB-stained sections. If only singly scattered swollen axons were present or if aggregates of βAPP-positive axons were rare, then careful search was required to detect axonal swellings with stains for either neurofilament or the 68-kDa subset. When axonal βAPP reactivity was not accompanied by swelling, then unequivocal alterations in neurofilament staining were difficult to identify. In our laboratory, silver impregnation stains were not any more helpful than routine histological stains in identifying swollen or tortuous axons.

Discussion

The clinical presentation of these patients is similar to those published in other series [5, 10, 12]. In particular the children present with severe, usually global neurolgical dysfunction and suffer brain death rapidly. Many of the younger children in this series lacked any evidence either clinically or at autopsy of cranial or facial blunt trauma. The tendency for the younger children to lack bruising might imply that less mature children are injured more easily. As noted earlier, the absence of bruising does not rule out injury from impact against padded surfaces. Anecdotal evidence, however, suggests that even in adults, relatively minor accelerations without craniofacial impact trauma can result in subdural hematoma [8].

The presence of βAPP-positive axons in all cases of SBS cannot be unequivocally interpreted as evidence of DAI, because children dying of atraumatic HIE also contained positive axons at a similar frequency and with a similar distribution, and hypoxic/ischemic injury was very common in SBS. The usual morphological accompaniments of DAI, i.e., petechial hemorrhage and dorsolateral quadrant injury to the midbrain, were often absent in these patients and in series of other patients of the same age [4, 5, 9]. In this group of patients, the initial traumatic injury might sometimes be relatively minor, and axonal injury may occur secondary to the effects of cerebral hypoxia/ischemia. The presence of white matter lacerations and frontal lobe contusions, as seen in this series, certainly suggests that the axonal injury seen is not all secondary to edema and poor cerebral perfusion alone. The pattern of axonal injury may differ between HIE and SBS, in that confluent aggregates of βAPP-positive axons were more frequent in SBS. The lack of statistical support for this observation in our study may be due to the small sample sizes involved.

One striking finding in this series is the high prevalence of cervical spinal cord and nerve root injury, which is much more frequent in cases of SBS than in HIE. Spinal cord injuries in children with shaking-type injury have been suspected on the basis of clinical findings and magnetic resonance imaging in clinical case reports [e.g. 16, 17]. A previous autopsy series has documented spinal cord contusions in SBS [9]. These diagnoses of contusion were made on the basis of gross examination at autopsy; histological confirmation is not recorded. The predilection for βAPP immunoreactivity for the glial head of spinal nerve roots suggests that this region might serve as an area of stretch-induced injury. This is the first histological documentation of spinal cord injury in SBS, and corroborates the early suggestion that extension-flexion injury to the spinal cord may be important in the pathogenesis of this syndrome. The infant head is relatively large, and the neck musculature is relatively weak; this disproportion is probably important in the development of flexion extension cord injuries [2, 3, 8].

In this study, the pattern of axonal injury did not vary notably between children with and without craniofacial bruising. Some authors have concluded on the basis of biomechanical models that impact trauma is necessary to produce the clincal syndrome of SBS [5]. Mathematical models have concluded that the infant brain might be more resistant to deceleration injury than adult brain because its smaller size gives it a lower moment of inertia [20]. However, infantile brain is considerably softer and more readily disrupted than adult brain. In keeping with this observation, children younger than 6 months tend to suffer a different spectrum of traumatic injuries with cleft-like tears in the deep cerebral white matter, whereas children of 2 years and older more frequently develop lacerations of the corpus callosum and dorsolateral quadrant midbrain injuries [11, 13]. Until the biomechanical properties of the infantile and prediatric brain in the various stages of maturity are measured and understood it is difficult to fully accept extrapolations from either animal models or adult human brain trauma to pediatric head injury.

The distribution of injured axons in SBS in part parallels that observed in adult DAI, with damaged axons frequently found in the corpus callosum, internal capsule, superior cerebellar peduncle and cerebral peduncles. Damaged axons were also frequently found in these same areas in cases of HIE, implying that the location of injured axons in traumatic damage may be a function of altered patterns of cerebral perfusion in the injured brain or differential patterns of sensitivity to hypoxic/ischemic injury, in addition to the type and degree of the mechanical forces of injury.

We conclude that immunohistochemical staining for βAPP may be a forensically useful technique when death occurs before the morphological alterations of axonal injury can develop. Axonal βAPP staining in the white matter tracts of the cervical spinal cord in this series seems to be associated with SBS. However, more studies with this technique are required before its specificity can be firmly established.

Acknowledgements We thank the technical staff of the neuropathology laboratory in the division of neuropathology at the Hospital for Sick Children, Toronto, for their professional expertise and Louise Cater at the Office of the Chief Coroner of Ontario for her assistence.

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