The Neuropathological Features of Fatal Pediatric Brain Trauma

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ABSTRACT:

Aims: This study aims to describe the neuropathological features of fatal pediatric brain trauma within a cohort with different survival durations and mode of primary injury mechanisms, and to review the exiting literature.

Methods: A cohort of 49 cases of fatal pediatric brain trauma were identified from the archive of the Academic Department of Neuropathology, University of Edinburgh. The pathological features were documented in a standardized proforma, and comparisons were made of the pathological features between cases of different survival durations and mode of injury.

Results: Brain swelling was the most common feature identified and was found in 94% of cases. Sixty-six percent of cases had evidence of ischemic brain damage. Survival beyond 24 hours did not increase the prevalence of ischemic brain damage. Traumatic axonal injury was identified in 24% of the cohort.

Conclusion: Brain swelling, ischemic brain damage, and traumatic axonal injury remain prominent features of fatal childhood brain trauma.

KEYWORDS: Forensic pathology, Brain injuries, Neuropathology

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INTRODUCTION

Traumatic brain injury (TBI) remains the most common cause of childhood death in western societies. Up to 20% of all cases of acute childhood brain trauma which require hospital admission are estimated to have a fatal outcome (1-3). A range of different mechanisms can result in significant head injury in children, and these may be impact or non-impact. The degree of nervous system injury is to some extent determined by the primary force and by the presence or absence of an impact, but is modified by the site of impact and the age of the child at the time of injury. However, low velocity impacts, such as low level falls, have been described to result in fatal head injury (4, 5), albeit rarely, despite the relatively low level of force applied when compared to road traffic accidents or high level falls. This emphasises that, to date, modelling of pediatric head injury has not defined the lowest levels of force required to produce a fatal head injury. Detailed neuropathological examination of fatal childhood brain trauma provides an insight into the effects of these different mechanisms of injury, and also the effects of survival durations, brain maturity, and clinical management in determining the distribution of brain damage patterns.

A number of studies have reported the neuropathological features of fatal blunt force head injury in adults and children (6-7), and others have focused on specific aspects of pediatric head injury, particularly those associated with abusive head trauma (AHT) (8-15). These studies demonstrate great diversity in their inclusion criteria, ages studied, and data collection methods, making comparisons between studies difficult.

A systematic postmortem reporting method was suggested in the 1980s, and highlighted that many important pathological features associated with fatal brain trauma could be missed at necropsy unless they were looked for specifically (16). This proforma was applied to a pediatric population in one study (17). Eighty-seven cases over a 17 year period were studied, aged between 2 and 15 years. They found very similar pathology to that seen in adult blunt force head injury, with the major difference being an overrepresentation of brain swelling.

Most other studies have looked at a younger cohort and focused on specific pathological features associated with AHT. Lindenberg and Freytag (8) reported a cohort of 16 infants with "contusional tears", age range 9 days to 12 months, although the majority were under the age of 4 months. This group was a mixture of accidental head trauma and AHT, trauma in some cases being diagnosed based on other pathological features in the absence of a history (scalp bruising, skull fractures, meningeal hemorrhage). Calder et al. (9) studied a cohort of 12 children with alleged AHT, aged from 12 days to 2.5 years. They described "contusional tears" in 7 of 9 cases under the age of 5 months, while the remaining 3 cases (all 2 years or older) showed adult type pathology. Case (10) reported a cohort of 160 children with fatal head injury, studied between 1975 and 1985, with 63 (39%) accidental deaths, 70 homicides (44%) and 27 undetermined (17%). This paper predominantly discusses crush head injuries and short falls.

Geddes et al. (11, 12) reviewed 37 infants and 16 children, age range 20 days to 8 years. All had a presumed diagnosis of AHT based on at least one of the following criteria: confession by the perpetrator; criminal conviction with unexplained extracranial injuries; head injury and unexplained extracranial injuries but no conviction; conviction but no extracranial injuries; injuries not compatible with the caregiver's explanation. It should be noted that the authors highlight the inherent flaws in this case selection protocol. They found statistically significant differences in the presentation and neuropathology between young infants (2-3 months) and children (>12 months). In the younger age group they highlighted craniocervical axonal injury and global ischemia with thin film subdural hemorrhage (SDH), while the older children were more likely to have extracranial injury. Four of 53 cases had "contusional tears", all within the infant age group. Other lesions described by Geddes et al. included diffuse traumatic axonal injury (TAI) and focal craniocervical axonal injury. The conclusion was that in AHT, diffuse TAI is very uncommon and when present is seen in older children in a pattern similar to that seen in adults. Further confirmatory evidence of this was provided by Reichard et al. (18). Diffuse TAI was described in 8 of 28 NAI cases examined in a prospective study, aged 6 weeks to 7 years, with only one case being an infant (10 months of age). This study also highlighted the importance of differentiating between ischemic and traumatic causes of axonal damage; ischemic axonal damage was seen in 22 of 28 cases. Ischemic axonal damage may account for the high incidence of diffuse TAI reported in early studies of NAI. Previous studies have reported a higher incidence of TAI in AHT, but it is likely that this reflects ischemic axonal injury rather than TAI (13, 14, 19).

As described above, infants are reported to show focal TAI with injury being seen at the cervicomedullary junction (12), a finding supported by other studies (15, 19). A similar pattern of injury is very uncommon in adults, being seen only in cases with forced hyperextension/hyperflexion injuries, such as may be seen in motorcycle accidents or falls from a height with significant neck injuries.

Many advances have been introduced into modern trauma care over the past twenty years. These changes included improvement in resuscitation training and its provision, early transfer of brain trauma patients to trauma centers, and early instigation of neurosurgical and intensive care intervention. However, little is known with regard to how these clinical management changes have affected neuropathological features of fatal childhood brain trauma.

This study aims to describe the neuropathological features of fatal pediatric brain injury within a defined cohort with different survival durations and mode of primary mechanisms of injury, and to compare these findings with the existing literature.

METHODS

Forty-nine cases of fatal pediatric head injury were identified from the archive of the Academic Department of Neuropathology, University of Edinburgh. Selection criteria were age less than 16, a full clinical history, and neuropathological examination including detailed histology. The study covered a continuous 14 year period between 1990 and 2003, and the cases were examined by retrospective assessment of all existing paperwork, including clinical information and neuropathological reports. All data was recorded using the standardized proforma which has been previously described (16). A range of pathological features were documented on the proforma. Skull fractures were documented as being either present or absent. Intracranial hematomas were documented in relation to the anatomical compartment involved (extradural, subdural, intracerebral). Contusions were assessed quantitatively using the total contusion index (TCI) initially developed by Adams et al. (20) and later modified (21). This assesses extent and depth of contusions in a variety of anatomical locators, producing a numerical score for each hemisphere which is then combined and interpreted as absent, minimal, moderate, or severe, the definitions being based on the descriptions used in previous studies (21).

Diffuse TAI, in which there is widespread damage to axons throughout the brain at the time of the original injury, was graded as previously described (22, 23). Grade 1 lesions had widespread axonal damage in corpus callosum, cerebral hemispheres, and brainstem. Grade 2 lesions, in addition, had small hemorrhages in the corpus callosum. In grade 3 lesions there was an additional lesion in the rostral brain stem.

Ischemic brain damage was assessed using a grading system developed by Graham et al. (24). Severe damage comprised those cases in which the lesions were diffuse, multifocal, and large within arterial territories; moderate damage when the lesions were limited to the arterial boundary zones, singly or in combination with subtotal infarction in the distribution of the cerebral arteries, or if there were 5-10 subcortical lesions; and mild damage if there were five or less subcortical lesions in the brain.

Raised intracranial pressure was considered to present if there were tentorial herniae, identified by wedges of pressure necrosis (25) and infarcts were detailed in relation to the anterior cerebral artery, posterior cerebral artery, cerebellum and brainstem.

All cases had the histological features reviewed by reexamination of all cases. The histological sections examined from each case in this study were the parasagittal cortex including corpus callosum, internal capsule and hippocampus, all sampled at the level of the lateral geniculate body; the cerebellum including dentate nucleus; and the pons including cerebellar peduncles. This represents the minimum recommended sampling when assessing TAI (23, 26). Tissue was fixed in 10% formal saline for three to four weeks prior to blocks being processed in a 60 hour cycle (Bayer® Diagnostics) and embedded in paraffin wax. Eight micron thick sections cut from each of the above named blocks were processed for immunohistochemistry. The sections were pretreated with formic acid (80% solution for 8 minutes) and subsequently immersed in a 0.3% hydrogen peroxide solution diluted in PBS for 30 minutes to neutralize endogenous peroxide activity. Sections were incubated overnight at 4°C with a monoclonal antibody against the N-terminus of the human APP molecule (clone 22C11, Böehringer, dilution 1:50) diluted in a PBS solution containing 2% horse serum, 0.3% triton X-100 and 0.1% sodium azide. Sections were then incubated with an anti-mouse biotinylated IgG antibody (Vector Labs, UK) for one hour and the antibody complex revealed using the avidin biotin peroxidase method (Vector Elite™ kit) using diaminobenzidine as a substrate. All sections were lightly counterstained with Meyer's hematoxylin. From each block a second section was cut at 8 microns and stained with hematoxylin and eosin (H&E).

The pathological features described were considered in relation to different age, survival durations, and mode of injury. The main comparisons included: "survived less than 24 hours vs. survived more than 24 hours"; "road traffic accidents (RTA) vs. non-road traffic accidents (non-RTA)"; "accidental injuries vs. AHT"; and "falls vs. non-falls". Non-parametric statistical analyses were conducted because the data did not follow normal distributions. AHT was defined using the same criteria detailed by Geddes et al. (11, 12), and, as with that study, we recognize the limitations of these inclusion criteria.

The study was approved by the local research ethics committee and was in accordance with the Human Tissues (Scotland) Act 2006.

RESULTS

Of the 49 cases within this cohort, 31 (63%) were road traffic accidents (RTA), 9 (18%) were AHT, 7 (14%) were falls and 2 (4%) were other mechanisms including sports related. There were 29 males and 20 females. The ages ranged from fetal (maternal RTA) to 14 years. Thirty-one subjects survived <24 hours, 19 of whom were documented as instantaneous deaths, and 18 subjects survived >24 hours. Detailed neuropathological features were documented in all 49 cases and are summarized in **Table 1**. Brain swelling was the most common finding and ischemic brain damage was found in 66% of cases. Of the 49 cases skull fractures were present in 17.

Survived Less Than 24 Hours vs. Survived More Than 24 Hours

The data comparing pathology with survival time is presented in **Table 2**. 31/49 cases survived <24 hours after brain trauma. The majority were RTA cases (24 cases), with falls (4 cases) and AHT (3 cases) making up the remainder, although no AHT cases were in the instantaneous death group (n=19). Using Fisher's exact test a significant difference was found between diffuse TAI (p=0.004), extradural hematoma (p=0.001) and supratentorial subdural hematoma (p=0.006). All of these pathological features were more common in the survival >24 hours group.

Road Traffic Accidents (RTA) vs. Non-Road Traffic Accidents (Non-RTA)

Thirty-one cases sustained brain injury after RTA. This group were significantly older than the non-RTA group (median age 105.2 months compared to 32.9 months in the non-RTA group, p=0.01, Mann Whitney U test). There was a trend to more extensive contusions in the RTA group (p=0.07 Mann Whitney U test).

Accidental Injuries vs. AHT

40 cases had an accidental head injury, while 9 cases were considered to be AHT. AHT cases were significantly younger than the accidental group (3.6 weeks compared to 107.2 weeks, $p<0.001$ Mann Whitney U test). 46% of accidental cases were classified as instantaneous deaths, while no AHT cases were classified as instantaneous. Contusions were less common in AHT cases ($p<0.01$ Fisher's exact test).

Falls vs. Non-Falls

There were 7 cases classified as falls, and there was no difference in median age, sex distribution and survival between fall and non-falls cases. Epidural hemorrahge was more common in the falls group ($p<0.01$ Fisher's exact test).

DISCUSSION

This study demonstrated that diffuse brain swelling, moderate and severe ischemic brain damage, and diffuse TAI remained prominent features of fatal pediatric brain trauma. The distribution of cases within injury mechanism catergories is similar to that previously published (17). We have confirmed the age differences between young infants and older children described by other authors (11, 12). Although global ischemia is common in both groups it is seen in a majority of AHT cases.

Diffuse Brain Swelling

Diffuse brain swelling is the most common pathological finding of fatal brain trauma. It was reported to be 4 times more common in childhood brain trauma fatalities than those in adults (17, 27). 94% of our cohort had evidence of brain swelling which was higher than the figure of 70% previously reported (17). We additionally demonstrated that brain swelling was found in all survival durations, indicating that brain swelling can develop rapidly. Our findings have, therefore, confirmed that immature brains are prone to develop brain swelling following trauma and it may occur at any time after trauma regardless of the survival period. In many cases there was histological evidence of ischemia, although in some this was absent. It must be remembered that histological evidence of ischemia requires a survival of approximately 8 hours, although shorter survival periods are described (28). Quinn et al. (27) reviewed post-traumatic brain swelling in 105 cases aged between 2 and 19 years; 44 had bilateral brain swelling, 25 with unilateral brain swelling and in 36 it was absent. In all cases a cause for brain swelling (global or focal ischemia, contusions, diffuse TAI) was identified. In our study the mode of brain trauma did not influence the prevalence of brain swelling.

Table 1: Detailed Neuropathological Features from Cases Within the Cohort (n=49)

Pathological Features	Incidence (%)
Brain Swelling	46/49 (94%)
Supratentorial Hemorrhage	40/49 (82%)
Raised Intracranial Pressure	33/49 (67%)
Evidence of Brain Ischemia Mild Moderate Severe	31/49 (63%) 7/31 (23%) 8/31 (26%) 16/31 (51%)
Contusions	30/49 (61%)
Infratentorial Hemorrhage	9/49 (18%)
Diffuse Traumatic Axonal Injury	12/49 (24%)
Skull Fracture	17/49 (35%)

Table 2: A Comparison of Pathological Features Between Survival Times

	Survival <24 Hours	Survival >24 Hours
Age (months)	90.6	69.6
Road Traffic Accidents	24	7
Abusive Head Trauma	3	6
Global Ischemia	11/30	9/19
Diffuse Traumatic Axonal Injury	3/31	9/18
Mean Total Contusion Index	11.23	14.74
Raised Intracranial Pressure	17/31	16/18
Epidural Hematoma	2/31	13/18
Supratentorial Subdural Hemorrhage	13/31	12/18
Infratentorial Subdural Hemorrhage	1/31	8/18

Mechanisms of cerebral edema in pediatric TBI populations are poorly defined, although diffusion-weighted imaging (DWI) studies are beginning to offer some insight (29), by allowing differentiation between vasogenic and cytotoxic injury. Whether the swelling is all due to ischemia or diffuse TAI, or whether seizures and other metabolic derangements such as hypercarbia play an important role, remains uncertain. Further work is needed in this area and close radiologic-pathologic correlation will be invaluable.

Ischemic Damage

Moderate to severe ischemic brain damage was evident in 51% of our current cohort which is similar to the figure of 51% previously described by Graham et al. (17), although the overall inci-

dence of ischemia reported in our group (66%) is lower than the overall incidence of 80% described by Graham et al. (17). The difference in the overall prevalence of ischemic brain damage between our current series and previous studies may be a reflection of the improvement of resuscitation measures and brain trauma treatment over the last 20 years. The frequency of moderate to severe ischemic brain damage is, however, similar between these series suggesting that changes in resuscitation training and provision, and neurointensive care treatment of brain trauma patients over the past two decades had failed to significantly alter the incidence of ischemic brain damage of this severity. This finding is consistent with a previous report which described similar prevalence of ischaemic brain damage between the late 1960s and the early 1980s (30). Alternatively, variations in prevalence may be explained by the differences in survival durations between the studies. Our cohort included patients who died shortly after the occurrence of brain trauma (instantaneous deaths), which meant their survival period after injury were insufficient for a secondary brain insult to evolve. In contrast, all of cohort reported by Graham and colleagues (17) had survived long enough to reach neurosurgical care which meant their survival period was long enough for ischemic brain damage to develop and be identified at postmortem. We additionally found that survival beyond 24 hours did not increase the prevalence of ischemic brain damage, suggesting that any patients who survived the initial brain trauma were as susceptible to ischemic brain damage as those who survived beyond 24 hours, and highlighted the importance of diligent acute trauma care (including prehospital management) to normalize the systemic and cerebral homeostasis as soon as possible after brain trauma.

Traumatic Axonal Injury

The prevalence of TAI in our study (24%) was similar to the other Scottish pediatric report (17). Adult studies have reported an incidence varying between 14% (16) and 33% (24). These differences seen in adult cohorts likely reflects differences in axonal damage identification, older studies using silver stains such as palmgren rather than immunohistochemistry, and an increased awareness of the role of ischemia in producing axonal injury. We consider the figure of 24% within our study to represent a reliable figure for diffuse TAI in fatal pediatric head injury as we used immunohistochemistry and differentiated ischemic from traumatic axonal injury in line with published protocols (31).

Survival durations after brain trauma and mode of injury also determine the frequency of TAI. Instantaneous deaths in our cohort had no evidence of TAI but it was found more frequently among those who had survived beyond 24 hours. This concurred with previous reports where TAI was found in 4% of patients surviving less than 24 hours (32) and 82% of fatalities that had survived more than 24 hours after brain trauma (33). This may reflect the time taken for diffuse TAI to develop after injury; although damaged axons may be seen within 35 minutes in adult practice (34), diffuse TAI almost certainly takes longer to develop. Alternatively longer survival periods may reflect different pathophysiology; diffuse TAI tends to have less brain swelling and may be associated with longer survival periods. Therefore, the longer the survival period the more likely that diffuse TAI is involved in the pathophysiology. The short survival cases tended to have severe brain swelling.

We saw no cases of diffuse TAI within the AHT but, similar to other studies, we did see focal traumatic axonal injury involving the brainstem. This was not a feature of non-AHT cases. It must be noted that we had only a small group of AHT cases, all at a young age, and diffuse TAI would likely have been seen in AHT cases if we had a larger cohort with a wider age range.

Pathology can offer only limited information about mechanisms of injury. However, the clear age difference in the distribution of cases with focal TAI and diffuse TAI may represent mechanistic differences or may represent differences in the responses of a child to a given force. As has been previously stated (12) the craniocervical junction is particularly susceptible to injury in the very young; whether this represents the immaturity of supporting neck muscles and a wider range of movement, or whether this represents an inherent developmental weakness with this region of brain due to myelination is uncertain. However, experience from adult motorcycle accidents with severe hyperflexion/ hyperextension injuries would suggest the former.

SUMMARY

We report a cohort of fatal pediatric head injury, age range from fetal to 14 years, and with varied injury mechanisms covering RTA, falls and AHT. The main limitation of our study is small cohort size consisting patients of different ages, survival durations, and mode of injury. The retrospective nature of our study also meant that missing data was inevitable with the potential to introduce bias into data analysis. We confirmed other studies showing that young infants have different pathology from older children, particularly in relation to diffuse TAI. TAI increases with survival time, whereas brain swelling and moderate to severe ischemia develop rapidly and are

seen with survivals of <24 hours. RTA remains the most common mechanism of traumatic brain injury in childhood. The increased incidence of epidural hematoma and contusions in RTA and falls groups probably reflects the increased forces associated with these injury mechanisms rather than any specific age-dependent differences. RTA and falls are more common in the older age group.

From a clinical perspective we were able to demonstrate that modernization of trauma and neuro-intensive care over the past decades has not reduced the frequency of brain swelling, TAI, and moderate to severe ischemic brain damage in pediatric brain trauma fatalities, offering a valuable addition to the currently limited literature in this important topic.

DISCLOSURES

The authors, reviewers, editors and publication staff do not report any relevant conflicts of interest.

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