An Overview of Inflicted Head Injury in Infants and Young Children, With a Review of β-Amyloid Precursor Protein Immunohistochemistry

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• ***Context.*—Inflicted traumatic brain injury of infants and young children results in a complex array of autopsy findings. In many cases, immunostains for β-amyloid precursor protein are used to detect axonal injury. Interpretation of the gross, microscopic, and immunostaining results requires the integration of the many facets of the individual case.**

***Objective.*—In this article we review the gross and microscopic findings associated with inflicted traumatic brain injury. The application and interpretation of β-amyloid precursor protein immunostains are discussed and photomicrographs are used to illustrate immunostaining patterns.**

***Data Sources.*—The pertinent literature is integrated into a review of the subject.**

***Conclusions.*—Inflicted traumatic brain injury often results in subdural, subarachnoid, retinal, and optic nerve sheath hemorrhage. These findings must be interpreted within the entire context of the case. β-Amyloid precursor protein immunostains may be helpful in illustrating the traumatic nature of the injuries in some cases.**

(*Arch Pathol Lab Med.* 2006;130:712–717)

The understanding of traumatic brain injury (TBI) in adults and in children has progressed and become better refined as our knowledge of the fundamental pathophysiology of this injury has increased. Pediatric TBI (inclusive of ocular, brainstem, and spinal cord injury) is not the same as adult TBI for several reasons. First, the mechanism of injury is often inflicted (nonaccidental); thus, the exact details of how the injury occurred are often unclear or deceiving. Second, it is difficult to extrapolate knowledge about TBI in adults to children because ''babies are not small adults'' in terms of both anatomy and response to injury.[1,2] Even the casual observer notices that an infant's head is larger in proportion to its body than is an adult's head. In addition, infants have relatively weak neck musculature and their cervical facets are shallower than those of an adult.[3] These features, which reflect a relatively large head mounted on a relatively weak neck, combined with an infant's small size, place the infant or young child at risk of unique types of inflicted trauma that are not expected in an adult. The mechanisms of injury producing such trauma are varied, including being thrown, swung, or shaken. Third, the composition of the infant's immature brain is different from that of an adult. The infant has a relatively hypomyelinated and relatively soft brain and spinal cord. These features contribute to different responses to traumatic and hypoxic-ischemic injury than in the fully developed brain and spinal cord of the adult.[1,2,4] Experimental models that mimic the unique features of infant TBI have been difficult to develop. Furthermore, the circumstances of an inflicted injury are often unclear or inaccurate, mitigating one's ability to correlate the mechanism of an injury with the pathophysiology of an injury.

In autopsies of infants and young children with TBI there is usually evidence of impact(s) of the head. Excluding a more convincing cause of death, the cause of death in these cases is often attributed to ''blunt force head injury'' or similar wording. In all medicolegal autopsies, in addition to the cause of death, the manner of death must be determined. When TBI is the cause of death, the mechanism of injury, whether inflicted or accidental in nature, must be determined to establish the proper manner of death. This determination is based on the autopsy findings in conjunction with investigative information and review of the child's medical history. This important determination has significant ramifications for the living. Misclassification of the death as a homicide, when it was an accident, results in the separation of caregivers from their other children and inappropriate criminal charges. However, if inflicted TBI (homicide) is misinterpreted as an accidental injury, then other children may be at risk of death as well, and justice is not served. Consideration of the complete case information and careful review of the account of the injury can optimize interpretation of an alleged accidental scenario, such as rolling off a sofa onto a floor. This type of open-minded and critical review of the case will help elucidate when the provided history is inconsistent with the autopsy findings and aid in determination of the correct manner of death.

Accepted for publication December 7, 2005.

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The authors have no relevant financial interest in the products or companies described in this article.

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GROSS EVIDENCE OF DIFFUSE TBI

All suspicious, unexpected, or otherwise unexplained infant or childhood deaths, such as cases of suspected sudden infant death syndrome, should undergo autopsy. Autopsies of infants and young children may reveal scalp contusions and even skull fractures (clear evidence of impact injury) without any observable external evidence of head injury.

Intracranial findings of inflicted TBI often include subdural and/or subarachnoid blood. Subdural blood commonly arises from torn bridging veins and, in the appropriate scenario, is often regarded as a marker of severe head injury. In some cases of severe head injury, subdural blood may be the only grossly evident finding. In many such cases, the subdural blood consists only of a thin layer of blood, rather than a large, space-occupying hematoma that would cause significant mass effect.

Parenchymal hemorrhages in the corpus callosum and the dorsal aspect of the rostral brainstem, although classically interpreted as being reflective of diffuse TBI in adults,[5] are rarely present in the pediatric brain. The various parenchymal hemorrhages are thought to arise from tensile and/or rotational/torsional forces along the midline and paramidline structures of the brain. These hemorrhages serve as markers of severe diffuse TBI even when widely distributed traumatic axonal injury, known as diffuse traumatic axonal injury (dTAI), cannot be demonstrated microscopically.

Typical cortical contusions rarely are produced in the infant and young child, even with significant head injury.[6] It is more common to see tears of the cortex and/or underlying white matter in young children. The cortical ribbon may be focally torn, separating it from the underlying white matter. This is in contrast to the cortical lacerations seen in adults that are essentially deep contusions/tears of the cortex with an associated tear in the overlying leptomeninges.

Brain swelling (flattened gyri, an increased brain weight, and/or herniation) and hypoxic-ischemic brain injury are common findings in cases of inflicted TBI. These findings may be secondary to trauma because trauma may have precipitated an apneic episode, hypotension, dysrhythmia, seizure, or some combination of events.[7–9] Also, trauma may disrupt cerebral vascular autoregulation, produce alterations in the blood-brain barrier, and lead to cellular edema or cause other changes that may contribute to brain swelling.[10,11] The complexity of the autopsy and neuropathologic findings of inflicted TBI require integration of all available information for accurate interpretation.

THE CONCEPT OF SHAKEN BABY SYNDROME

Historically, the term *shaken baby syndrome* (SBS) was coined to describe the mechanism of injury that resulted in subdural, subarachnoid, and retinal hemorrhages in babies who often had metaphyseal fractures.[12] The theorized mechanism of injury is that of inertial TBI sustained as a result of shaking. Specifically, shaking causes forces to be transmitted through the torso, which ultimately result in the head snapping back and forth. As the head moves back and forth, the brain rotates within the confines of the skull. This causes the cortical veins draining into the superior sagittal sinus (bridging veins) to tear, resulting in subdural and subarachnoid hemorrhage. The rotational injury also damages axons throughout the brain, resulting in dTAI. This mechanism of injury is also proposed as a cause of retinal and optic nerve hemorrhages.

Research and experience, however, have called into question the precise mechanism of inflicted TBI in cases described as SBS. Various types of assaults on infants and young children, including severe shaking, are difficult to mimic experimentally. Some forensic pathologists consider the current medical literature sufficient evidence to support the concept of SBS, and others disagree. The skeptics of SBS argue that all such cases have head impact(s), regardless of whether the impact injury can be demonstrated at autopsy. It is argued that even a significant head impact may leave no head contusion or skull fracture identifiable at autopsy. Factors supporting this view include the elasticity of youthful tissues that may not bruise as readily as those of an adult, the possibility that the impact may have been to the face that is not normally dissected at autopsy, or that the head may have been impacted against a soft, or otherwise giving, surface, which may diffuse the impact force over a large surface area.

Skeptics of SBS additionally point out the nonspecific nature of the head injuries. In other words, the hemorrhages can result from impact injury alone and therefore are not specifically diagnostic of a shaking episode. Furthermore, why opine that an infant was shaken when all of the injuries could be explained by impact injury alone? In fact, not all of these findings are necessarily diagnostic of physical injury because retinal, optic nerve, and subdural/subarachnoid hemorrhage may be found in babies who are severely coagulopathic from sepsis or a variety of other nontraumatic causes.[13–15]

Supporters of the concept of SBS express that shaking alone can generate enough force to cause intracranial hemorrhages and fatal TBI.[16] Proponents of the concept of SBS point to the findings of retinal and optic nerve hemorrhages, subdural and subarachnoid hemorrhage, and dTAI as characteristic features of this entity.[17] Additional injuries that may support a diagnosis of severe shaking may include thoracic contusions, rib fractures, and classic metaphyseal fractures of the extremities.[18] A confession of violent shaking may or may not be provided. The term *shaken impact syndrome* has been coined for cases in which there is evidence of head impact, which is often seen.[19] The concept is that the assault consists of a combination of shaking as well as impact to the head, typically of the head against a fixed object.

One may conclude that disagreement remains in the medical profession as to the diagnostic implications of particular findings, their relevance in determining the precise mechanism of an injury, and whether an infant was shaken. Even after careful review of all case information, aside from stating that there was an impact of the head, it is often not possible to state precisely how a particular injury was sustained.

DETECTION OF INJURED AXONS

Detection of traumatically injured axons in the pediatric brain on routine sections stained with hematoxylin-eosin (H&E) is difficult and often impossible without at least an 18- to 24-hour posttrauma survival time. This is because traumatically damaged axons are not usually ''snapped'' and disconnected immediately at the time of injury. Instead, traumatic injury typically creates small tears in the wall of the axon, which allow for the subsequent inward flux of calcium, proteases, and other substances into the

axon. These substances then lead to a progressive physiologic disruption of the integrity of the axon, resulting in wall weakening, dilatation, and finally disconnection of the axon, a process known as secondary axotomy.[20,21] As a result, the damaged axon undergoes gradual morphologic changes, becoming more and more irregular, wavy, and thicker, eventually assuming a beaded appearance (axonal swellings) and finally a bulbous appearance as axonal disconnection occurs (axonal bulbs). Thus, the old descriptor of ''retraction balls,'' previously believed to occur from the sheared axon retracting, is not accurate.

Because axons gradually enlarge and undergo characteristic morphologic changes over time, it is tempting to use this feature to aid in timing of injury. However, the inaccuracy of dating the time of injury from the swelling characteristic has been reported.[22] This is because the evolving traumatic axonopathy is a dynamic process occurring over time and relates to axonal size, not the time since injury.

THE β-AMYLOID PRECURSOR PROTEIN IMMUNOSTAIN

Immunostaining with antibodies directed against β-amyloid precursor protein (β-APP) provides a much more sensitive means of detecting injured axons than H&E or silver staining. The *APP* gene, located in chromosome 21, makes the transmembrane protein β-APP. The β-APP is a normal constituent of the neuron; however, because it is present in such small amounts in normal conditions, it is not highlighted by β-APP immunohistochemistry. Its exact function is not known. The β-APP can be cleaved into multiple forms of β-amyloid, which are important in the pathogenesis of Alzheimer disease. The antibody used to detect β-amyloid is directed at the similar segment of the molecule as the antibody used to detect β-APP. Thus, β-amyloid immunostains may highlight β-APP.

The β-APP immunostains highlight the subtle morphologic features of axonal injury within 2 to 3 hours after injury,[23] changes that would not be evident with H&E or silver staining. The β-APP is normally produced in the neuron and anterogradely transported down the axon. When the axon is injured, normal axonal transport is disrupted; however, the neuron continues to produce β-APP. This results in β-APP accumulation proximal to the site of injury and the ability to detect it with immunostains. Any injury to the axon will result in a similar process. In other words, β-APP immunostaining is not specific for traumatically injured axons because it also will stain axons injured by other, different mechanisms. This is one of the caveats to the accurate use of β-APP immunostaining.

HISTOLOGIC SAMPLING OF THE BRAIN

The use of β-APP immunostains for the diagnosis of dTAI requires a systematic approach to sampling and application of the immunostain. The details of β-APP immunostain preparation have been described in previous publications.[24–26] Appropriate and thorough sampling is crucial for the accurate diagnosis of dTAI. One should not attempt to diagnose dTAI on the basis of the evaluation of one section or a limited number of sections.

Routine sampling of the brain, including the neocortical border-zone region, hippocampi with subiculum, basal ganglia, thalamus, and cerebellum, will optimize documentation of hypoxic-ischemic injury.[27] Sampling of the corpus callosum just rostral to the splenium, the body of the corpus callosum with parasagittal white matter, posterior limb of the internal capsule, midbrain, pons, medulla, and cervical spinal cord will optimize documentation of axonal injury.[28] If dTAI is not identified in these sections but there is some axonal staining, then bilateral sampling is required. Geddes et al[28] have demonstrated that without bilateral sampling, a significant number of cases of dTAI will be missed. For practical and economical reasons, we initially take sections from both sides of the cerebral hemispheres, but do not do parallel sampling and immunostaining. If the diagnosis cannot be made initially, bilateral sampling and immunostaining is performed. It is important to sample for hypoxic-ischemic injury as well as axonal injury because the patterns of ischemic and traumatic axonal injury often coexist in the same brain.

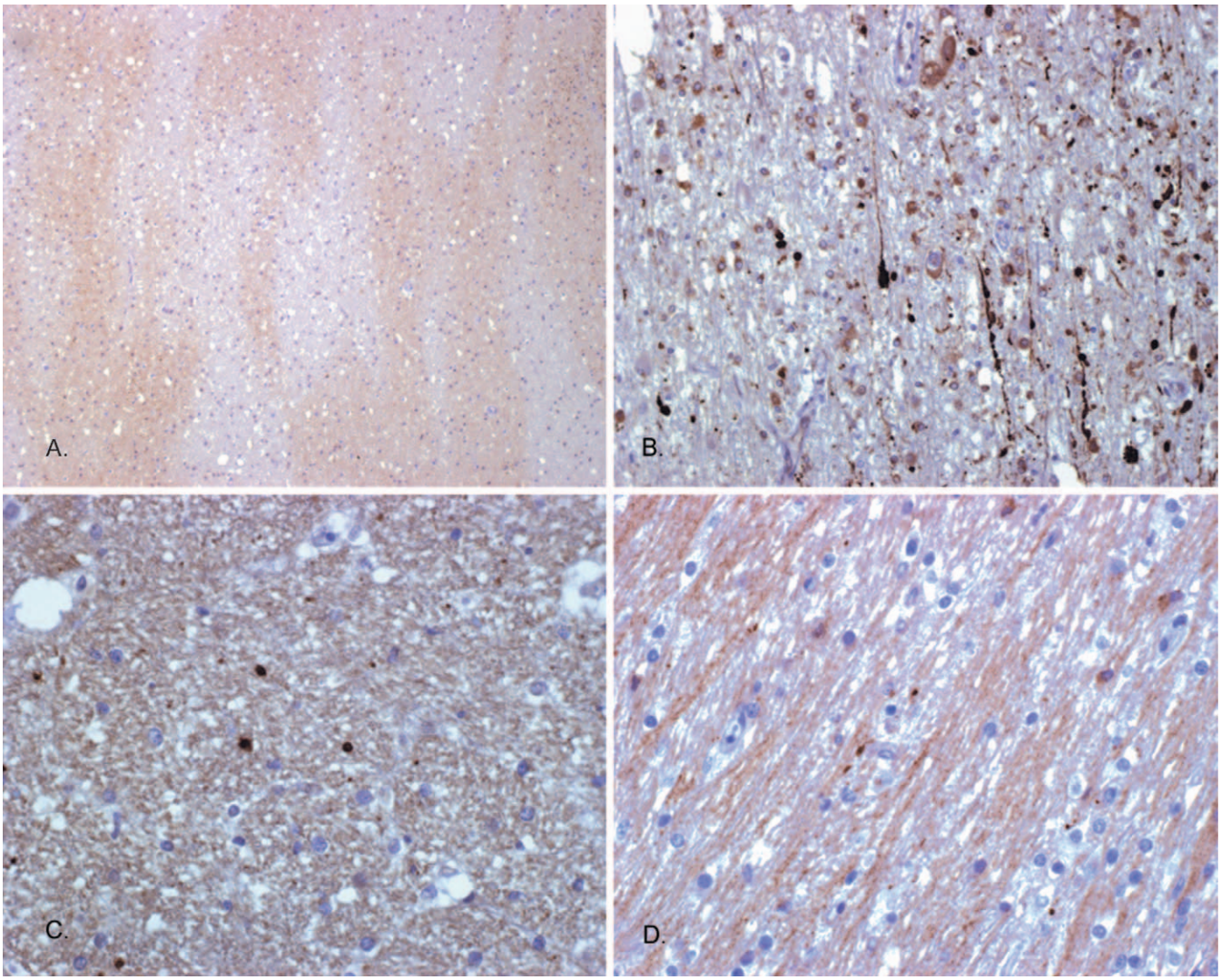
Widespread histologic sampling is necessary when attempting to make a diagnosis of dTAI because, by definition, *diffuse* TAI implies and requires the widespread distribution of traumatically injured axons throughout the brain, including the cerebral hemispheres and the brainstem/cerebellum (that is, involving both supratentorial and infratentorial regions). Thus, terms such as *dTAI in the brainstem* or dTAI in any other specific singular location do not represent recognized diagnoses.

INTERPRETATION OF POSITIVE β-APP IMMUNOREACTIVITY

In recent years, dTAI has become an integral component of the diagnosis of inflicted TBI. The advent of β-APP immunostaining has furthered our appreciation of axonal injury. However, the interpretation of β-APP immunostains may be challenging. The β-APP immunostains will highlight some normal structures such as glia, dorsal root ganglion cells, and leptomeninges. As such, one should guard against the overinterpretation of positive staining when one is, in fact, simply visualizing normal background staining.[24]

It has been theorized that β-APP may act as an acute-phase reactant and is upregulated (and immunoreactive) in neurons that have virtually any type of axonal injury. The β-APP immunostains will highlight all injured axons, whether resulting from trauma, infarction, multiple sclerosis, human immunodeficiency virus encephalitis, or other conditions. Therefore, the detection of injured axons within the corpus callosum, cerebral hemispheric white matter, and brainstem is not necessarily diagnostic of dTAI. There are several articles that illustrate patterns of axonal injury that are most likely caused by early infarction (vascular axonal injury [VAI]) and not by trauma (Figure).[25,28–30] In other words, the sensitivity of β-APP immunostains allows early detection of injured axons (within 2 to 3 hours of the incident), before H&E sections may reveal corresponding hypoxic-ischemic neuronal injury or white matter infarction. Thus, the diagnosis of dTAI requires the presence of scattered individual axonal swellings/bulbs within the corpus callosum, cerebral hemispheric white matter, and brainstem, located away from areas of VAI. Because there are different causes of axonal injury besides trauma, one should be as specific as possible when describing the pattern(s) of axonal injury detected. Hence, the term *diffuse axonal injury,* widely popular in the past, is a general term, and the pattern/nature of axonal injury is better reflected using more specific terminology such as dTAI or VAI.[24,25,31]

To better categorize and communicate about axonal in-



A, Vascular axonal injury (hematoxylin-eosin, original magnification ×100). B, Axonal swellings and bulbs (β-amyloid precursor protein immunostain, original magnification ×200). C, Axonal swellings and bulbs within the pyramids (β-amyloid precursor protein immunostain, original magnification ×400). D, Punctate axonal staining (β-amyloid precursor protein immunostain, original magnification ×400).

jury detected by β-APP immunostains, we describe the axonal injury on the basis of what we believe is the underlying etiology. For example, axonal injury around areas of early infarction is classified as VAI. In these situations, β-APP immunostains often highlight a zig-zag or wavy pattern of axonal injury (Figure, A). Vascular axonal injury may also appear as clusters of immunoreactive axons. This is in contrast to traumatic axonal injury (dTAI), which classically appears as diffusely scattered immunoreactive axons or as immunoreactivity in groups of axons when viewed along the long axis of the axon[25] (Figure, B). Although a pattern of dTAI is useful to document the severity and extent of TBI, it is not absolutely specific in differentiating among the various mechanisms of injury. Scattered axonal swellings/bulbs in a pattern resembling dTAI have been detected in cases of hypoglycemia.[32] We classify this type of axonal injury as metabolic axonal injury. The pattern and distribution of axonal injury seen in hypoglycemia may mimic dTAI. We have reported that when slides that are β-APP immunostained and H&E stained are reviewed by an investigator who is blinded to the clinical history, traumatic axonal injury can be correctly identified in 82% of the cases.[31]

In some cases, exuberant β-APP immunoreactivity may preclude accurate interpretation of the staining pattern. For example, cases with severe brain swelling and multiple areas of infarction may have such an intense and widespread background staining of VAI that the presence of dTAI either cannot be deciphered or may be underappreciated.[25] Alternatively, in some cases, VAI but not dTAI is detected, and is genuinely reflective of the nature of the traumatic head injury. This is because some cases of traumatic head injury will not produce dTAI, yet may prove fatal by causing apnea, seizure, cardiac dysrhythmia, or a host of other severe cardiorespiratory derangements that could lead to significant ischemic brain injury. In these cases, neurohistologic examination may document only the resultant ischemic component of the brain injury (VAI) and not detect any dTAI.

Midline β-APP immunostaining within the brainstem is often attributed to early ischemic injury with subsequent hemorrhage (secondary brainstem or Duret hemorrhage).

Thus, only traumatic axonal injury within the dorsal quadrants of the brainstem and/or in ascending/descending tracts should be interpreted as traumatic axonal injury. In children younger than 1 year of age, traumatic axonal injury within the corticospinal tracts of the brainstem may occur without supratentorial traumatic axonal injury[25,33] (Figure, C). It is theorized that traumatic brainstem injury may be a cause of apnea that ultimately results in brain swelling seen in many cases of inflicted TBI. In our experience, axonal injury of the dorsal root entry zone can be seen in cases without any traumatic injury. Thus, we use caution when interpreting β-APP immunostains of this region.

The lesson from β-APP immunostain studies is that immunoreactive axons do not automatically mean there has been trauma. We consider any β-APP immunoreactivity within axons as part of a pathologic process. For example, in cases of sudden infant death syndrome there may be diffuse punctuate β-APP immunostaining, which we consider a pathologic process (Figure, D). In contrast, individuals who die rapidly, such as from drowning or motor vehicle accident, will not have significant β-APP immunostaining. Rare, scattered β-APP immunoreactive axonal swellings have been described in both children and adults. However, our studies have demonstrated that widespread β-APP immunoreactivity is not normally present. In a case with truly negative findings there will not be widespread axonal swellings/bulbs or even punctate axonal immunostaining.

INTERPRETATION OF NO β-APP STAINING

In cases in which there is no β-APP staining, there may have been no TBI. However, the absence of β-APP staining does not exclude TBI because the survival interval may be insufficient to allow for the visualization of increased β-APP immunoreactivity. In some cases, death or cessation of cerebral perfusion occurs rapidly (minutes to hours) after head injury and no β-APP immunoreactive axons will be detected. This is because TBI and hypoxic-ischemic insults of the central nervous system may cause significant brain swelling and possibly cessation of cerebral perfusion within an hour or 2 of the incident, before axonal accumulation of significant amounts of β-APP has had the opportunity to occur. This occurs because reactive changes in the brain (including the progression of physiologic and subsequent morphologic changes in injured axons) are halted when cerebral perfusion is impaired or halted because the tissues are more or less metabolically static. Because of this, there may be no convincing evidence of axonal injury, even with prolonged existence and yet brain dead on the ventilator. Thus, even if postinjury survival has lasted many hours or even days, β-APP staining may still, on occasion, be negative in the setting of severe TBI.

This illustrates that even though axonal swellings/bulbs may not be detected, it does not mean that TBI has not occurred. This underscores the importance of interpretation of the entire case. Clearly, it would be ridiculous to ignore the traumatic etiology of an impact site (with or without skull fracture), subdural hemorrhage, and subarachnoid hemorrhage just because there was no β-APP immunostaining. However, it would be equally as erroneous to diagnose dTAI on the basis of β-APP immunoreactive axons (in a pattern of VAI) in a case with subdural blood from a well-documented natural disease process with associated coagulopathy. Also, in cases of no β-APP staining, one must consider possible technical issues with the immunostain that may have resulted in suboptimal staining.

OCULAR EXAMINATION

Examination of the eyes in cases of inflicted TBI is necessary for a complete evaluation of the central nervous system. Retinal and optic nerve sheath hemorrhages are additional evidence of a severe TBI in infants and young children, but are not pathognomonic for TBI. The β-APP immunostaining has been shown to be useful in detecting traumatic axonal injury of the optic nerves in some infants dying of inflicted TBI.[26] The ocular findings of inflicted TBI are an integral component of an autopsy in the setting of child abuse.

NEUROPATHOLOGIC EVIDENCE OF REMOTE dTAI

The β-APP immunostaining begins to fade in about 7 to 10 days after injury as organizational/reparative processes proceed, which may make it difficult to diagnose dTAI. In cases with increasingly extended posttrauma survival intervals, evidence of injury may be identified by collections of macrophages or reactive astrocytes in the white matter in locations characteristic of dTAI. Immunostains such as CD68 and glial fibrillary acidic protein, to highlight macrophages and reactive astrocytes, respectively, may facilitate the detection of injury. In cases with a long posttrauma survival interval, the patient is often in a persistent vegetative state. In fact, dTAI is the most common cause of persistent vegetative state in patients with blunt head injury.[34] Gross indications of diffuse damage to white matter include a thin, possibly torn corpus callosum and shrunken/discolored (tan/gray) cerebral hemispheric white matter, often with relative preservation of the cortical ribbon. Sampling protocols in these cases are the same as those described previously. The histologic appearance of the white matter damage in the distribution of dTAI changes in the weeks, months, and years after injury. Days after the injury, macrophages begin to infiltrate and eventually clean up injured tissue, which may lead to cavitary lesions of the corpus callosum, dorsal quadrants of the brainstem, or other regions. Swollen axons are only transiently visible histologically because they eventually will degenerate and disappear with prolonged survival time. After approximately 1-month survival time, most axonal swellings/bulbs are no longer visible.[30]

With prolonged survival for many months to years, the histologic appearance of the brain may be limited to nonspecific gliosis. On occasion, one may see residual glial scars composed of clusters of glia and possibly some mineralized dystrophic axons at the site of microtears in the tissue. In these cases, the thalamus often has degenerative changes characterized by the shrinkage of neurons and gliosis.[34] Ultimately, the degeneration of the white matter, often with marked thinning of the corpus callosum, may lead to hydrocephalus ex vacuo. If there has been no significant ischemic brain injury, the cerebral cortex will be relatively well preserved.

CONCLUSION

β-Amyloid precursor protein immunostains are currently a useful diagnostic tool in the neuropathologic evaluation of inflicted TBI. The β-APP helps determine whether there is traumatic, vascular, and/or metabolic axonal injury. As is true for the use of any immunostain, a correct

interpretation requires knowledge of the strengths and weaknesses of the antibody. The β-APP results are but one part of the complete case investigation and evaluation.

In conclusion, autopsies of abused infants and young children who die of inflicted TBI are often complex for several reasons. First, the provided histories are often misleading and erroneous. Second, the pathologic findings of inflicted TBI are frequently complicated by multiple different and often overlapping pathophysiologic processes such as trauma, global hypoxic-ischemic injury, and brain swelling. Third, the cases are often high profile, with increased media coverage and multiple experts offering differing opinions on the autopsy findings. The forensic pathologist must carefully integrate the scene investigation, medical records, radiologic findings, gross and microscopic findings; interpret β-APP immunostains; and evaluate metabolic, vitreous electrolyte, and toxicology studies to understand the entirety of the case. One should consider all reasonable possibilities before deciding whether the injuries are consistent with the manner in which they were stated to have occurred. Each case of inflicted TBI is unique and requires placement and interpretation of the autopsy findings in the context of the child's medical history and the overall death investigation. In most fatal cases, there has been significant impact injury of the head. As is true with most topics of medicine, our understanding of pediatric traumatic head injury is incomplete, but continues to advance. With continued experience and research, we will continue to gain a fuller understanding of pediatric head injury.

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