Traumatic Brain Injury from Forensic Approach: Brief Overview

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Abstract

Background: In those under the age of 45 all around the world, traumatic brain injury (TBI) is the leading cause of disability and death. Focusing on exterior, radiographic, autopsy, and histological exams with special focus to immunohistochemistry and molecular biology, this mini-review seeks to standardise the forensic method in neuropathological studies. Based on the findings of this brief review, a thorough forensic approach should be required whenever a suspected traumatic brain injury (TBI) of medico-legal significance is being investigated, with the goal of amassing as much evidence as possible to support the diagnosis of a lesion as the cause of death or a contributing factor in the cause of death. When various neuropathological disorders (ischemia, neurodegeneration, neuro-inflammation, dementia) could have contributed to mortality, only by following a process supported by evidence could a proper diagnosis be made. This is especially important when examining bodies in an advanced stage of decomposition, as radiological, macroscopic, and histological analyses often yield inconclusive results.

Keywords: traumatic brain injury.

Introduction

Traumatic brain injury (TBI) is the leading cause of disability and mortality among people younger than 45 years old in developed countries.[1]. TBI is defined as "an abnormality in brain function, or other signs of brain pathology, produced by an external trauma" by the Brain Injury Association of America (2011). There were 56,800 fatalities in the United States attributable to TBIs in 2014; 2,529 of them were children. According to reports, the leading causes of death from TBI include self-inflicted injuries, unintended falls, and car accidents. Of the recorded TBI-related deaths, 32.5% were caused by motor vehicle accidents, 28.1% by falls, and 18.7% by other causes. Adults over the age of 75 had the highest rates of TBI-related mortality (78.5), followed by those between the ages of 65 and 74 (24.7), and those between the ages of 55 and 64 (11.6). [2]. A European retrospective investigation of twenty-three European national reports yielded an aggregate TBI incidence rate of around 235 per 100,000, including both hospitalized and dead cases. From this data, we calculated mortality rates of roughly 15 per 100,000 and 11 per 100 for individual cases.[3].

Thirty percent of traumatic brain injuries (TBIs) involve an open head injury, in which an object pierces the skull and causes damage to brain tissue, leading to neurological disability. Seventy percent of traumatic brain injuries result from closed head trauma, such as from a blow to the head or an object impacting the head.[4]. The most prevalent explanations include mishaps involving motor vehicles, falls, attacks, bicycles,

and sports. Young children, older teens, and the elderly have the highest rates of traumatic brain injuries (TBIs), whereas men are 1.5- 3 times more likely than women to get a TBI.[5].

When considering the method by which a head injury is caused, we can divide it into two groups: impact injuries and acceleration/deceleration injuries. Collision injuries, which occur when something heavy hits a person's head, are caused by the local impacts of this impact. Soft tissue injuries (such cuts and scrapes) are extremely common, as are skull fractures, brain contusions, epidural hematomas, and even intracerebral hemorrhages.[6, 7].

Head trauma caused by a sudden acceleration or deceleration after the initial impact causes a shift in intracranial pressure gradients and shearing and tensile stresses on the brain. Subdural hematomas (caused by the ripping of subdural bridging veins) and widespread axonal damage are the most common outcomes (the consequence of axonal injury)[8-10].

From a neuro-pathological perspective, there are two main phases to TBI development in regards to brain damage after a head injury: primary damage, which occurs at the moment of the lesion and includes things like scalp lacerations, skull fractures, surface contusions and lacerations of the brain, the diffusion of the axonal injury, and intracranial haemorrhage; and secondary damage, which is caused by complex processes triggered at the moment of the injury but clinically manifests itself later.[11, 12]. In the past few years, specific techniques of neuroradiology have contributed to the classification of brain injury after a head injury [13]. These imaging techniques [14] provide functional correlations of the structural damage, subsequently confirmed by autopsy. As a result, the classification of focal damage - which includes laceration of the scalp, fracture of the skull, surface contusions and lacerations, intracranial hematoma, and raised intracranial pressure, and diffuse damage which includes ischaemic brain damage, diffuse axonal injury, and diffuse brain swelling - is now largely recognized.

Considering the aforementioned reasons, the aim of this review is to establish a single systematic evidence-based post mortem protocol for a better objectification of TBI damage.

FORENSIC IMAGING

As the study of traumas in clinical settings cannot be made without the use of radiology, forensic pathology can benefit from the use of imaging techniques to plan the subsequent autoptical approach in cases of cranium-encephalic injuries [15]. Among the different imaging techniques, post-mortem computed tomography (PM-CT) certainly plays the main role, guaranteeing the highlighting of typical lesions. First of all, this technique can detect the presence of fractures involving neurocranium, and viscerocranium, up to the cervical vertebrae. Furthermore, the presence of cranial open-fractures can be associated with another characteristic, seen with the same method, that is the presence of air, such as: gas embolism in the cerebral and pulmonary circulation (both venous and arterial), or pneumoencephalon and pneumorachis. The interpretation of this finding, however, deserves two considerations: on the one hand, the presence of bubbles is difficult to detect during autopsy, thus it is possible to plan particular autoptical approaches, on the other hand, it enters into the differential diagnosis with putrefactive gases [16, 17]. Furthermore, PM-CT is useful in detecting intracranial hematomas with epidural, subdural, and subarachnoid localization or intraventricular hemorrhages; as well as intraocular hemorrhages associated with fractures of the base of the orbit or skull or in cases of shaken baby syndrome (SBS) [18]. In addition, in the study of bleeding, compared to PM-CT, post-mortem magnetic resonance imaging (PM-MRI) shows a high sensitivity to highlight subarachnoid hemorrhages and subgaleal hematomas, as well as detecting lesions in cases of trauma with typical blow and kickback dynamics [19]. On the other hand, the absence of the use of ionizing radiation in MRI would legitimize its use on living people. In fact, in cases of SBS, MRI can demonstrate the presence of intracranial bleedings in different stages of evolution, providing information on the time of production, although a precise dating is unlikely. Furthermore, clinical forensic medicine can benefit from the use of MRI in attempted homicide in cases of strangulation, allowing the visualization of bleeding or edema of the soft and muscular tissues of the neck, as well as the suffering of the lymph nodes of this anatomical district. Moreover, always in a clinical field, the possibility of this diagnostic technique for the

evaluation of bone age is discussed through the study of cartilage and their modifications with growth, always without the use of radiation [20].

Aghayev et al., also demonstrated the ability of PM-MRI to identify herniation of cerebellar tonsils through the foramen magnum as a sign of elevated intracranial cerebral pressure [21]. Finally, PM-MRI can count on diffusion tensor imaging (DTI) to assess traumatic brain damage: tractography can highlight dislocation and rupture of the fibers in cases of post-traumatic cerebral hemorrhage, or the interruption of the fibers following the passage of a bullet [22, 23]. However, for the detection of suspected foreign bodies, the gold standard is PM-CT, which allows them to be identified in terms of number, shape, size, integrity, and localization. This technique also allows the identification of a penetrating tract, both from a firearm or a sharp weapon, usually conical with the base of the entrance wound [24]. The limitation of this technique is, obviously, the fact that the presence of metallic elements leaves artifacts that cover further injuries, for example hemorrhages.

Post-traumatic subarachnoid hemorrhage can be showed by post-mortem computed tomography angiography (PM-CTA), with evidence of the origin of the vascular lesion, frequently breaking the vertebrobasilar artery. Furthermore, PM-CTA can highlight the presence of post-traumatic aneurisms of the intracranial vessels, which are difficult to detect on macroscopic autopsy or on the investigation after formalin fixation of the brain, according to the site [25]. Therefore, this technique is particularly effective in traffic accidents [26].

As far as this kind of death is concerned, a case is reported dealing with a 79-year-old man, involved in a frontal-impact vehicle crash. He was taken to the Emergency Department by ambulance where he arrived comatose (GCS 3). The patient immediately underwent brain CT scan and angio-CT scan, directed, in particular, to study epiaortic vessels. The results were extensive hypodensity in the subcortical areas of the left frontal lobe and extensive hypodensity of the cortico-subcortical regions of the parietal, occipital and cerebellar lobes of probable ischemic origin, bilaterally. The angio-CT study documented a complete occlusion of both vertebral arteries from their origin, where they appear threadlike, up to the C3 vertebral body. From this level, they appeared reperfused, even if the right one seemed to be reduced in size and less opacified than the left one. The man died about 4 days after his admittance to the hospital. The external examination of the body was not remarkable for any signs of trauma. However, a PM-CT conducted the day after detected a large hypodense area in the parietal and frontal lobe, bilaterally, of probable infarct origin; parietal calcifications of the carotid axes at the level of bifurcation and of the siphons; parietal calcifications of the right vertebral artery. Dislocation of C5 from C4 with large dehiscence of the disc space and associated thickening of paravertebral tissues.

Thus, a posterior approach during autoptical examination was preferred. The splenic muscles of the head were uncovered, the semi-spinal muscle was exposed and appeared hemorrhagic, bilaterally. The nuchal ligament was removed, the spinous process of the C4-vertebra was detected and this vertebra was dislocated from the C5-vertebra with posterior exposure of the spinal cord and hemorrhagic dural sac. Through the use of a rongeur, the transverse processes were sectioned to visualize the course of the vertebral arteries into the transverse foramen; which presented a regular course. Thereafter, the brain was removed with the spinal cord up to the upper border of the C5-vertebra.

The right vertebral artery showed a lumen reduction. Microscopic examination with Hematoxylin and Eosin (H&E) showed extended intraparenchymal erythrocyte collections that substituted large tracts of nervous tissue; eccentric atherosclerotic plaque, causing a lumen reduction of about 35-40%. Above all, there was an interruption of the dura mater and the arachnoid layer at the C4-C5 spinal specimen with contextual erythrocyte presence below and in the context of the sheets themselves. The cause of death was then attributed to a progressive multi-organ failure resulting from trauma that occurred after the road accident, determined by: vertebro-basilar insufficiency, causing a massive cerebral ischemia with a state of coma; respiratory failure with the need for mechanical ventilation; acute renal failure; pre-existing comorbidities.

UTOPSY

Autopsy has the aim of identifying both primary and secondary brain damage. The scalp incision takes place with the well-known bimastoid resection [27]. If necessary, in order to visualize the orbital cavities,

for example in Shaken Baby Syndrome (SBS), the sectioning of the skin and subcutaneous tissues of the splanchnocranium can be performed, according to the Rutty technique [28]. SBS combines subdural hemorrhage, acute encephalopathy, retinal hemorrhage, optic nerve sheath hemorrhage, and sparse or absent signs of external injury [29]. Searching for these signs, the removal of the eyeballs can be useful for subsequent histological studies. Moreover, considering that asymmetry between the eyes of an individual can occur, both eyes should be collected and studied [30]. After the overturning of the scalp strips, the examination and the description of the scalp are carried out before dissection. In cases of hemorrhagic infiltration or gunshot wounds, the fragments of bone and skin are removed for microscopic examination. In traumatic skull injuries, the evaluation and description of various fracture types are performed before skull removal [31-33].

Once the skull is removed, the brain has to be observed and described. At the macroscopic level, the visualization of the brain can evidence lacerations, contusions and hematomas [34, 35].

Subdural hematomas can be classified as acute (symptoms occurring within 72 h), subacute (3 days to 3 weeks) or chronic (more than 3 weeks after the injury). This acceleration/deceleration injury is the result of a shearing force acting upon the parasagittal bridging veins [10] and can be located either on the ipsilateral or contralateral side of the impact area or bilaterally, but is not associated with skull fractures (even though some studies suggest a dural origin for the subdural bleeding seen in young infants) [35].

Hemorrhages are streak-like and can be both solitary and multiple, while the amount of bleeding that continues until death depends on the type of vessel injured and on the presence of necrosis. In cases of profuse bleeding, this area may expand into the white matter and the subarachnoid space (intracerebral hemorrhage) [36, 37].

Subarachnoid hemorrhage is the most common consequence of traumatic head injury. Lacerations of the internal carotid, vertebral or basilar arteries have been proved to cause traumatic subarachnoid hemorrhage over the base of the brain, therefore being immediately fatal [38, 39].

Subarachnoid hemorrhage can be produced postmortem due to the lysis of blood cells, loss of vascular integrity with consequent blood leakage in the subarachnoid space. Furthermore, during the evisceration of the brain, minimal subarachnoid hemorrhage may be produced. While removing the skullcap, cerebral veins and the arachnoid membrane are torn, with subsequent diffusion of blood into the subarachnoid space in the posterior aspect (dependent portion) of the cerebral hemispheres and cerebellum. Despite the fact that this hemorrhage is usually minor, if the brain is not removed from the cranial cavity immediately but rather left to sit for a while, a considerable quantity of subarachnoid hemorrhage may accumulate [10].

Brain swelling can occur following significant head injury [39, 40], due to the development of a severe state of brain swelling for a certain time, herniation of the brain or secondary brain stem hemorrhage. A rapid progression of this process can result in tonsillar and/or transtentorial herniation of the brain, with consequent necrosis, secondary infarction, and Duret hemorrhages [41]. Violent hyperextension of the head and neck can cause lacerations at the junction of the pons and medulla [42-46].

After the evisceration of the brain, which in this case must be in toto, it is formalin-fixed for further studies, and it is possible to observe the basilar skull fractures, which are very common because of the construction and irregular shape of the base of the skull: hinge fractures (consisting in basilar fractures that completely bisect the base of the skull), ring fractures (circular fractures of the base of the skull that surrounds the foramen magnum, may be due to impacts on the top of the head that drive the skull downward onto the vertebral column and impacts the tip of the chin), contrecoup fractures of the anterior cranial fossae (isolated fractures of the anterior cranial fossae associated with contrecoup injuries of the brain, with the impact point on the opposite side of the skull) [47-49].

Severe injury to the vertebral arteries is caused by blunt traumas to the neck. The upper third of the cervical region is the area where the vertebral artery is most susceptible to traumas of two types: a traumatically induced dissection in the vessel wall with rupture into the subarachnoid space at the base of the brain; a similar type of dissection characterized, however, by the presence of thrombosis of the lumen with infarction of brain tissue, instead of the rupture of the vessel wall. Injury of the vertebral artery should be suspected when an individual collapses and dies almost immediately after receiving a blow to the neck. The

most common causes of vertebral artery trauma are blows to the neck, motor vehicle accidents, falls, and cervical spine manipulation [50, 51].

The autoptic method in cases of access to the dorsal spine is a posterior approach consisting in a semicircular bisacromial incision or a median perpendicular/sagittal incision (Fig. **22**), for the inspection and isolation of the posterior neck muscles, paravertebral muscles, ligaments, vertebrae (spinal and transverse processes as well as vertebral bodies), and vertebral arteries. This approach gives easy access to the cervical trunk, consenting the immediate visualization of the cranial–cervical joint, and, of course, allows for complete resection and isolation of the cord. This method is preferable in cases when death happens as a result of surgery [26]. In cases where visualization of the vertebral arteries is necessary, as in the case already mentioned in the radiology section, the posterior approach is certainly the gold standard technique; furthermore, in that specific case, to limit the possibility of damaging the vessels, a Kerrison rongeur was used to access the transverse holes of the cervical vertebrae and visualize the arteries in situ.

After evisceration it is possible to proceed with the observation of the brain and its dissection with Virchow or Ludwig procedure [27]: the occurrence of macroscopic damage will be observed, e.g. intra-parenchymal bleedings and contusions [38, 52].

There are six types of contusions: coup contusions, which occur in the site of impact, inflicting tensile force injuries to the brain; contrecoup contusions, which occur in the brain at locations directly opposite to the point of impact; fracture contusions, associated with fractures of the skull; intermediary coup contusions, which consist in hemorrhagic contusions in the deep structures of the brain (the white matter, basal ganglia, and corpus callosum, typically observed in falls); gliding contusions, focal hemorrhages located in the cortex and underlying white matter of the dorsal surfaces of the cerebral hemispheres, principally in the frontal region (observed in falls and vehicle accidents); Herniation contusions, typically caused by impaction of the medial portion of the temporal lobes against the edge of the tentorium, or the cerebellar tonsils against the foramen magnum [36, 42].

TOXICOLOGY

TBI is frequently associated with substance abuse, in a two-way relationship [53]: on the one hand, the use of substances represents a risk factor in the genesis of TBI, also influencing outcomes; on the other hand, subjects with TBI are at greater risk of developing a substance abuse disorder. Among the different substances abused, alcohol is certainly the most studied and investigated in cases of TBI [54] followed by drugs, including marijuana and cocaine [55]. Moreover, in the last few decades, the use of anabolic androgenic steroids (AAS) has been constantly increasing in the general population, not only in athletes, particularly for aesthetic purposes. In this regard, a recent review described the correlation between AAS use/abuse and anxiety or aggression, analyzing the two pathways that could be involved in AAS-induced behavioral disorders [56]. On this theme, as suggested in the paragraph on Molecular Biology, the use of new molecular biomarkers, such as miRNAs, could become very important for forensic purposes. For example, in a pilot study, in drug abuser tissue, the expression levels of miR-132 and miR-34 were higher than control groups, suggesting a specific pathway in consumption-induced neurodegeneration [57].

Furthermore, a study also linked the pattern of injury and the severity of the lesions according to the different concentrations of alcohol in the blood by detecting how concentrations higher than 2.5 g/l were statistically related to head injuries and more serious injuries [58]. Recent studies, however, present contrasting results between the severity of TBI and substance use, noting how high blood alcohol [59] or methamphetamine [60] values can constitute protective factors with respect to mortality in head traumas. Although further studies are needed in order to better understand these phenomena, it clearly emerges as a complete understanding of the toxicological examination.

However, when questioning whether a substance has caused or simply contributed to death, the reflection cannot focus only on illegal substances. Even drugs legally prescribed for therapeutic purposes can influence the evolution or extent of head trauma. The chronic use of anticoagulants at the time of the traumatic event may cause, indeed, a hemorrhage greater than in free-from-drug individuals or may be associated with a rare but sufficiently dangerous complication, such as delayed traumatic subarachnoid hemorrhages [61]. In addition, the activity of warfarin can be influenced by the genetic component, which

should be explored in cases of autopsies. The most important pharmacogenetic association has been identified in the polymorphisms in the gene encoding the epoxide reductase of vitamin K and in the cytochrome P450 CYP2C9 gene [62]. In these cases, the finding of a high dose of warfarin in pre-mortem blood samples could be therapeutic and not a sign of overdose or over-prescription, excluding any medical liability.

On the other hand, it has been shown that the same head trauma alters the pharmacokinetics of some substances, thus a higher dose is necessary to reach therapeutic plasma concentrations, such as paracetamol [63], cyclosporine A [64] and phenytoin [65].

However, as with all substances, post-mortem concentrations cannot be easily interpreted to ascertain the ante-mortem concentrations. Therefore, further studies should be performed to define a direct relationship between the ante- and post-mortem concentrations of these substances.

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