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Short Communication

Traumatic axonal injury: Clinic, forensic and biomechanics perspectives



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ABSTRACT

Identification of Traumatic axonal injury (TAI) is critical in clinical practice, particularly in terms of long-term prognosis, but also for medico-legal issues, to verify whether the death or the after-effects were attributable to trauma. Multidisciplinary approaches are an undeniable asset when it comes to solving these problems. The aim of this work is therefore to list the different techniques needed to identify axonal lesions and to understand the lesion mechanisms involved in their formation. Imaging can be used to assess the consequences of trauma, to identify indirect signs of TAI, to explain the patient's initial symptoms and even to assess the patient's prognosis. Three-dimensional reconstructions of the skull can highlight fractures suggestive of trauma. Microscopic and immunohistochemical techniques are currently considered as the most reliable tools for the early identification of TAI following trauma. Finite element models use mechanical equations to predict biomechanical parameters, such as tissue stresses and strains in the brain, when subjected to external forces, such as violent impacts to the head. These parameters, which are difficult to measure experimentally, are then used to predict the risk of injury. The integration of imaging data with finite element models allows researchers to create realistic and personalized computational models by incorporating actual geometry and properties obtained from imaging techniques. The personalization of these models makes their forensic approach particularly interesting.

1. Introduction

According to the French Medical Academy dictionary [1], traumatic axonal injury (TAI) is a specific form of brain injury resulting from the rupture of white matter axons following violent trauma, which usually has a poor outcome. They can cause severe neurological dysfunction and impairment of cognitive and psychiatric functions. Their identification is critical in clinical practice, particularly in terms of long-term prognosis, but also for medico-legal issues, to understand whether lesions can be attributed to sequelae or death. These lesions correspond to a disruption of the axons [2] by shearing, stretching or even tearing in the areas of least resistance (primary axotomy) [3,4]. Damage to microstructures adjacent to neurons, biochemical cascades or changes to the

cytoskeleton secondary to the injury may also be the cause of later axonal damage (secondary or even tertiary axotomy) [5]. There is a physiopathological continuum with petechial haemorrhages or petechiae, which are common in severe traumatic brain injury (TBI) and result from rapid acceleration and deceleration forces producing shearing of the capillaries, as when TAI occur. These are visible on imaging at an early stage in the form of "micro-bleeds" and are therefore an indirect marker of TAI. The spatial distribution of TAI is not homogeneous, but there is a tendency to focus on specific areas, generally the junction between white matter and gray matter, the corpus callosum in the periventricular and splenium areas, and the brainstem, particularly the dorsal part of the midbrain [4,6]. There is wide variation in the clinical manifestations of TBI, which can be attributed to the extent of

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the lesions, but also to the lesion mechanism involved in the trauma.

In forensic practice, it is important to try to identify and understand the injury mechanism to try to answer the questions most commonly asked by the courts:

- What area of the head was hit?
- How many impacts can be identified?
- What is their sequence?
- What intensity was required to produce these injuries?
- Are they the result of a direct or indirect impact?
- Is the death or after-effects attributable to trauma?

Multidisciplinary approaches are an undeniable asset in solving these problems, as it is often difficult to provide clear answers. Some of the information will be accessible via imaging, clinical studies, neuropathology (in case of death) and biomechanics. The aim of this review is therefore to list the different techniques needed to identify axonal lesions and to understand the lesion mechanisms involved in their formation.

2. Clinical tools

In clinical practice, the diagnosis is made by a combination of clinical and imaging features. Following trauma, the coexistence of loss of consciousness or a low Glasgow Coma Scale (GCS) score (less than or equal to eight) for more than six hours and the presence of micro-bleeds at the gray-white matter junction, are considered highly suggestive of TAI [7]. However, the assessment based on patient severity is highly nonspecific, and there are currently no definitive pathognomonic to confirm the diagnosis of TAI [7].

3. Imaging assessment

In current clinical practice, patients with severe head trauma are initially assessed with a computed tomography scan of the head (CT). Magnetic resonance imaging (MRI) is generally indicated subsequently in various clinical situations: it can clarify lesions when the neurological examination is inconsistent with the initial CT, or when there's unexplained patient deterioration, necessitating new imaging. In case of a prolonged coma, the use of MRI allows to better study lesions, particularly in the brainstem. TAI can be difficult to diagnosed using CT, and is more likely to be detected in the presence of associated hemorrhagic components.

Due to the slice thickness of a conventional CT, typically less than ten millimetres, TAI may be missed, falling within the limits of the CT sensitivity [8]. CT scanning is more routinely used in the acute phase due to its faster scan time and its wider availability. It allows a rapid assessment of the patient's pathological context and primary lesion, which may determine the course of treatment. It can be used to decide on the indication for surgery, or to assess the need for specific monitoring, such as intracranial pressure or the placement of an external ventricular drainage. Although practices vary widely from one centre to another, rapid brain imaging using CT scan in the event of TBI remains the standard practice, as does imaging reassessment with MRI in the event of secondary neurological deterioration [9].

Conventional MRI is more sensitive than CT in detecting TAI [10,11], especially for lesions in the deep white matter and brainstem. Abnormal hyperintense signals are observed on FLAIR and diffusion weighted imaging (DWI) sequences. Gradient echo sequences, such as T2* and SWI (Susceptibility Weighted Imaging), excel at detecting haemoglobin and its degradation products, thereby rendering TAI will detectable through hypointense signals on these sequences. These tools are particularly suited for screening small haemorrhagic lesions [12]. SWI is a high-resolution MRI imaging sequence that surpasses conventional imaging in sensitivity for detecting small haemorrhagic lesions, which manifest as areas of hypointensity [13,14]. SWI is based on the same

principles as T2* and GRE sequences, but is more sensitive for haemorrhagic lesions, making it more effective for diagnosing TAI. However, the literature frequently mentions the occurrence of measurement artifacts. Such artifacts can lead to an overestimation of lesion size, resulting in images that do not accurately reflect the anatomopathological damage [8].

DWI quantifies the movement of water molecules within brain tissue. This sequence's primary advantage lies in its capacity for the early detection of TAI lesions. Furthermore, DWI can discern between the cytotoxic and vasogenic edema. Such information is helpful for prognostication and predicting the clinical outcome [15].

Diffusion tensor imaging is used to visualise nerve fibers as it measures water diffusion across multiple directions. Damaged axons may restrict water movement, leading to a decrease in fractional anisotropy (FA) and an increase in radial diffusion. FA is a parameter quantifying the direction preference of diffusion of water in nerve tissue. This sequence aids in TAI detection, characterized by reduces FA values. These anomalies possess significant long-term prognostic value, enabling detailed prognostication through this imaging sequence [16]. Tractography, which maps nerve fiber bundles, is a technique derived from the DTI sequence through mathematical reconstruction. Abnormalities in tractography, including discontinuities or breakage of bundles, may indicate axonal damage. However, it is crucial to note that tractography, a postprocessing technique, may not correlate at the histological level with the lesions present, despite its exploratory value [17,18].

Functional MRI (fMRI) provides an indirect measure of brain activity through blood oxygenation levels and can identify regions of the brain where axonal injuries affect functional connectivity [19,20]. However, it is important to remember that there are several functional MRI modalities, including resting state MRI, task-free MRI and other task-based functional MRI. Although several studies have been carried out to aid prognosis, there are no specific data on TAI and functional MRI. Moreover, these images rely on the principle of regional cerebral blood flow autoregulation (BOLD effect) during cerebral activation, a mechanism that is not well understood in the context of TBI [21].

Spectroscopic MRI offers insights into metabolic or neurochemical alterations associated with axonal injury, particularly through the measurement of N-acetylaspartate (NAA), creatine and lactate levels. A notable example is that a decrease in the NAA/creatinine ratio can signal axonal damage [22].

Imaging can thus be used to identify indirect signs of TAI, to explain the patient's initial symptoms and even to predict the patient's prognosis [23]. However, identifying the mechanism of injury based solely through the analysis of brain tissue presents challenges; although three-dimensional skull reconstructions can reveal fractures indicative of trauma [24–26]. Overall, imaging is used to assess the consequences of trauma. In the case of fatalities, postmortem imaging, which to date has relied solely on CT scans, offers limited diagnostic utility for TAI. Conversely, emerging studies of postmortem MRI are showing promising results [27].

Nonetheless, these imaging modalities are not typically included in the initial paraclinical evaluation for patients with cranial trauma, except under specific circumstances. In fact, MRI should be performed in a traumatic context if the patient's neurological state contrasts with the CT data. Moreover, MRI can provide crucial information about prognosis by enhancing the detection of brain lesions. However, TAI serves as a surrogate marker of the severity of trauma violence and is frequently incorporated into prognostic scales. These are based on the presence of TAI on MRI, location and bilateral nature of the lesions. The two most commonly used scales are the diffuse axonal injury (DAI) score [28] and the Firsching scale [29] and are associated with different prognostic outcomes depending on the severity (Table 1 and Fig. 1).

Table 1

DAI score and the Firsching scale associated with different prognostic outcomes depending on the severity.

	Grade	Définition	Outcomes
Firsching Score	Grade I	Supratentorial lesions only	70 % Good outcome (GOS 5)
	Grade II	Unilateral brainstem lesion at any level	30 % Good outcome (GOS 5) 30 % Moderate outcome (GOS 4) 30 % Vegetative state or death
	Grade III	Bilateral lesions of the midbrain	30 % Vegetative State
	Grade IV	Bilateral lesions of the pons	25 % Mortality 100 % Mortality
DAI Score	Grade 1	Axonal damage in the white matter of the cerebral hemispheres including the corpus callosum	15 % GOSE \leq 5
	Grade 2	Focal lesion in the corpus callosum in addition to diffuse axonal damage	20 % GOSE \leq 5
	Grade 3	Focal lesions both in the corpus callosum and the dorsolateral quadrant of the rostral brainstem	55 % GOSE \leq 4

4. Neuropathological tool

Microscopic and immunohistochemical techniques are currently considered as the most reliable tools for the early identification of TAI following trauma. However, this practice is only possible on deceased patients, during a neuropathological examination.

Following trauma, TAI are characterized by sequential changes: disruption of axonal transport with axonal swelling, then retraction of the axon towards the cell body and formation of a bulb, called a retraction ball, with a diameter greater than 5 μ m. This retraction ball is the result of multiple breaks in the fiber bundles. The evolution of the lesion, at a distance from the traumatic event, will result in degeneration of the myelin sheath, downstream of the section, progressing in the cellulite direction and known as Wallerian degeneration.

Neuropathological studies of mild traumatic brain injury (TBI) patients who died of other causes have shown that aberrant accumulation of amyloid protein precursor (APP) in axons due to inhibition of axonal transport occurs a few hours after TBI [5,30,31]. APP is a membrane glycoprotein expressed in all body tissues, mainly in the brain, in small quantities, undetectable by immunohistochemistry in non-pathological conditions [32].

In pathological conditions, particularly traumatic ones, APP accumulation is visible thanks to APP Beta immunostaining: this immunostaining is currently the most reliable to be used to identify TAI (Fig. 2) [32,33]. These axonal lesions remain visible for weeks or even months after TBI [34].

TAI can be identified post-mortem under light microscopy. The recommended identification method for TAI depends on the times after death:

- within thirty minutes of death: TAI can be identified by the presence of anti-APP immunostaining in the white matter. However, three main principles must be observed before any interpretation is made [35]:
 - survival time after cardiocirculatory arrest must be sufficient (between 35 and 120 min, depending on the series).
 - cerebral vascular perfusion must be sufficient during this survival time.
 - on the other hand, overly prolonged survival may result in a false negative (with the appearance of non-traumatic axonal damage, hypoxia, ischemia, hemorrhage and edema)[36].

- within the first 72 h after death, TAI can be identified by the presence of:
 - abnormal accumulation of amyloid precursor protein, with axonal swelling or axonal retraction ball visible with standard staining,
 - structural degeneration revealed by anti-neurofilament immunostaining (structural proteins present in axons) [37] or the detection of proteolytic fragments of alpha spectrin (SNTF), one of the proteins at the interface between the axon's membrane skeleton and the cell membrane [38].
 - microglial activation (with clusters of microglial activation close to axonal or perivascular lesions) revealed by anti-CD68 or anti-HLA-DR immunostaining [36].
 - perivascular astrogliosis in the white matter, revealed by anti-GFAP immunostaining.

5. Biomechanical approach

Recent advances in imaging and neuropathology have enabled better detection and visualization of TAI and their evolution over time, sometimes even explaining death. However, these techniques do not provide information on the mechanisms that lead to these lesions. This is problematic in medico-legal cases that require identification of the injury mechanism that led to the TAI (such as which impacts induced which brain injury). To investigate the pathophysiology of traumatic brain injury, a biomechanical approach has been proposed: the finite element (FE) modelling of the brain [39–41]. FE models use mechanical equations to predict biomechanical parameters, such as tissue stresses and strains in the brain, when subjected to external forces, such as violent impacts to the head. These parameters, which are difficult to measure experimentally, are then used to predict the risk of injury [41].

A precise prediction of brain damage relies on accurately characterizing and modelling the behavior of brain tissues. This is challenging due to the brain's unique mechanical properties and anatomical characteristics (suspended in cerebrospinal fluid inside the skull). Furthermore, TAI are not easily identifiable and their mechanisms are difficult to predict. The primary methods for predicting TAI involve calculating either the strain or stress in the brain and correlating these mechanical parameters with the risk of TAI (Fig. 3)[42–44]. The following sections describe these two mechanical parameters and their associated injury thresholds [42–44].

Brain strain (or brain tissue deformation) is the deformation of a material resulting from the application of a force or load. Forces and stresses can be classified as tension, compression, bending, torsion and shear (see Fig. 4).

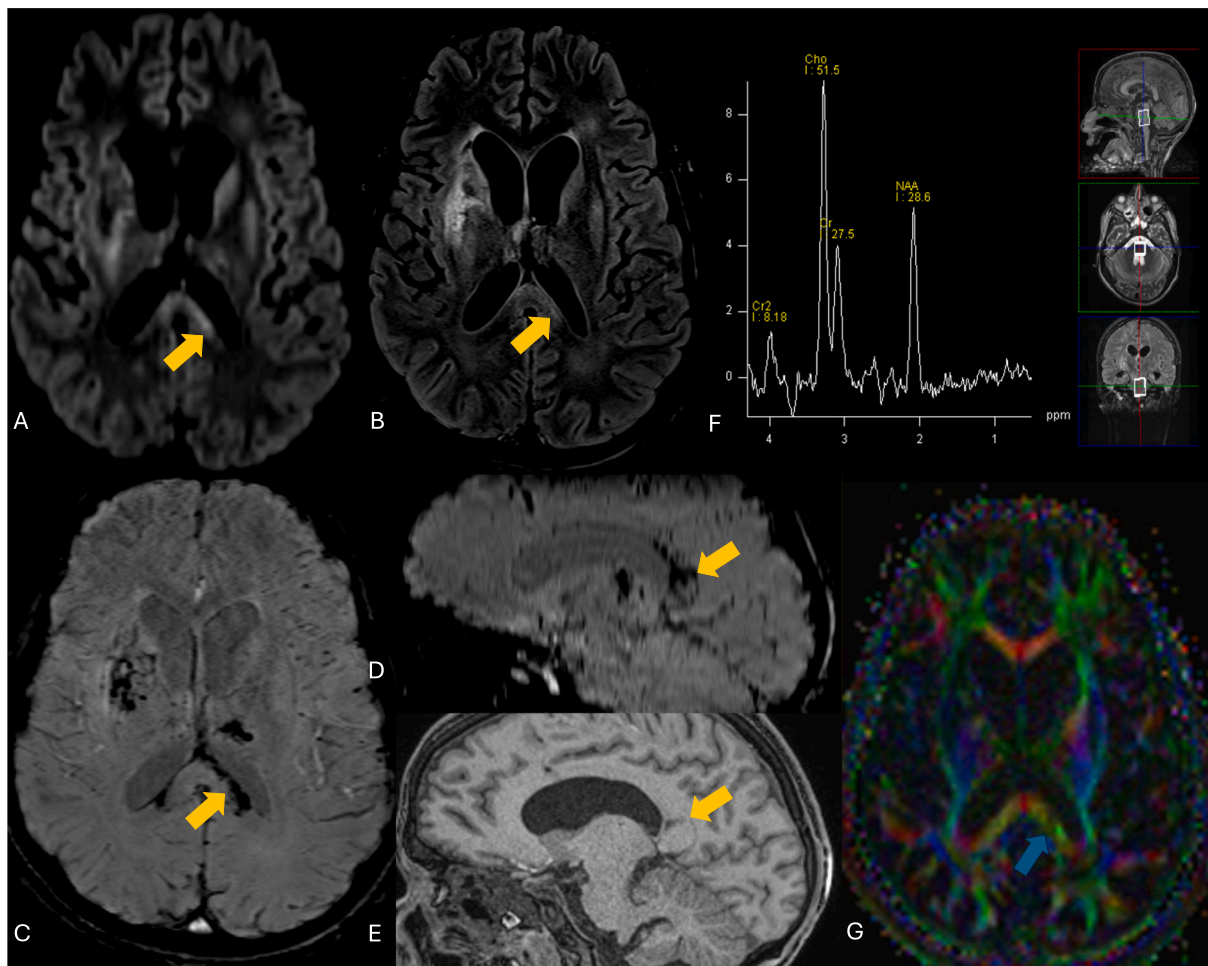
In the case of intracranial tissue, this refers to elongation/tension, compression or shear at the level of the axon or the tissue as a whole. Based on the computed deformation of brain tissue, researcher have developed injury threshold to predict the likelihood of injury. Axonal deformations of between 5 % and 20 % would constitute a continuum of thresholds for neurological lesions of varying severity [44].

The statistical measure PSSP (peak shear strain possibility) is a percentage considering a shear strain of 30 % as the critical threshold for the appearance of TAI [45].

The addition of DTI imaging in FE models has enabled the integration of fractional anisotropy (FA) in white matter and an approximation of an axonal network [46]. Thanks to this integration, a new criterion, axonal deformation, proved to be a better predictor of TAI than the other parameters evaluated, with a 50 % risk of brain damage associated with an axonal deformation of around 14.65 % [47,48].

The anisotropic equivalent strain is a metric based on the maximum strain within a critical volume element, which depends on the orientation and direction of tissue deformation. It is also described to enable better prediction of TAI [49]. However, the determination of a threshold value is not clearly defined.

These threshold data, depending on the study and model, may vary according to the material properties, and the geometry of the brain



	Grade	Définition	Outcomes
Firshing Score	Grade I	Supratentorial lesions only	70% Good outcome (GOS 5)
	Grade II	Unilateral brainstem lesion at any level	30% Good outcome (GOS 5) 30% Moderate outcome (GOS 4) 30% Vegetative state or death
	Grade III	Bilateral lesions of the midbrain	30% Vegetative State 25% Mortality
	Grade IV	Bilateral lesions of the pons	100% Mortality
TAI Score	Grade 1	Axonal damage in the white matter of the cerebral hemispheres including the corpus callosum	15% GOSE ≤ 5
	Grade 2	Focal lesion in the corpus callosum in addition to diffuse axonal damage	20% GOSE ≤ 5
	Grade 3	Focal lesions both in the corpus callosum and the dorsolateral quadrant of the rostral brainstem	55% GOSE ≤ 4

	Firshing Score	TAI Score
MRI findings	Grade 3	Grade 3
Neurological Outcome	30% Vegetative State 25% Mortality	55% of patients with GOSE ≤ 4

Fig. 1. Example of patient with a grade 2 axonal injury with TAI and Firshing Scores (personal case). TAI involving the splenium of the corpus callosum, with hyperintense diffusion signal (A), hyperintense FLAIR, haemorrhagic component (C and D), corresponding to malacia (E). Spectroscopic analysis reveals an increase in choline associated with a decrease in N-Acetylaspartate (F) and disruption of myelin fibers (G).

model and these internal structures. For example, a 50 % risk of concussion was associated with deformation levels of 0.13 in the thalamus, 0.15 in the corpus callosum and 0.26 in the white matter for a model without the addition of FA [50]. After addition of FA with integration of axonal direction, a concussion risk of 50 % was associated with deformation levels of 0.07 in the corpus callosum and 0.15 in the brainstem [51,52]. Marjoux et al. found a 50 % risk of developing mild neurological lesions with a Von Mises stress of 26 kPa, a Von Mises strain of 0.25 and a first principal strain of 0.31 [53].

Brain stress represents the forces exerted in the brain tissue per unit area. It is expressed in Pascal (Pa). Forces and stresses can be classified as tension, compression, bending, torsion and shear. Tension and compression act perpendicularly to the material surface. While tension tends to lengthen the material and narrow the cross-section, compression shortens and widens it. Theory predicts that a ductile material

begins to fail when the von Mises stress reaches a level equal to the limiting stress. According to Baumgartner, von Mises stresses in the brain model of respectively 18 kPa and 38 kPa indicate a risk of moderate and severe neurological lesions [54]. According to Sahoo et al. there is a 50 % risk of developing moderate neurological lesions for maximum stresses of 16.8 kPa; this risk rises to 95 % for maximum stresses of 20.8 kPa [55]. Shear stress in the brainstem is described by Newman et al. as the best predictor of injury, with a shear stress of 7.8 kPa proposed as a 50 % risk of moderate head injury [56].

6. Integration of imaging data with finite element models

The integration of imaging data with finite element models is a powerful approach in various fields, including biomechanics, materials science, and medical research. This integration allows researchers to

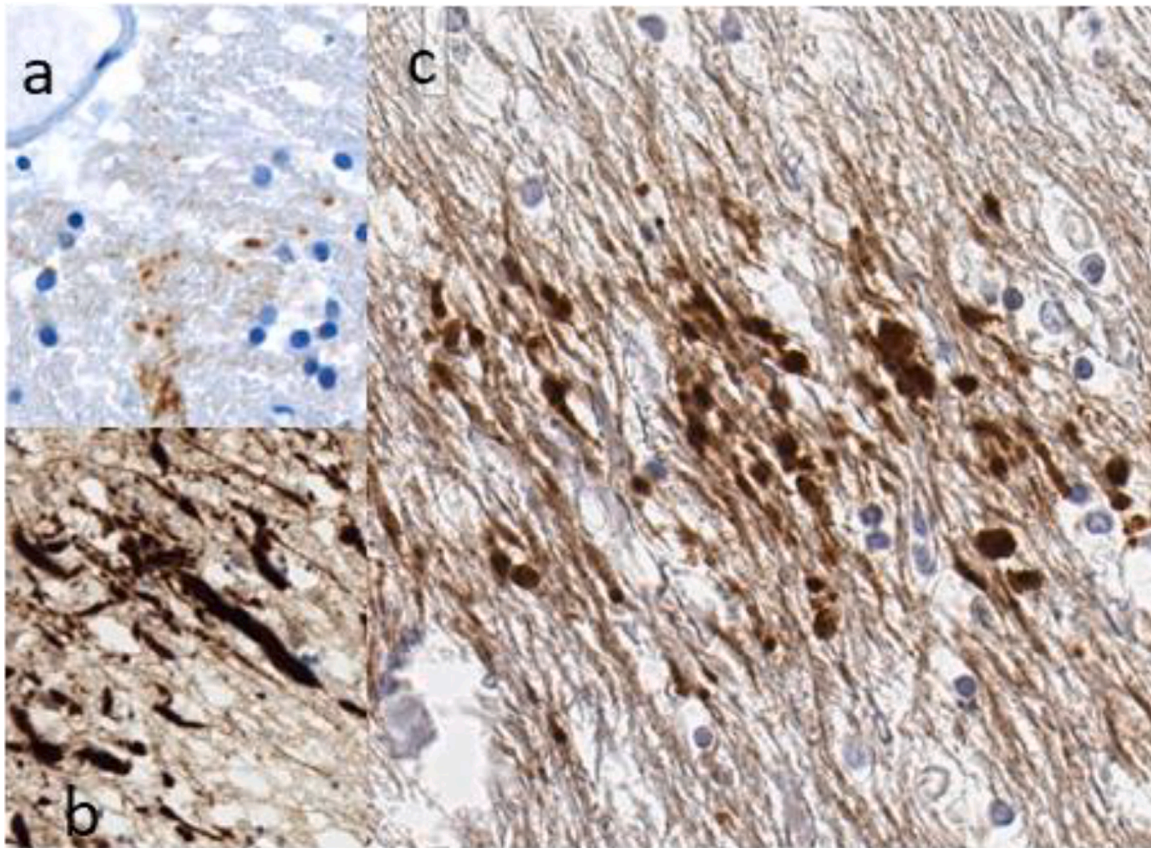


Fig. 2. Photo of neuropathological examination of patient deceased following head trauma (personal case): different types of anti-APP immunostaining: granular labelling (a) magnification $\times 120$, axonal dilation magnification $\times 250$ (b), axonal retraction balls (c) magnification $\times 200$.

create realistic and personalized computational models by incorporating actual geometry and properties obtained from imaging techniques. The personalization of these models makes their forensic approach particularly interesting. This personalization phase can be reported in two ways: firstly, by adapting the brain's geometry such as ADAPT [57] or CAB-20MSym [58], and secondly, by adapting its mechanical properties with magnetic resonance elastography [59,60].

These FE models are modeled from a database of pre-registered images to facilitate the modification of the model according to the clinical case being analyzed. "Registration-based morphing pipeline (RBM)" or "image registration" is the name given to this technique which is used to align a fixed image with a more mobile one, such as an MRI [57,58]. This method objective is to perform automated brain tissue segmentation using masks and can quantify anatomical differences within the images of a study group. A global or case-specific numerical model is generated for each brain structure with an appropriate mesh [57,58].

Specifically, the most advanced finite element models allow for the integration of white fiber characteristics collected by DTI combined with segmentation of white matter, cortex, deep grey nuclei, meningeal structures and CSF. In addition, axonal properties such as orientation, location, myelination and length also predict the likelihood of axonal injury, with long unmyelinated axons being more vulnerable. Differences in the mechanical properties of the white/gray matter and CSF compartments also influence injury, with maximal strain occurring in the softer materials. These models show significant differences in brain and axonal deformation as a function of baseline data, with large inter-individual variations, even when the biomechanical forces applied are identical. This highlights the importance of using these models to better understand and assess the extent and spatial distribution of brain damage [56–58]. These methods make it possible to analyse the distribution of biomechanical deformations and shear forces with high

spatiotemporal resolution [61,62]. It's also allow for the integration of a high-fidelity model of the human brain with a precise description of the gyri. This allows detailed prediction of the biomechanical forces observed in different tissues after CT injury. Ghajari et al. has shown that different types of CT result in high deformations and shear forces concentrated in the depths of the sulci, a topography often associated with chronic traumatic encephalopathy [63].

Finally, it would be conceivable to use a co-registration of FE model with MRI mappings in order to deduce, once the MRI lesions have been identified, what the original lesion mechanism was, based on the different simulations generated by a reverse engineering method.

In this way, the various techniques cited allows you to carry out an analysis taking into account the geometric specificities of the patient and therefore to refine the response of the model and the understanding of the mechanisms. The second advantage of implementing imaging techniques with biomechanics is to make long-term predictions (3–6 months after the accident) of the patient's condition to analyze the evolution of a lesion which can help determine when the condition is stabilised and thus the after-effects [64].

7. Conclusion

While medical imaging plays an essential role in visualizing traumatic brain lesions, these techniques can only identify structural alterations in the brain following trauma. Their application in post-mortem care is debatable, but they are of undeniable interest in the assessment of after-effects in victimology practice.

Progress has also been made in understanding traumatic brain lesions at the histological level. Neuropathological examinations can reveal signs of cellular damage, inflammation and other direct or indirect changes associated with trauma. This practice is only accessible in a

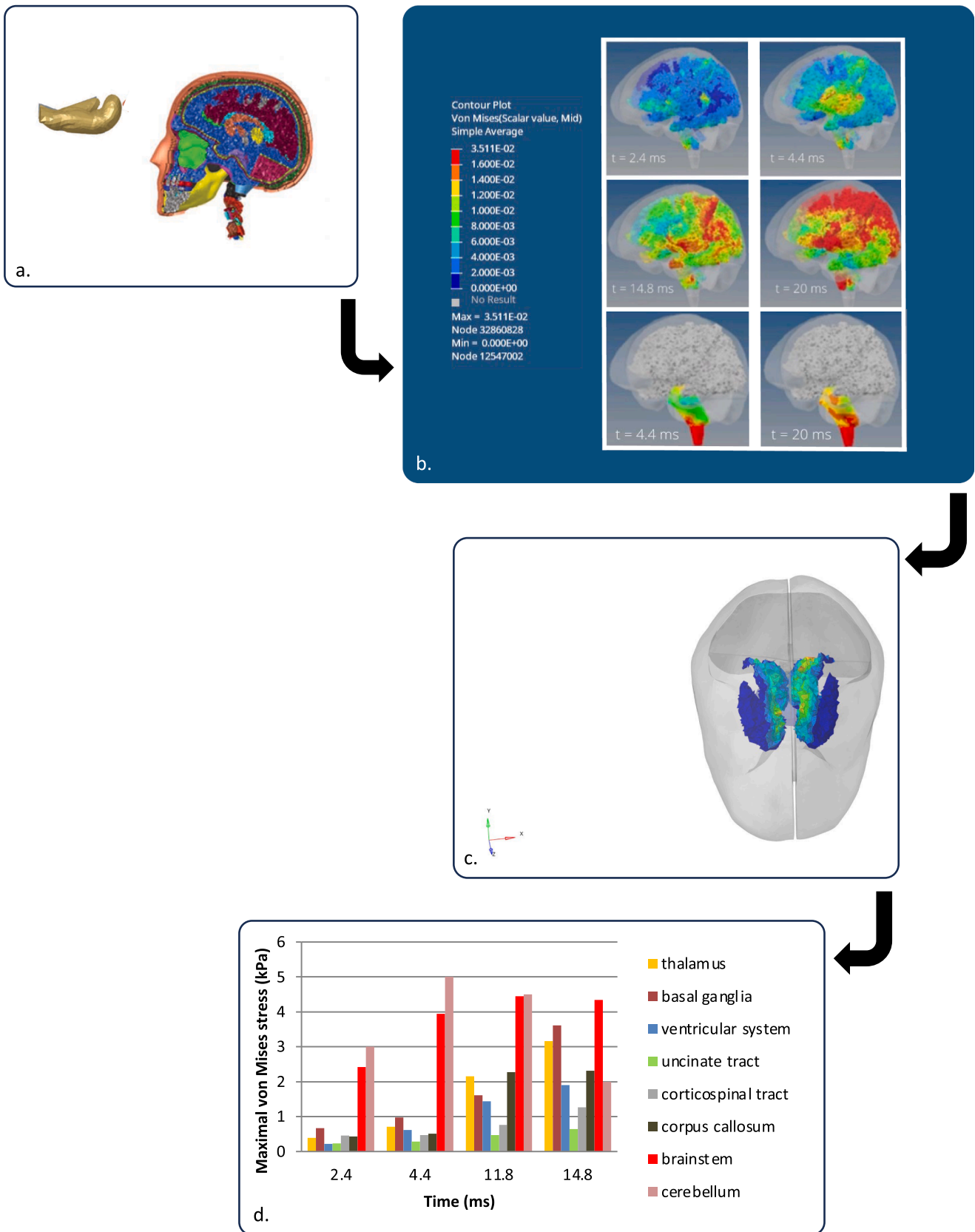


Fig. 3. Example of data obtained from a finite element model (here, a model from the Applied Biomechanics Laboratory in Marseille) A. from scenario of a frontal impact; B. visualization of Von Mises stress distribution in brain tissue; C. possibility to focus on some structure to research the injury threshold in the central gray nuclei and thalami; D. analyze the distribution over time (ms) of maximum von Mises stresses (kPa) in brain organs during and after the impact.

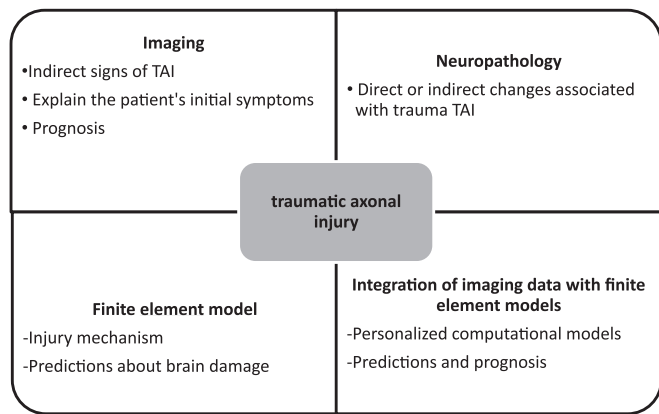


Fig. 4. Overview of TAI in imaging, neuropathology, finite element model and integration of imaging with finite element models.

post-mortem context, under specific conditions of death and with the body in a suitable state of preservation.

FE models are a powerful tool for tackling head injury issues in a variety of contexts, from neurology to biomechanics. Recent advances in these modelling techniques have deepened our understanding of the mechanisms underlying TAI, opening the way to new discoveries and applications in the field of neurology, particularly in terms of prevention.

Forensic biomechanics focuses on exploring the causality of forensic phenomena that are often decisive factors in injury cases, both civil and criminal. Forensic biomechanics has become an important branch of forensic science, providing the means for more objective and quantitative forensic investigations, and is one of the research areas of forensic science that still has great potential for development.

8. Authorship

- (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data: C. Delteil, Thais Manlius, J-F Hak, L Velly, P Simeone.
- (2) drafting the article or revising it critically for important intellectual content: N Bailly, Y Godio-Rabouteux, M-D Piercecchi-Marti, L Tuchtan, L Thollon
- (3) final approval of the version to be submitted: all the co-authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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