Original Article

Medicolegal Importance of Histological Examination in Cases of Mild Traumatic Brain Injury

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ABSTRACT

Introduction: The management of traumatic brain injury is challenging as patients with apparent mild head trauma may develop late complications. Some patients may develop an intracranial hemorrhage several days after the injury. Hence, emergency doctors may be more liable to malpractice claims. Also, histological examination can reveal forensic evidence in cases of unclear death. Therefore, it is of great importance to highlight the medicolegal and histological aspects of traumatic brain injury(TBI).

Aim of the Work: To highlight the medicolegal and histological aspects of mild traumatic brain injury.

Materials and Methods: Thirty adult female albino rats were included.The animals were divided into three groups: Group I (Control group). Group II:it included10rats, they were sacrificed 6 hours after closed head impact model .Group III: It included 10 rats , which were sacrificed 7 days after closed head impact model. At the end of the experiment, the specimens were taken and processed for immunohistochemical and histological studies.

Results: Examination of frontal cerebrum sections after 6hours revealed dilated congested blood vessels of pia matter .The cerebrum showed dark shrunken neurons with swelling of neuroglia .Inflammatory cells and rod shaped microglia. The medulla showed widely separated nerve fibers. After 7 days, the cerebrum showed apparent decrease in neurons and inflammatory cells. This was confirmed by increase in GFAP reaction (gliosis).The medulla showed thinning of nerve fibers.

Conclusion: Histological examination can be used to seek forensic evidence for TBI in absence of gross findings. Even with apparent mild head injuries, significant microscopic cerebral changes may be found. So, some patients will require in-hospital observation and cannot be safely discharged. In patients who can go home, discharge instructions need to be clear and documented. Also, in unclear deaths, brain tissue blocks may reveal evidence of TBI.

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Key Words: Brain trauma, forensic evidence, GFAP, histological examination, medicolegal.

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INTRODUCTION

Traumatic brain injury (TBI) is one of the most common causes of death and disability around the world. Head injury (HI) cases have increased in both developed and developing countries. Therefore, it is of great value to evaluate the medicolegal and histological aspects of head injury[1].

TBI could be classified to mild, moderate, and severe TBI as the following: Mild traumatic brain injury is with loss of conscious less than 30 minutes without skull fractures, moderate traumatic brain injury is that with loss of consciousness more than 30 minutes but less than 24 hours with or without skull fractures and severe traumatic brain injury is that with loss of consciousness more than 24 hours with appearance of contusions, hematoma or skull fractures[2].

Mild TBI could be defined as a pathophysiological process affecting the brain, induced by direct or indirect biomechanical forces which lead to acute neurological deficits that typically resolve without structural injuries[3].

Although some patients with Mild traumatic brain injury may be admitted to the hospital overnight, Most of them are treated and released from emergency departments with basic discharge instructions. This group of TBI patients represents the greatest challenges to accurate diagnosis and outcome prediction[4].

Mild traumatic brain injuries are not always evident on EEGs, CT scans and neurological examinations. However, the absence of evidence does not necessarily mean there is no cerebral injury, and such a missed diagnosis could lead to medical malpractice claims[5].

In cases of death from TBI, the cause of death is obvious when there are gross findings, but histologic examination is of great medicolegal importance to seek evidence in absence of macroscopic finding[6].

The current work was carried out to highlight the medicolegal and histological aspects of mild traumatic brain injury and emphasize the importance of follow up in cases of mild brain trauma to avoid increased malpractice claims against emergency doctors. Also, shows the importance of histological examination as forensic evidence.

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MATERIAL AND METHODS

All of the animals were purchased and grown at Ain Shams University's Medical Research Center. Thirty adult female albino rats of an average weight of 200–250 g were utilized. The animal experiment was carried out at the Ain Shams University Faculty of Medicine's Research Center Institute (MASRI). It was approved by the Faculty of Medicine, Ain Shams University Research Ethics Committee (FMASU REC) organized and run under the International Council on Harmonization (ICH) and Islamic Organization for Medical Science (IOMS) guidelines, as well as the US Office for Human Research Protections and US Code of Federal Regulations and is covered by Federal Wide Assurance N.FWA 00017585.The animals were divided into three groups:

Group I (Control group): included 10 rats that received only food and water.

Group II: it included10 rats in which sedation of the rats was done. Animals

were anesthetized with a thiopentone sodium at a dose of 40 mg/kg[7] then they were placed and fixed on a horizontal surface to avoid any head movements after that,180 gm weight has been dropped following closed head impact model[8]. Rats were sacrificed 6 hours later.

Group III: It included10 rats in which same maneuver of closed head impact model was done as that of group II but rats were sacrificed 7 days later.

At the end of the experiment, the rats were anesthetized with ether inhalation. The skull was opened and fresh brain specimens were taken and prepared for the following studies

Histological and immunohistochemical studies

For light microscopic study, specimens were fixed in 10% buffered formalin and 5-mm thick paraffin sections were prepared and stained with hematoxylin and eosin[9].

Immunohistochemical study Immunostaining was performed using an avidin biotin– peroxidase technique for showing microglia using CD68 mouse monoclonal antibody (purchased from Novocastra labs, UK, at a dilution of 1 : 20). This antibody has been shown to react selectively with a specific cytoplasmic glycoprotein present in mononuclear phagocytes, microglia, and epidermal langerhans cells[10]. Paraffin sections of the brain were incubated with biotinylated antimouse antibody (diluted 1: 200) and the avidin biotin-conjugated peroxidase complex (Vector Lab. Inc., USA). The reaction was developed with 0.05% diaminobenzidine (DakopattsGlostrup, Denmark) as the substrate for peroxidase; finally, the slides were counterstained with hematoxylin[11]. The cytoplasmic site of the reaction stained brown whereas the nuclei appeared blue. The specificity of the immune reaction was tested by replacing the primary antiserum with phosphate-buffered saline as a negative control[12].

Avidin–biotin staining was used also in GFAP immunohistochemical staining and hematoxylin was used for counter-staining. The primary antibodies were rabbit anti-glial fibrillary acidic protein (GFAP) (1:200, Sigma). GFAP is a class-III intermediate filament and a structural constituent of the cytoskeleton. It is a cell-specific marker that is used to distinguish astrocytes from other glial cells during the development of the CNS[13].

Morphometric study

The image analyzer computer system Leica Qwin 500, UK in the Histology Department, Faculty of Medicine, Ain shams University, was used to count the Mean area percentage of GFAP using the immunostained sections and the mean number of oligodendrocytes using the H&E stained sections. Ten nonoverlapping high-power fields (x 400) from each slide of all animals of each group were used.

Statistical analysis

The data obtained from the image analyzer were expressed as means ± standard deviations. The morphometric results were analyzed using an analysis of variance one-way test. The results were considered statistically significant when the $P\ value < 0.05$ and highly significant when the $P\ value < 0.001$[14].

RESULTS

All injured rats survived without macroscopic evidence of a skull fracture or cerebral hemorrhage. Examination of brain sections of the control group of frontal cerebrum showed appearances of normal brain parenchyma consisting of neurons, neuroglia, nerve fibers and blood vessels. Neurons are of two types granules cells and pyramidal cells. Granules cells are small rounded cells. Their nuclei had granular chromatin. Pyramidal cells are triangle cells with apical and basal dendrites. They had a large, round nucleus with a single prominent nucleolus. Medulla showed, oligodendrocytes arranged in rows with compact nerve fibers in between (Figure 1).

Examination of frontal cerebrum of group II showed neuronal pyknosis, congestion of blood vessels was evident in all sections, presence of inflammatory cells, rod shaped microglia and swollen astrocyte,destructed, widely separated nerve fibers with decreased oligodendrocytes as compared to control group was noticed (Figure 2).

Examination of brain sections of group III showed apparent decrease of cells in the frontal cerebrum, most neurons are severely shrunken. Oligodendrocytes were severely decreased in amount with disrupted rows and spaced nerve fibers (Figure 3).

Immunohistochemistry for GFAP in the control group showed that many astrocytes did not express detectable levels of GFAP ,While that of group II showe dmoderately reactive astrogliosis in which most (if not all) protoplasmic astrocytes have up regulated expression of GFAP with preservation of individual astrocyte domains.

Immunohistochemistry for GFAP in group III showed severe diffuse reactive astrogliosis, and pronounced overlap of astrocyte processes resulting in disruption of individual astrocyte (Figure 4).

Immunohistochemistry for CD68 in the control group showed almost negative reaction, While that of group II showed mild positive reaction in rod shaped microglia. Immunohistochemistry for CD68 in group III showed strong positive reaction as compared to control and group II (Figure 5).

Morphometric and Statistical results

Statistical analysis using one-way ANOVA test revealed a notable ($P< 0.05$) elevation in the mean area percentage ofGFAP in both groups II and III respectively (Figure 6),while Mean number of oligodendrocytes showed significant decrease ,that was more noted in group III (Figure 7, Table 1).

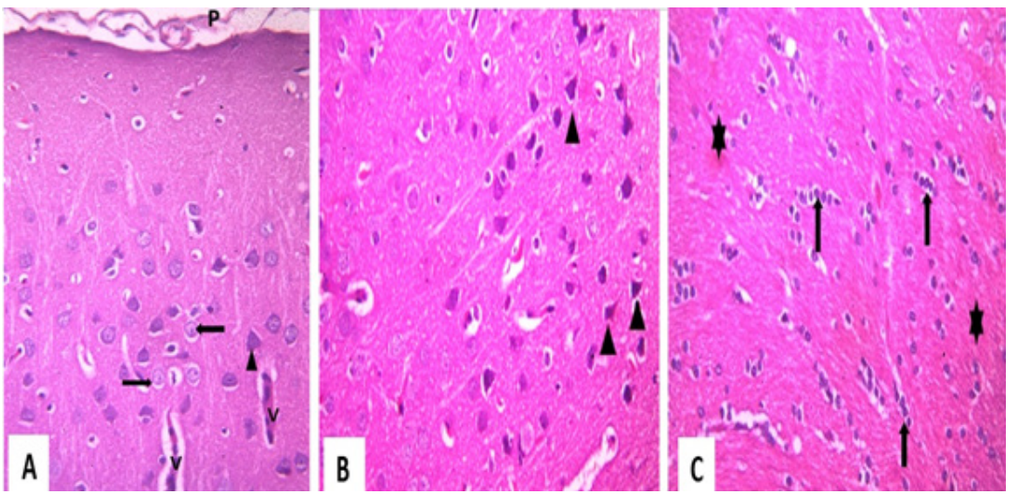

Fig. 1: Photomicrographs of H&E stained section of frontal cerebrum of the control group showing (A,B) grey matter of cortex covered by pia matter(P) with blood vessel, small rounded granular cells(↑) and triangle shaped pyramidal cells (▲) nerve fibers and blood vessels (V) . (C) White matter containing oligodendrocytes(↑)arranged in rows with nerve fibers in between (*) (H&Ex400).

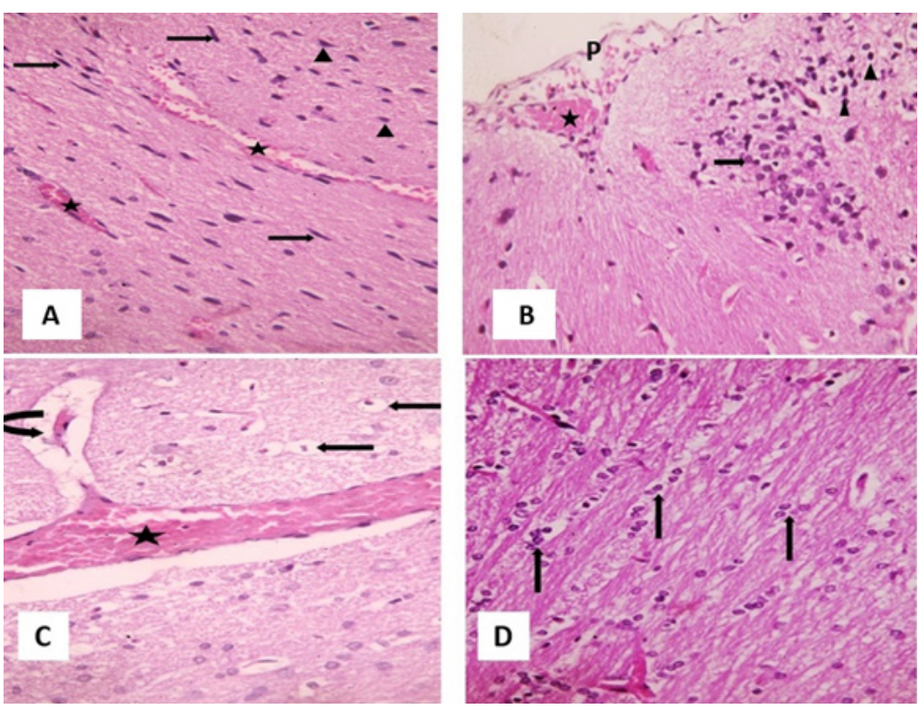

Fig. 2: photomicrograph of grey &white matters of frontal cerebrum of group II showing ,(A)grey matter with dark shrunken neurons (▲),prominent microglia with spindle shaped nuclei (↑),congestion of blood vessel(*).(B) dilatation of subpial space containing congested, ruptured blood vessel (*),mononuclear cellular infiltration(↑),dark shrunken neuron with small deeply stained nuclei(▲) (C)neuroglia with swollen acidophilic appearance(↑)& dilated congested blood vessel(*)and swollen astrocyte( ).(D) white matter with destructed, widely separated nerve fibers and apparent decrease of oligodendrocytes(↑) (H&E x400).

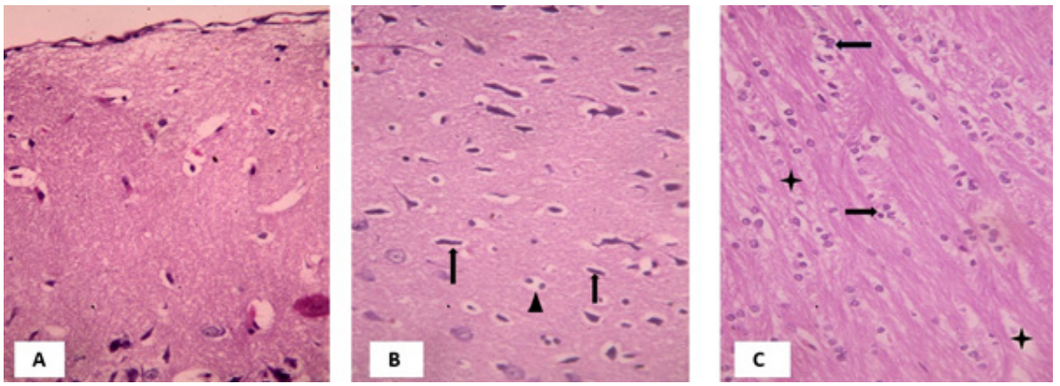

Fig. 3: photomicrograph of grey &white matters of frontal cerebrum of group III showing (A) grey matter with apparent decrease of neurons. (B) Numerous flat spindle shaped microglia (↑) and astrocytes (▲). (C) White matter with apparent decrease of oligodendrocytes (↑) and disrupted nerve fibers rows (✦). (H&E x400).

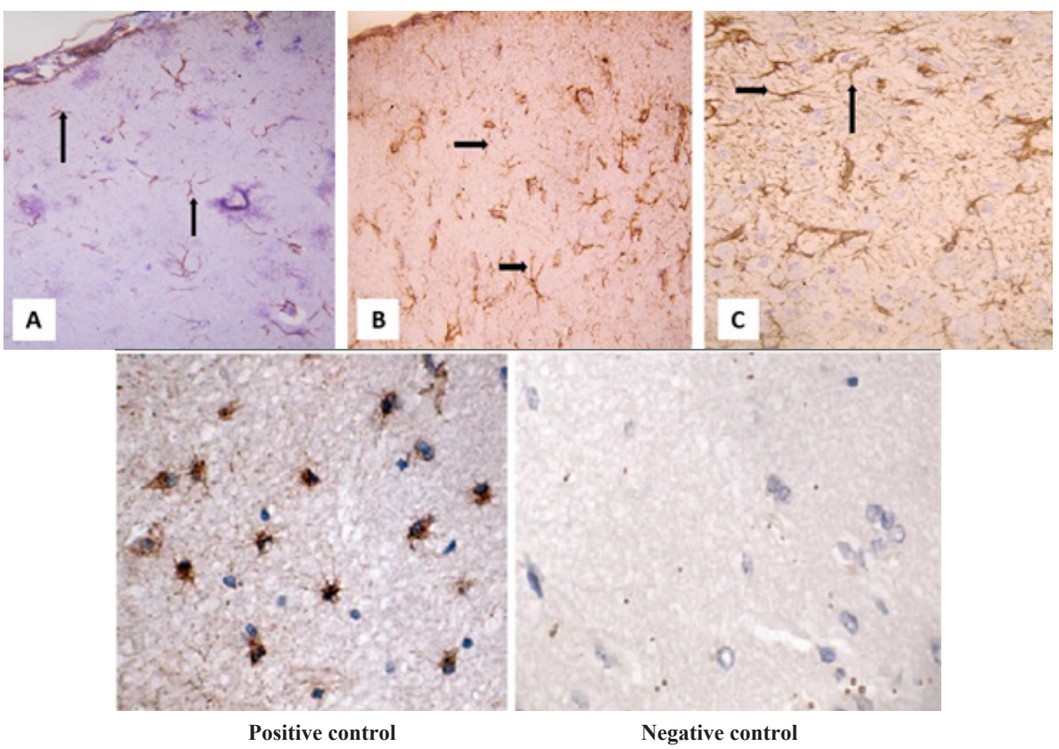

Fig. 4: a photomicrograph of GFAP stained cerebral cortex sections (A) control group , showing weak GFAP positive reaction .(B) group II showing mild GFAP positive reaction .(C) group II I showing strong GFAP positive reaction . (Immunostaining of GFAP &Hx X400)
N.B:Positive control showing GFAP positive reaction in brain tissue.

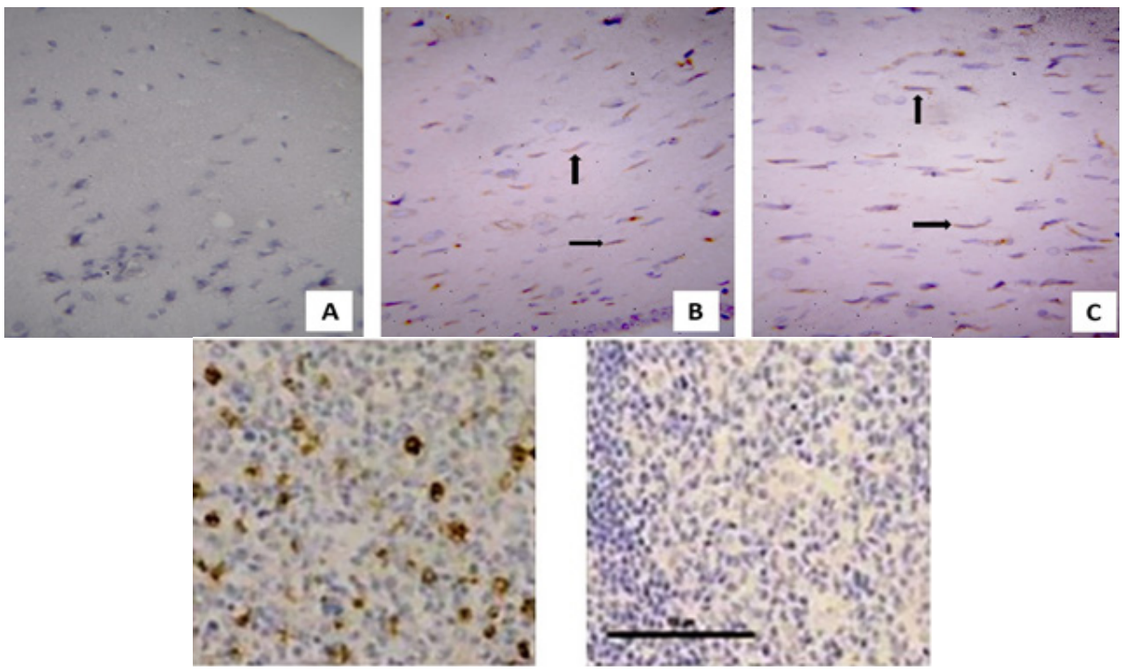

Fig. 5: a photomicrograph of CD 68 stained cerebral cortex sections showing (A) control group, showing almost negative CD68 reaction.(B)group II showing mild CD68 positive reaction .(C)group III showing strong CD68 positive reaction .(Immunostaining of CD68&Hx X400) .
N.B: Positive control showing CD 68 positive reaction in endometrium.

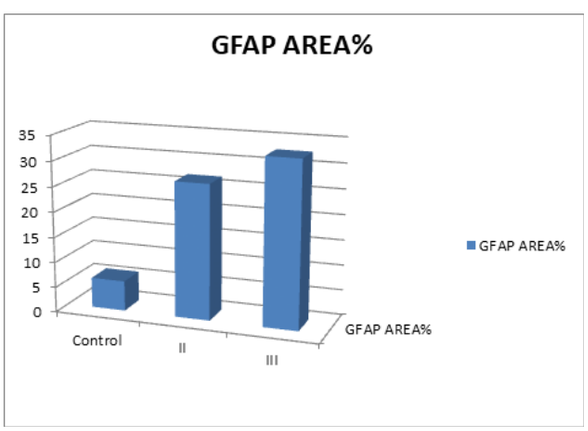

Fig. 6: Differences of the mean of area percentage of GFAP between the studied groups

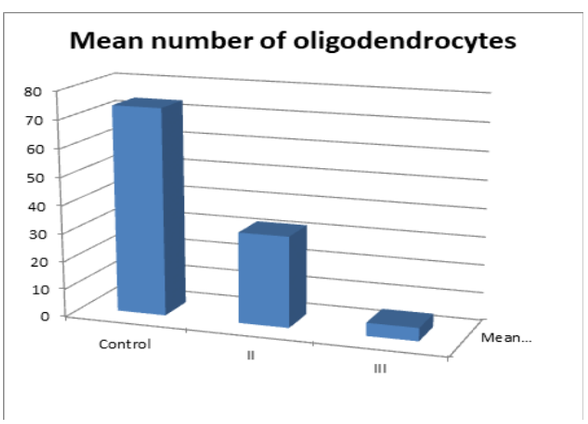

Fig. 7: Differences of the mean number of oligodendrocytes between the studied groups

Table 1: Differences of the mean of area percentage of GFAP and the mean number of oligodendrocytes between the studied groups

groups	Control (I)	II	III
Mean area percentage of GFAP	5.09± 1.50	26.78±3.2(■)	32.78± 4.1(■)(♠)
Mean number of oligodendrocytes	73.836±1.668	32.45±.634(■)	21.39±.715(■)

Values are means ± SD
(■) significant compared to group I ($P < 0.05$)
(♠) significant compared to group II ($P < 0.05$)

DISCUSSION

Traumatic brain injury (TBI) is one of the most common causes of hospital admission that contributes to 1/3 of all injury related death in the population under 45 years of age worldwide, it is therefore frequently faced by pathologists in the coronial and medicolegal services[15].

Most studies found that there is a small but significant number of patients with apparently mild head trauma who appear well on examination may have severe intracranial injuries requiring immediate intervention[16].

Also, forensic pathologists could make decisions regarding cause and manner of death by careful histologic examination of retained tissue blocks that serve as forensic evidence for TBI in the absence of gross findings[6].

In the present study, frontal cortex was chosen for TBI model as it is the most frequently affected due to its anatomical position against rigid bone[17].

we investigated early and late effect of TBI also other investigators stated that damage of neural tissue associated with TBI falls into two categories primary injury which is caused directly by mechanical force during initial insult secondary injury refers to further tissue and the cell damage following primary insult[18].

Mononuclear cellular infiltration of frontal parenchyma, with the presence of many shrunken dark neurons were detected in Group II of the present study, however in Group III marked neural loss was detected.

Neuronal degeneration was caused by dendritic and synaptic destruction with significant decrease in cellular density in the affected area[19].

Moreover, another explanation was that an increase in extracellular glutamate resulted in hyperstimulation of glutamate receptors with persistent depolarization of neurons. Decrease ATP with ionic disruption occurred leads to an increase in intracellular calcium that will be sequestered in Mitochondria. Opening of mitochondrial pores with release of cytochrome C could activate neuronal apoptosis[20].

Other researchers explained that neuronal death following TBI was attributed to disruption of blood brain Barrier and cerebral ischemia[21].

Others added to that the rule of cellular infiltration which release toxic cytokines leading to neuronal death[22].

In addition to neural affection axonal destruction appeared in Group II of the present study, marked vaculation of nerve fibers occurred with destruction and disconnection of nerve fibers appeared in the white matter. Thinning of white matter was also detected in group III of the present study.

Some investigators stated that following TBI axons became brittle they added that, diffuse axonal injury occurred in white matter as it is vulnerable to injury[23].

Changes in the white matter were manifested actually as immediate loss of consciousness or confusion and persisted as coma cognitive dysfunction[24].

It was reported that Wallerian degeneration of axons within minutes after TBI due to production of reactive oxygen species(ROS) by inflammatory cells this led to demyelination and disruption of axonal cytoskeleton. Disruption of axonal transport occurred with subsequent death of neurons[25].

Accumulation of transport protein at axons caused death of neurons and neuroglia[26].

Long term neuronal and axonal degeneration might continue for years after injury this might have a rule in the development of Alzheimer's disease[27].

In the present study group II and Group III there was significant loss of oligodendrocytes between nerve fibers of white matter. Also the presence of a swollen neuroglia with acidophilic cytoplasm and pyknotic nuclei could be detected

The former investigators stated that oligodendroglia degeneration distal to the site of axonal injury was attributed to the lack of traffic support of injured axon.

limited replacement of oligodendrocyte from their progenitor cells resulted in incomplete myelination and thinning of nerve fibers of white matter[28].

Another evidence was recorded that loss of oligodendrocyte was noticed seven days following contusion injury of the brain[29].

The present study revealed presence of subpial space filled with blood cells In Group II of the present study. Vasodilatation and congestion of cortical blood vessels were evident.

These agree with previous study that recorded the presence of subpial hemorrhage following TBI due to brain ischemia[6].

Focal disruption of basement membrane of cerebral blood vessels with pooling of blood in to subpial space was recorded by other investigators[30].

Dilation of perivascular space was detected in Group II of the present study. A previous study declared that dilated perivascular space was hallmark for mild traumatic brain injury in rodents[31].

However, it was reported that dilated perivascular space was unique bio mark for small vessels disease and suggested presence of dementia and stroke and impaired cognition[32].

Vasodilation of blood vessels could lead to edema. Edematous changes of the brain following TBI was recorded in Group II of the present study. In grey matter swelling of neuroglial cytoplasm (end feet off astrocyte). In white matter, nerve fibers were widely separated by edema fluid.

Another explanation that edema was the major change after TBI was the movement of water and proteins into interstitial spaces due to damage of blood brain barrier. Swelling of neuroglia was explained the by disruption of ATP generated by mitochondria with subsequent disruption of sodium potassium pump[33].

It was also recorded that pallor and expansion of neuroglial cytoplasm following TBI were due to intracellular edema[34].

Regarding neuroglial behavior following TBI, the present study revealed infiltration of frontal area with rod shaped elongated nuclei of microglia.

It was reported that after brain trauma, activation of innate immunity cells like macrophages and neutrophils occurs[33]. Also incompetent blood brain barrier allowed passage of inflammatory cells[35].

Furthermore, it was revealed that there are two types of microglia,M1 microglia, have weak phagocytic activity but could release ROS and TNF alpha following TBI. M2 microglia have enhanced activity but they were t transiently present and replaced by M1 microglia[36].

Prominent activation and the proliferation of astrocytes could be detected especially in Group III of the present study, presence of two or three nuclei in astrocyte cytoplasm together with significant increase in GFAP immune reaction confirmed astrocyte activation.

Moreover, it was established that following acute injury to the brain, astrocyte underwent changes in the activity of channel transporters. Decrease channel transporter activity of astrocyte could lead to ionic transport disruption and edema.Also, abnormal astrocytes behavior could be seen following TBI. Astrocyte release pro inflammatory cytokines this led to disruption of blood brain barrier and edema, moreover glial scar formed by astrocytes imped growth of axons[37].

CONCLUSION

Histological examination can be used to seek forensic evidence for TBI in absence of gross findings. Even with apparent mild head injuries, significant microscopic cerebral changes may be found. So, some patients will require in-hospital observation and cannot be safely discharged. In patients who can go home, discharge instructions need to be clear and documented. Also, in unclear deaths, brain tissue blocks may reveal evidence of TBI. The histopathological analysis allowed to keep close relation with impact injury.

RECOMMENDATIONS

Considering the heterogenicity of TBI, scientific hypothesis should be tested in multiple rodent models. Weight-drop model should be used at different weights and different heights with changed positions.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

الاهمية الطبية الشرعية للفحص النسيجى فى حالات اصابات الرأس الرضية الخفيفة

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مقدمة: تعتبر إدارة إصابات الدماغ الرضية الخفيفة هي تحديًا لأن المرضى الذين يعانون من صدمة خفيفة في الرأس قد يتطور الامربهم في وقت متأخرلحدوث مضاعفات. قد يصاب بعض المرضى بنزيف داخل الجمجمة عدة ايام بعد الإصابةوبالتالى قد يصبح اطباء الطوارىء اكثر عرضة لادعاءات سوء ممارسة المهنة. ايضا الفحص النسيجى قد يظهردليل طبى شرعى فى حالات الوفاة غير واضحة السبب.لذلك ، من الأهمية بمكان تسليط الضوء على الجوانب الطبية الشرعية والنسيجية لإصابات الراس الرضية.

هدف العمل: إبرازالجوانب الطبية الشرعية والنسيجية لإصابات الدماغ الرضية الخفيفة.

المواد والطرق: تم ضم ثلاثين أنثى بالغة من الجرذان البيضاء و تقسيمهم إلى ثلاث مجموعات: المجموعة الأولى (المجموعة الضابطة) المجموعة الثانية: ضمت ١٠ فئران تم التضحية بها ٦ بعد ساعات من تطبيق نموذج اصطدام الرأس المغلق المجموعة الثالثة: وضمت ١٠ فئران تم التضحية بها بعد ٧ أيام من تطبيق نموذج تأثير الرأس المغلق. في نهاية التجربة ، تم أخذ العينات و معالجتها للدراسات المناعية والنسيجية.

النتائج: كشف فحص أقسام الدماغ الجبهى للمجموعة الثالثة انخفاض واضح في الخلايا ، تتقلص معظم الخلايا الحبيبية مع صغر حجمها النوى المتحدبة ، والدبق الدبقي البارز وانخفاض واضح في oligodendrocytes ، زيادة تعبير GFAP و CD٦٨ مقارنةً بمجموعة التحكم.

الخلاصة: الفحص النسيجى بمكن ان يستخدم للحصول على دليل طبى شرعى فى حالة عدم وجود دلائل واضحة. حتى مع إصابات الرأس الخفيفةقد توجد تغيرات ميكروسكوبية دماغية هامة ، و لذلكسوف يحتاج بعض المرضى إلىالخضوع للملاحظةبالمستشفى ولا يمكن اخراجهم بأمان. كما ان في المرضى الذين يمكنهم الذهاب الى المنزل ، يجب أن تكون تعليمات الخروج واضحة وموثقة.ايضا فى حالة الوفاة الغير واضحة السبب يمكن للفحص النسيجى لمقاطع من انسجة المخ ان تظهر دليل على اصابات الدماغ الرضية.