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Epidemiologic, pathologic and prognostic factors in assessing traumatic brain injury in children

Ph. D. Thesis Abstract

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I. STATE OF KNOWLEDGE

Traumatic brain injury (TBI) represents a major medical emergency, not only by their own gravity, but also by the repercussion that may be instated in time. Assessing and rapid implementation of certain diagnostic and therapeutic methods, may enhance the patient's TBI prognostic, thus preventing the recurrence of this type of events on the general population.

This paper points out a new image over TBI in children, but also presents the current epidemiologic situation in Oltenia region, all by trying to enhance the available methods of diagnosis and prognosis.

By combining early diagnosis using biomarkers with pathologic results obtained after some necropsy, we try to offer new alternative for young children which presents with either mild or sever TBI and to act accordingly to obtain better results on a long term.

1. TBI epidemiology

The world health organization estimates that over 90% of traumatic deaths are encountered in countries with medium or low income, where most of the population actually live, this being a major health problem worldwide. Of all traumatic injuries, TBI represent a third or maybe even half of them and considered the main cause of disability for people under 40 years old. The social and economic impact is a major, mostly due to the high costs of treating an acute lesion, rehabilitation, as well as permanent damage to some patients.

Globally, mild TBI are estimated at 81%, moderate at 11% and sever at 8%.

2. TBI – characteristics.

2.1 Minor TBI

In the acute phase of minor TBI, a person may suffer o short loss of memory, transitory confusion or dezorientation, loss of memomry during the trauma (amnesia) or even neurologic or neuropsychic manifestations such as convulsions, headaches, dizziness, irritability, fatigue and low concentration.

After a traumatic lesion, there is a drop in the cerebral blood flow (few hours after the trauma) which may be sustained for several days proportionally to the severity of the trauma. This low blood flow, might be the expression of a high value of nitric oxide after the trauma, which causes vasodilation, rather than constriction inducted by pressure. These changes are also associated with a lower level vessel density in the nearby region of the TBI. In the next days, maybe weeks, a comeback occurs tu a normal cerebral blood flow, which is similar in time with a raise of vessel density in the specific region. This perfusion should be maintained and this generally occurs due to the vasodilatation cause by the stimuli, and this process is called cerebrovascular reactivity. Unfortunately, after brain damage, the blood vessels have a lower capacity of responding to these stimuli, thus a low prognostic is at risc and may also lead to an end stage diagnosis.

2.2 Moderate and severe TBI

After a severe injury, patients may present with some physical limitations (ex. Headaches, nausea/vomiting, pupil dilation, dysarthria, aphasia, sensory impairments), cognitive limitations (memory, attention), and also dysfunctional emotions such aggressivity. Even though a moderate TBI may cause brain damage, the lesions may be recovered with treatment or / and by learning to compensate any acquired physical problem, when a severe TBI occurs there is the possibility to not be able to do anything. Thus, a major factor for future patient's management consists in lesion's gravity but also includes the age and gender.

3. Biomarkers

To ensure new imaging clinical alternatives, a new approach was tried for the rapid assessment of TBI, while still using a non-invasive method.

A fluid biomarker is defined as a molecule that may be measured in a biological fluid or within a pathologic process which takes place in a cell or an organism. Thus, several biomarkers have been studied for TBI diagnosis, hoping to provide new methods to appreciate the severity, adaptability, recovery process and the response to therapy.

Biomarkers level in patient's blood is currently used for TBI may provide information about disease extension, neuronal and glial cell loss. They may also be used for severe TBI, especially in the acute posttraumatic phase to highlight the injury severity and also to predict clinical evolution.

II. PERSONAL CONTRIBUTIONS

Objectives

Our objective was to follow the TBI steps from an early non-invasive diagnosis, to the pathologic findings and even to assess the epidemiologic data that might confirm the necessity of a different approach of TBI.

Main objective

- Identification, assessment and interpretation of several biomarkers for a rapid and efficient TBI diagnosis in children;
- Pathologic findings assessment in children after in necropsy, caused by a TBI;
- Epidemiologic findings with a general focus on generate costs in a University hospital in Romania regarding TBI involvement.

1. Serologic diagnosis in TBI children

1.1 Objective

To assess children TBI immediately after emergency presentation by using noninvasive serologic methods.

1.2 Methods

This a prospective study and included 23 patients, with an aged lower than 18 years, which presented in the emergency department secondary to a TBI. We harvested from every patient 2 samples for biomarker analysis of S100B and GFAP, initially at 6 hours, and after 24 hours after admission. The one that were discharged and wanted to participate in the study, came the second day for sample harvesting. 24 hours later, the samples were centrifuged for 20 minutes at -80 C for future analysis. After all probes were collected, by using a sandwich immunoassay technique (ELISA) we analyzed both S100B and GFAP samples. Optic density was measured un microtitration plate of 450 nm and the values were set in μg/l.

Normal values for S100B were 0,06 μg/l and for GFAP 0,006 μg/l.

1.3 Results and discussion

This study offers a new alternative for fast TBI diagnosis, so useful for children, where the anamnesis might be rather difficult to obtain mostly because of the trauma, but also due to age. Moreover, the use of these type of biomarkers may be very useful, as they may be used as an immediate procedure that may propose the patient for a future MRI.

An important aspect of this study, was the biomarkers dynamic, by harvesting them at 6h and after 24 hours. Our results showed that S100B was higher after a day from the TBI, rather than 6 hours. Thus, we may confirm that the values may increase progressively immediately after the TBI, which may confirm that this could an ideal biomarker for this situation.

As for GFAP, it had an advantage over S100B because it considered to be more specific for the central nervous system. Just like S100B it is running through the

blood flow after a TBI. Increased values were seen just after the trauma after 6 hours, however, the level started to decrease after a day. This could pose GFAP only as an immediate-use biomarker.

2. Pathologic TBI findings in deceased children secondary to a TCC

2.1 Objective

Express the histopathologic and immunohistochemistry findings in children with severe TBI, that underwent a necropsy within de Legal Medicine Institute in Craiova, from 2011 to 2016.

2.2 Methods

For this pathologic study, we harvested brain samples from the TBI and nearby TBI regions, which were fixed in 10% formalin solution and prepared for paraffin embedddment according to the general pathologic procedure.

For the IHC study we used the following antibodies: CD68 (KP1 clone, 1/100 dilution, Dako) for macrophages reaction enhancement, as well as brain microglia; GFAP (clone ab7260, 1/150 dilution, Abcam) for microglia enhancement.

2.3 Results and discussions

Within the Legal Medicine Institute of Craiova, Romania, during 2011-2016, there were 3942 autopsies performed with legal purposes, of which 2414 suffered a violent death. From all the TBI that were encountered we selected only 29 cases (1,2%) which were seen in children with an age lower than 18 years.

From all the cases there, 20 (68,96%) were the result of traffic accidents. Gender distribution showed that most of the trauma was to male 19 (65,51%), and only 10 children were female (34,48%).

25 children had skull fracture, yet only in three cases we did saw an extradural collection, which may be explained by the powerful adherence of the dura-mater to the endo-skull, in children.

Complex meningocerebral lesions were seen in 27 cases, leptomeningeal hemorrhage was associated with brain contusion and intraventricular blood flood, more or less abundant, and in some situations even brain dilacerations. Only 2 cases showed meningeal lesions, without any external visible markings. In 14 cases we observed major dilacerations in the concussion areas.

The fourth day after trauma, pathologic findings were more severe. Perineuronal and perivascular edema was more visible; a part of the cortex had cytoplasmatic vacuolations or condensations, pycnosis and nuclear karyolysis, phenomena of neurornal apoptosis and autopysis, with the formation of “neural phantoms”.

The neuropil appeared disorganized, slightly granular, with a slight peripheral edema, showing the presence of lesions in the dendrites and axons. In the nervous parenchyma, the activation of larger macroglia was observed, with a large nucleus, hypochrome and long, thick extensions and with an intense reaction to the anti-GFAP antibody (active glucose). The presence of perivascular macrophages was also observed, with a rich, vacuolar cytoplasm and an intense reaction to the anti-CD68 antibody.

Seven days after the trauma, the histopathological lesions around the contusion foci were more obvious. The brain parenchyma had a spongy appearance caused by the death of neurons and glial cells, disorganization of neuronal extensions, the presence of apoptotic bodies, perineuronal and perivascular edema. Also, isolated areas of intraparenchymal microhemorrhages and hemorrhagic perivascular infiltrates were identified

through the Virchow-Robin spaces, in the regions far from the post-impact TBI area.

3. Costs assessment of patients diagnosed with TBI

3.1 Objective

Exposing the direct costs of patients diagnosed with CBT in a university center in order to provide an epidemiological profile of the various lesions and types of TBI encountered.

3.2 Methods

This was a retrospective study, which took place for a period of 1 year within the Craiova County Emergency Clinical Hospital, starting with 01.01.2016. During this interval, the data obtained by selecting the hospitalization files from the Emergency or by transfer from the other hospitals in Dolj County in the first 12 hours after injury, the discharge sheets and the statements of the patients diagnosed with CBT were analyzed.

3.3 Results and Discussions

We noticed that the highest incidence of TBI was registered among the elderly population (> 60 years) which amounted to 242 cases, representing 40.88% of the total. Adults aged 40-60 years who suffered from CBT totaled a number of 203 (34.29%) cases, and those in the age group 20-40 years were 99 (16.72%). 48 cases, representing 8.11% were less than 20 years old. Children and young people (category <20 years) suffered in about 80% of cases only concussions.

The patients' background proved to be an important parameter for the study, as 401 (67.74%) patients came from rural areas.

The direct cost calculated by us in the mentioned period, amounted to RON 894,110,523 RON, which represents 200,923 euros. The average cost calculated per patient was 6,296,552 RON, ie 1,414 euros (calculated at the NBR exchange rate for January 2017). Patients were hospitalized for an

average of 10 days for investigations and specialized treatment. The costs were significantly higher in patients who underwent surgery with general anesthesia and post-anesthetic supervision in intensive care (approximately 30% of the total number) and in those who had an indication for CT or MRI imaging (approx. 30% of patients).

4. Conclusions

- CBT continues to be a major health problem and occupies an important place in major emergencies
- The 3 studies presented in this paper offer a broad approach to CBT in children by including significant details in the multidisciplinary approach
- Biomarkers can be an alternative in the rapid diagnosis of CBT, so useful in minors, where often the history may be deficient either in terms of trauma symptoms. The use of such biomarkers can also be very useful, and can be used as an immediate investigation in order to guide patients to a subsequent CT scan.
- Pathological and IHC studies have shown an increase in neuronal damage in the perilesional areas of the brain, simultaneously with the increase in the survival period of patients.
- The analysis of the costs of medical care and the risk factors of some accidents that can be prevented through population education programs can influence the budgets allocated for carrying out such campaigns in order to reduce the number of victims.
- The 3 studies together give a major basis to this thesis in terms of addressing the various issues that are put together to provide an overview of the approach to a CT scan in children and beyond. Thus, the preconditions are created for future high-fidelity studies that offer major alternatives in the diagnosis and prognosis of CBT.

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