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A comprehensive review

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ABSTRACT

The "Talk and Die" Syndrome is described as the clinical deterioration following a mild to moderate traumatic brain injury. In the face of this event, individuals are able to articulate recognizable words and then deteriorate within 48 hours of the injury. This syndrome represents a major public health challenge due to its high morbidity and mortality rate; it develops from an intracranial haemorrhage causing an increase in intracranial pressure and leading the person to a neurological crisis with focal signs, coma and later death.

INTRODUCTION

The talk and die syndrome represents a major public health challenge because of its high mortality and disability rate, it can occur at any age, but the risk is significantly higher as the age increases [1]. People who

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"talk and die" after a head injury may suffer late complications that may be highly preventable if detected early [1,2]. Intracranial hematoma is the main reason why a patient whose injury does not appear serious at first, subsequently dies [1,2]. [3].

The high risk of death following this event is that the victim initially appears stable after receiving an apparently minor head trauma, while intracranial hemorrhage either inside or outside the brain is ongoing. Major warning signs include loss of consciousness on impact and severe headaches. If the hemorrhage progresses without being treated in time, the affected person may fall into a coma and even die [4].

The epidemiological study by Dylan Dean et al. found that patients who talk and died were older (median age, 81 years; interquartile range, 67-87 years), normotensive (median systolic blood pressure, 138 mm Hg; interquartile range, 116-160 mm Hg), commonly fall-injured (71.3%), and often (52.4%) died in non-trauma hospitals [5].

The prognosis is related to the amount of hemorrhage found at the time of diagnosis, so it is essential to take early action regarding the management and follow-up of these individuals, especially if they are high-risk groups such as elderly adults [6]. Based on the above, the objective of this review is to provide information that favors the detection and timely treatment of this syndrome, thus having an impact on the reduction of deaths due to this cause.

DEFINITION

"Talk and die" represents a small number of patients with mild head trauma who, due to intracranial causes, deteriorate and die [7]. Really et al in 1987 first introduced the term "talk and die," used to describe a group of patients with potentially recoverable head injuries in whom the primary injury was not severe enough to destroy higher cognitive function. Their ultimate demise was thought to represent a combination of secondary brain injury as well as other potentially preventable factors. For this reason, patients who talk and die have been the focus of multiple studies, most of which were relatively small with limited ability to identify associated factors [1].

The main cause leading to this syndrome is penetrating trauma [8]. In lower frequency are also found falls (28%), traffic accidents (20%), road traffic

accidents (19%), assaults (11%), unknown cause (9%), bicycle (3%) and suicide (1%) [9].

Injury severity is associated with risk factors such as older age, lower Glasgow scale score on admission, higher injury severity score (ISS), hypotension on arrival and comorbidities such as congestive heart failure, chronic kidney disease, liver cirrhosis and hematological disorders, subdural hemorrhage, contusion and vault fracture) [10]. Therefore, it is essential to perform a multifocal approach in these individuals in terms of the etiology of the injury, pre-hospital care, initial treatment including the neurocritical care unit and surgical treatment in order to avoid progressive deterioration and multi-organ failure leading to death during the postoperative period [11,12].

MECHANISM OF INJURY

The magnitude of the brain injury and the time of duration depends on the severity of the resulting concussion, which is defined as a transient interruption of brain functions caused by a mechanical force. Memory, consciousness, motor control or brainstem functions may be temporarily disrupted or impaired during this phenomenon. The mechanical deformation of brain tissue in a concussion injury is sufficient to interfere with both the functions of polarized neuronal membranes and synapses and render numerous brain neurons temporarily dysfunctional. A concussion is usually not sufficient to cause structural damage, but may result in abnormal brain metabolism for weeks after the initial injury [13].

The basic physiological sequelae that constitute the state of vulnerability induced by traumatic brain injury appear to be due to cellular ionic and metabolic alterations [14]. These pathological changes in the aging brain may trigger secondary brain injury contributing to more severe and irreversible damage in middle-aged and elderly patients, which explains why age plays an important role in the prognosis of those affected [15].

In the growing attempt to understand the pathophysiology of fatal non-projectile head injuries, three grades of diffuse axonal injury have been identified. In grade 1, histologically, axonal injury is seen in the white matter of the cerebral hemispheres, corpus callosum, brainstem and, less frequently, the cerebellum; in grade 2, there is also a focal lesion in the corpus callosum; and in grade 3,

there is also a focal lesion in the dorsolateral quadrant(s) of the rostral brainstem. It is worth mentioning that focal lesions can only be identified microscopically in most cases [16].

Intracranial hematomas are the most frequent cause of deterioration in head trauma patients, so rapid diagnosis and decompression are the most important factors in saving these patients. [17]. The above is due to the increasing volume of accumulated blood which causes a progressive increase in intracranial pressure that can even force the brain down through the foramen magnum causing a brain herniation. This compresses the brain stem with such force that the centers controlling consciousness, respiration, heart rate and blood pressure cease to function, resulting in coma and death [4].

The area in which the intracranial hemorrhage occurs will be a determining factor in its pathophysiology. Intra-axial hemorrhages occur directly in the substance of the brain due to the rupture of blood vessels caused by impact [4]. As for traumatic intraventricular hemorrhages, regardless of the presence or absence of neurological deficits should have close follow-up by emergency physicians because of the possibility of acute obstructive hydrocephalus requiring prompt surgical evacuation before unexpected but avoidable deterioration occurs [12].

On the other hand, among extra-axial hemorrhages, there are epidural, subdural and subarachnoid types of hemorrhage; the latter, for example, its mechanism is that blood leaks into the subarachnoid space, filled with cerebrospinal fluid and reaches the ventricles, causing severe headache, nausea and vomiting. Meanwhile, in subdural hematoma, the bridging veins that drain the surface of the brain into the venous sinuses are torn generating a low-pressure venous hemorrhage. Among the adverse consequences of hemorrhage is hydrocephalus, which, if uncontrolled, can lead to coma and death. Another complication is an intense vasospasm, which can be so marked that it restricts blood flow to that region of the brain, leading to ischemic stroke [4]. Vasospasm is proposed as the cause of secondary ischemic hypoxia associated with a high incidence of acute subdural hematomas and brain swelling. Suggestions for further testing this hypothesis and implications for preventive management are discussed [13].

It is recognized that an apparently minor head injury can cause diffuse cerebral edema with serious consequences. Among the two possible mechanisms described by McCrory are, first, cerebral hyperemia and increased blood volume as a result of disordered cerebrovascular autoregulation, commonly known as "malignant cerebral edema". The second is due to true cerebral edema [18].

The distinction between cerebral swelling and cerebral edema was made by Klazko, who observed that cerebral edema could be cytotoxic or vasogenic and that both could occur after craniocerebral trauma. Therefore, the mechanism of death would be a transtentorial herniation of the brain stem as a consequence of elevated intracranial pressure, which would affect the cardiorespiratory centers of the brain stem [18]. Findings from diffusion MRI and apparent diffusion coefficient (ADC) mapping suggest that cellular swelling is predominant in the peripheral area for a period of 24 to 72 hours while cells in the central area of the contusion undergo shrinkage, disintegration and homogenization [19].

CLINICAL MANIFESTATIONS

The fact that the patient is talking implies a less severe primary brain injury, but does not necessarily place the patient in the mild head injury category (GCS 13-15) as there are cases with an eye-opening score of 2 or 3, a verbal score of 3 and a motor score of 5 or 6 (GCS of 10-12), which gives a GCS between 9 - 12, placing the patient in the moderate injury group, which of course is associated with a worse prognosis [20]. In addition, in children admitted with head trauma caused primarily by motor vehicle accidents or falls, they had initial Glasgow Coma Scale scores equal to or greater than 9 and demonstrated irritability and restlessness just prior to deterioration [21].

The main primary clinical manifestation is a severe headache followed by problems with speech, vision and even coma. It should be noted that at the beginning people usually do not present any symptoms, but in the course of time may manifest severe headaches, weakness and confusion resulting from lesions of intracranial masses and increased intracranial pressure (ICP) that were progressively established [22]. The mean age, the degree of midline shift observed on computed tomography (CT) and the presence of subdural hematoma are the main factors influencing the

evolution (recovery or death) of patients who talk [23].

The difference between those with and without a lucid period is related to the degree of primary lesion by diffuse white matter impingement and the presence of ventriculomegaly with large sulci rarely found in lucid patients [24]. In the study by Kim et al. it was observed that the median age of patients who died due to hematomas was 82.5 years, compared to 54.0 years for patients who died from refractory ICP elevations ($p = 0.003$). Hyponatremia occurred during the first 7 days in 38.9% of patients who died due to hematomas and in only 14.3% of patients in the ICP group ($p = 0.236$). No seizures were observed in any of the patients in either group. Skull fractures were present in four of the 18 (22.2%) patients who died of hematomas, in contrast to four of the seven (57.1%) patients who died of refractory ICP [25].

The presence of a fracture line proved to be significant, as it was accompanied by approximately 38% intracranial abnormalities versus 6% in non-fractured cases. In addition, high-volume hematomas are associated with more brain injury after a worse clinical course of the patient prior to evacuation, but evacuation does not improve executive functioning in these individuals. Early detection of any asymptomatic intracranial pathology allowed immediate transfer of patients to the neurosurgical center, where surgical treatment was performed, when indicated, without mortality or morbidity [26,27].

In 2 cases of severe traumatic brain injury (TBI) with acute subdural hematoma in which cerebral blood flow (CBF) and cerebral blood volume (CBV) measurements were obtained before evacuation of the subdural hematoma and immediately after removal. The younger patient had the highest preoperative CBF. Thus, it is possible that the cerebral circulation is more easily compromised in older patients; however, it is also possible that the brains of younger patients are more tolerant to similar low levels of CBV [22]. Likewise, patients whose CBF returns to normal 2-3 weeks after severe traumatic brain injury after being abnormally low in the acute phase of the injury can be expected to achieve a good neurological outcome [28].

DIAGNOSIS

To diagnose an intracranial hemorrhage we can detect as warning signs: loss of consciousness at the

moment of impact, nausea, vomiting, severe headache, focal neurological deficits, confusion, lethargy, any change in neurological status, seizures, use of antiplatelet drugs, anticoagulants and individuals with coagulopathies that result in poor clotting ability [4]. Despite the above, diagnosis is often slowed down by the lack of knowledge of these signs on the part of medical personnel and by the existence of underestimation predictors such as the characteristics of the lesions (severe cranial and pelvic lesions), the characteristics of the patients (middle-aged and conscious) and the time of day (nocturnal) [29].

Generally, the level and duration of consciousness is related to the prognosis of those affected, for this reason, it is common to assume that the individual is stable after he/she speaks after having suffered a brain injury, however, this is the trigger for these patients to have a high mortality rate despite the fact that they may be potentially survivable [30]. Although talking indicates a non-lethal impact brain injury, deterioration is a marker of poor prognosis. Thus, outcome depends on early recognition of deterioration and rapid removal of mass lesions. The challenge for emergency physicians is to distinguish patients at risk for deterioration from the many patients evaluated after traumatic brain injury [31].

The following are independent predictors of outcome (in order of importance): Glasgow Coma Scale score after deterioration into coma, highest intracranial pressure during the patient's evolution, degree of midline shift, type of intracranial injury, and patient age. In contrast, the mechanism of injury, the Glasgow Coma Scale verbal score during the lucid interval, and the time to deterioration or to surgical intervention did not influence the final outcome [32]. The diagnostic value of GCS ≤ 8 for severe TBI in patients with multiple injuries has low sensitivity (56.1%) but higher specificity (82.2%). Because of the low sensitivity of GCS, we suggest the use of the anatomic scoring system with AIS head ≥ 3 to define severe TBI in patients with multiple lesions [33].

Computed tomography (CT) constitutes a gold standard in the evaluation of patients after TBI. None of the available guidelines address the role of repeat CT as a follow-up procedure after head injury in pediatric patients. Experience suggests that a repeat CT scan should be a routine component of

postoperative management, especially in pediatric patients after neurosurgery or in a barbiturate coma [34]. Age, type of injury, loss of consciousness, posttraumatic seizures, otorhinolaryngologic bleeding, vomiting, scalp injury, and polytrauma were not found to be predictors of a positive CT scan. GCS score on admission, focal neurologic deficits, and fractures detected by skull radiography were found to be statistically significant predictors of positive CT findings [35].

Studies have found considerable variation among institutions and individual physicians in ordering CT scans for patients with minor head injuries. Although emergency physicians were selective in ordering CT, the yield of radiography was very low across hospitals. These findings suggest great potential for a more standardized and efficient use of CT of the head, possibly through the use of a clinical decision rule [36]. Increased pulsatility index after mild to moderate TBI is cause for concern about the possibility of further neurological deterioration so CT and Doppler measurements could be combined to detect on admission patients at risk of secondary neurological deterioration in order to improve their initial disposition [37].

Forensic autopsy is important in patients with "Talk and Die" to clarify the causal relationship with the head injury in relation to any other forensic disputes. The deaths of these patients raise medicolegal questions, about the precise causes of death and the possible correlation of death with the head injury, especially when such deaths occur after a prolonged period of time following the event [30]. In an investigation of 13 autopsies with examination of the brain, it was found that 5 patients died with severe brain injuries not complicated by iatrogenic factors and 4 patients died with associated severe injuries. Iatrogenic factors significantly complicated the death of 40% of the patients, a considerable alarming figure [12].

Using a decision tree analysis, studies have found hypotension and low cerebral perfusion pressure (CPP) to be the best predictors of death [38]. Other parameters are also found to be predictors of mortality such as (in order of importance): Glasgow coma scale score after deterioration into coma, the highest intracranial pressure score during the patient's evolution, the degree of midline shift, the type of intracranial injury, and the patient's age. In contrast, the mechanism of injury, the Glasgow

Coma Scale verbal score during the time interval between lucidity and clinical deterioration or until the patient underwent surgery, did not prove to influence the final outcome [32].

Evidence suggests that 92% of patients with ICP plasma levels greater than 15 $\mu\text{g/ml}$ or D-dimer levels greater than 5 $\mu\text{g/ml}$ died regardless of their level of consciousness on admission, whereas all patients recovered well when their ICP levels were less than 2 $\mu\text{g/ml}$ or D-dimer levels were less than 1 $\mu\text{g/ml}$. Thus, it was revealed that plasma ICP and D-dimer levels on admission are reliable prognostic markers of head injury. Using these markers, patients with unfavorable outcomes (progressive brain injury), such as the talk and deteriorate type, could be easily identified on admission [39]. The D-dimer value was significantly higher in the talk and die group at any time and was considered the best coagulation/fibrinolytic parameter to monitor from the early stage of injury predicting outcome [40,41].

TREATMENT

The most important factors in saving these patients are prompt diagnosis and immediate surgical decompression before irreversible brain damage occurs [42]. In 1983, a uniform protocol for the initial treatment of patients with head injuries was introduced, based on knowledge of the epidemiology of head injuries, the importance and frequency of preventable factors in the region, and also adjusted to the specific geographic conditions. This protocol is guided by the level of consciousness prior to arrival at the hospital, the initial assessment of the level of consciousness and neurological status on arrival at the hospital and, finally, subsequent changes in the level of consciousness and neurological status [43].

Most people admitted to the emergency department for traumatic brain injury are discharged after one or two days [3]. The study by Eric Cevala Peterson *et al.* found that all patients were managed with observation in the intensive care unit and hyperosmolar therapy to maintain serum osmolarity at 300. Overall, 7 of 13 (54%) suffered clinical deterioration with a mean of 4.5 days after the injury. Of those injured with immediate surgical decompression, all had good results and returned to work. There was no difference in contusion or edema volumes between patients with and without clinical deterioration. Based on this series and experience in

other TBI patients, prophylactic hypertonic saline (HTS) infusions are no longer used in the setting of head trauma. Management of these patients with intensive care unit, admission and early intracranial pressure monitoring is recommended. If they deteriorate despite these measures, rapid bifrontal decompression may lead to good functional outcomes [44]. Potential adverse events that have been associated with HTS include renal failure, central pontine myelinolysis rebound ICP elevation [45].

For individual therapeutic management there is currently the use of transcranial Doppler (measuring mean cerebral artery systolic, diastolic and mean cerebral artery (MCA) flow velocities and a derived value, pulsatility index, jugular venous oxygen measurement, intracranial pressure waveform analysis and near infrared spectroscopy. In addition, it has been suggested that the complexity of the lesion may necessitate the administration of combinations of neuroprotective agents acting at various steps in secondary self-destructive injury cascades. Each cascade may have its own critical window for treatment, so sequential or concurrent combinations of therapeutic agents may be necessary. For example, administration of a single intravenous bolus of Mg salts for up to 12 h after injury has demonstrated improvement in neurological recovery after injury in rats [46].

Studies by the Adelaide Head Injury Group suggest that the beneficial effects of Mg may be related to the positive mRNA regulation of beta-amyloid precursor protein (APP), which is a normal component of neurons and there is evidence of its role in the repair and regeneration of these cells. On the other hand, the APOE genotype, specifically the apolipoprotein 4 allele, has been associated with increased odds of having a poor outcome at 6 months, increased odds of having plaques of amyloid protein deposits, and have a 10-fold increased risk of Alzheimer's disease [46].

Controversy exists regarding prehospital intubations in patients with severe and moderate head injuries. It is unclear whether field intubations actually improve neurologic outcome or survival. Failed attempts at field intubations may increase out-of-hospital time and increase the risk of aspiration or hypoxia. Hypoxia and hypotension have been found to worsen outcome in head trauma [47].

With respect to surgical procedures, all strategies of craniotomy, decompressive craniectomy, and initial trepanation appear to be effective, but the superiority of each procedure has not yet been established. Since Glasgow Coma Scale (GCS) scores, age, papillary reaction, and computed tomography findings are strongly correlated with outcome, each factor has been investigated as an indicator of resiliency [48]. Individuals with CT-proven anisocoria, trephination of the skull prior to transfer resulted in uniformly good results without complications. Time to relief of intracranial pressure was significantly shorter with trephination and neurological outcomes were not different [49]. As for craniotomy for evacuation of hematomas and/or intracranial contusions, it was the most common treatment recorded (performed in 30% of all cases), followed by treatment of barbiturate coma (8%) and decompressive craniectomy (6%) [50].

Repeated use of CT should be a routine component of postoperative management, especially in pediatric patients after neurosurgery or in a barbiturate coma, because it prevents such revelations as a case of a previously undetected acute epidural hematoma in the right frontoparietal region with mass effect that displaced contiguous brain tissue to the contralateral side and, following this finding, the hematoma can be evacuated and bleeding from the ruptured middle meningeal artery can be stopped without any problems [34].

Preventing secondary insults will remain the primary goal of treatment, but the next major advances in the treatment of head injury are likely to be through cell biology, with therapy. Targeting specific intracellular targets and perhaps promoting genes that lead to repair and regeneration [46].

CONCLUSIONS

In order to reduce the morbimortality rate of the talk and die syndrome, it is essential to educate the population about the risks of suffering apparently mild or moderate cranioencephalic traumas that are not monitored by a health professional. In turn, in the medical field, specifically in the area of emergency and traumatology, health personnel should be educated about this syndrome in order to increase clinical suspicion and with it, the strict and constant monitoring of the vital functions of these patients, in order to be able to detect in time possible warning signs that can prevent serious sequelae and

even death of those affected. It should be noted that this syndrome can affect any age group; however, greater emphasis should be placed on high-risk populations such as older adults and individuals who use anticoagulants or antiplatelet drugs.

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