SYNDROME OF TREPHINED-UNDERESTIMATED AND POORLY UNDERSTOOD COMPLICATION AFTER DECOMPRESSIVE CRANIECTOMY

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English | http://dx.doi.org/10.18071/isz.69.0227 | www.elitmed.hu

Decompressive craniectomy (DC) is still a matter of debate, with a numerous complications as expansion of haemorrhagic contusions, external cerebral herniation, subdural hygromas, post-traumatic hydrocephalus (HC). The often overlooked "syndrome of the trephined" (ST) as a delayed complication of DC also known as sinking skin flap sy initially described in 1939.ST is characterised by the neurological changes associated with alteration of the pressure/volume relationship between intracranial pressure (ICP), volume of cerebrospinal fluid (CSF), blood, and brain tissue in patients with large bone defects. This review aims at elucidating the mechanisms responsible for the development of ST, and providing useful tips and red-flag signs for healthcare professionals involved with care of post DC patients. Symptoms identified on time could help to develop appropriate treatment strategies for this suddenly deteriorating, but possible reversible condition.
Although the treatment strategy is straightforward, calling for a prompt cranioplasty, the correction of HC through CSF diversion devices might require a lengthy optimisation period. Continuous changes in the setting of the shunting systems or spinal tap might lead to dangerous swinging of the midline structures causing further neurological deterioration. Thus, finding the right balance in terms of clinical management often represents a significant challenge.

Keywords: *traumatic brain injury, decompressive craniectomy, syndrome of the trephined, CSF hydrodynamics, posttraumatic hydrocephalus*

A TREPHINED-SZINDRÓMA – EGY ALULBECSÜLT ÉS KEVÉSSÉ ÉRTETT KOMPLIKÁCIÓ DEKOMPRESSZÍV CRANIECTOMIA UTÁN

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Ideggyogy Sz 2016;69(7–8):227–232.

A mai napig intenzív vita övezi a dekompresszív craniectomiát (DC). Ez az eljárás olyan jelentős szövődményeket rejt magában, mint a korábbi állományi vérzések növekedése, az agyállomány herniálódása, subduralis hygroma keletkezése, vagy hydrocephalus internus kialakulása. A DC késői lehetséges szövődményeinek egyike a trephined-szindróma (ST), más néven „sinking bone flap syndrome", amit már 1939-ben is leírtak. Az ST az intracranialis nyomás térfogatváltozással összefüggő neurológiai tünetek kialakulását foglalja magában, mivel kiterjedt koponyacsont-defektussal rendelkező betegekben megváltozik az intracranialis nyomás (ICP), valamint a liquor, a vér, és az agyszövet térfogatainak aránya.
Ezen áttekintés célja a kórkép és a kialakulásához vezető lehetséges patofiziológiai mechanizmusok ismertetése, illetve az alarmírozó tünetek és egyéb olyan információk összegzése, melyek hasznosak lehetnek a dekompresszív craniectomián átesett betegekkel foglalkozó társdiszciplínák számára. Ennél a hirtelen állapotromlást mutató, de többnyire reverzibilis kórképnél az időben felismert tünettan optimalizálhatja a terápiát.
Általános kezelési stratégia a mielőbbi cranioplastica, ugyanakkor a gyakran társult agyvízkeringési zavar hosszas korrekciót igényelhet. A söntrendszer nyomásának gyakori változtatása, illetve a lumbálpunkció veszélyes szövődményeket, állapotrosszabbodást eredményezhet a középvonali struktúrák vongálódásán keresztül.
A fentiek miatt az ideális kezelés megtalálása sokszor kifejezett klinikai kihívást jelent.

Kulcsszavak: *traumás agykárosodás, dekompresszív craniectomia, trephined-szindróma, liqourkeringési zavar, poszttraumás hydrocephalus*

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Érkezett: 2015. január 21. Elfogadva: 2015. május 28.

Traumatic brain injury (TBI) is characterized by both a primary and a secondary insult; the first is immediately consequent to the trauma, the second as a complication of this primary insult is reflecting both intracranial and systemic impairment and being highly correlated with some early predictive factors of mortality[1]. In particular, the increase in intracranial pressure (ICP), which according to the pressure-volume relationship described by Monroe-Kelly doctrine is typically caused by cerebral oedema representing the most important single source of secondary insult. Although few data regarding the monitoring of ICP are available from randomized controlled trials, such monitoring is recommended by international clinical practice guidelines, and first-tier therapies are used to control ICP[2]. Decompressive craniectomy (DC) has been advocated in patients with severe diffuse TBI and clinical conditions with increased ICP refractory to first-tier therapies.

The DECRA (Decompressive Craniectomy in Patients with Severe Traumatic Brain Injury) study compared patients who underwent early DC for diffuse TBI with patients who received standard medical therapy: the unfavourable outcome was 70% in the craniectomy group versus 51% in the standard care group. Based on these results, the authors concluded that, as compared with standard care, DC decreased the mean ICP and the duration of both ventilatory support and the Intensive Care Unit stay, but was associated with a significantly worse outcome at six months, as measured by the score on the Extended Glasgow Outcome Scale[3]. Nonetheless, the DECRA trial has received a great deal of criticism because of problems with randomisation and of its inferable recommendations in the clinical practice. Some authorities have therefore claimed that the results should not influence the decision making process, and to date the role of DC when ICP continues to increase 20 mmHg remains to be established. The international scientific community's glimmers of hopes to address this issue are now put on the RESCUEicp (Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intra-Cranial Pressure) study, which recently concluded its randomization and enrolment phase.

The indications for DC are still uncertain and numerous complications of this life-saving procedure are well known. These complications can be classified as early ones (occurring in the first postoperative week), including contusion or hematoma expansion, epilepsy, herniation of the cortex through the bone defect, CSF leakage through the scalp incision, infection, subdural effusion, and delayed ones (occurring after the first postoperative month), such as post-traumatic hydrocephalus (HC) and the "syndrome of the trephined" (ST). With specific regard for the latter complications, whereas the relationship between DC and post-traumatic HC remains controversial because it may affect any TBI patients regardless of the surgical procedure (with an incidence ranging from 0 to 88.2%)[4]; the ST is typical of individuals with iatrogenic skull defects.

The term was actually coined in 1939 by *Grant* and *Norcross* to describe the symptoms of headache, vertigo, tinnitus, fatigue, insomnia, memory disturbance, seizures, mood swings, and behavioural disturbance that were observed in some individuals with large cranial defects[5]. Over the decades, a number of other terms such as "Syndrome of the Sinking Skin Flap – SSSF", or the more recent "Neurological Susceptibility to a Skull Defect – NSSD" have been introduced to describe this clinical picture all revolving around a common pathophysiological theme: the neurologic changes associated with alteration of the pressure/volume relationship between ICP, volume of cerebrospinal fluid (CSF), blood, and brain tissue in patients with large bone defects.

This review aims at elucidating the mechanisms responsible for the development of ST, and at providing healthcare professionals with useful tips to timely identify the most common red-flags and the most appropriate treatment strategies for this suddenly deteriorating, but hopefully treatable condition.

Materials and methods

A systematic review of scientific literature was conducted through the US National Library of Medicine, National Institute of Health – PubMed Central, the Cochrane Library, and the citation database Scopus to identify all articles revolving around the ST, from those discussing its pathophysiology to those describing its specific management strategies. The primary keyword used to launch the research query was therefore "syndrome of the trephined"; afterwards all the landmarks papers on the related arguments, such as "cranioplasty AND CSF hydrodynamics" 5, "craniectomy AND hydrocephalus" 251, "hydrocephalus AND CBF" 116 were selected to complete the study of the relevant literature. All those not related to TBI were excluded from the analysis. Preference was given to the following article types: reviews, case series, and technical notes.

Results

The time frame for the articles are taken into account during this review was from 1939 to 2014. Out of a total of 32 articles retrieved on ST more than 1/3 classify as case reports; noteworthy during the last five years only two reviews were published in the literature on this subject (data not shown). Particularly, those papers on CSF hydrodynamics changes occurring in ST patients after DC and after cranioplasty were analysed in depth: while few articles relate to experimental findings (analysis of CSF variables, CBF parameters), most of them are only limited to clinical observations or description of surgical outcomes.

The main findings highlighted from this review of the literature are discussed in the following sections.

Pathophysiology's insights

The pressure-volume relationship, known as the Monro-Kellie doctrine, states that the cranial compartment is incompressible, and the volume inside the cranium is a fixed volume, thus blood, CSF, and brain tissue are routinely in a state of volume equilibrium, such that any increase in volume of one of the cranial constituents must be compensated by a decrease in volume of another. The pathophysiology TBI is the classic example for the infringement of this equilibrium with alteration of pressure/volume relationship; no surprises if the ST occur in a situation when volume inside the cranium is not fixed anymore due to a large skull defect.

It is intuitive that while the intracranial pressure is normally negative in the upright position in a closed skull. In case of cranial defect the ICP will tend to equalise with the atmospheric pressure, which in turn will cause an increase in the ICP in the sitting position[6]. Furthermore it is known that the size of the cranial bone defect is proportionally related to the abnormality in the brain parenchyma volume and elastance variables[7]. All these factors act as concurrent causes for the derangement of CSF hydrodynamics which in turn plays a pivotal role on the development of regionally impaired cerebral blood flow (CBF)[8–10], as confirmed with CT perfusion in both the symptomatic and contralateral side hemispheres after cranioplasty[11, 12].

The importance of those changes in CSF hydrodynamics following DC for TBI has been experimentally confirmed by some research groups who focused their attention on those CSF variables that appeared to be compromised before and normalized after cranioplasty, such as: resting pressure, sagittal sinus pressure, buffer volume, elastance at resting pressure and pulse variations at resting pressure[6]. *Fodstad* et al experimentally demonstrated that since the resting pressure depends primarily on a) the CSF formation rate, b) the conductance of the outflow across the sagittal sinus and c) the sagittal sinus pressure, then a change in resting pressure must be caused by changes in some of those components[6]. They clinically confirmed that the low resting pressure seen in DC patients correlates with a low pressure in the sagittal sinus, thus the rise in its pressure after cranioplasty also explains the increase in resting pressure, and related clinical improvements. The abnormal hydrodynamics of CSF in ST also explains the correlation between this syndrome and HC: as arachnoid granulation function is dependent on the pressure difference between the subarachnoid space and draining venous supply; so the disruption of pulsatile ICP dynamics secondary to the skull vault defect results in decreased CSF outflow and absorption; thus, leading to dilation of the ventricular system. The attempts to restore the equilibrium between CSF production and drainage through external lumbar, ventricular or ventriculo-peritoneal CSF diversion devices might require a lengthy optimization period. Continuous changes in the setting of the shunting systems are not only associated with dangerous swinging of the midline structures but also bear the risks of further ischaemic, haemorrhagic and infective complications **(Figure 1)**.

Highlight to the discipline

Herein, the practical aspects related to the management of DC patients at risk of developing ST will be thoroughly discussed, with a particular focus on some operative nuances and on a management algorithm for this complex clinical syndrome.

Classification of ST patient

ST is generally described following unilateral DC either performed on the dominant or nondominant hemispheres, nonetheless also bifrontal DC patients might be at risk of this late complication[13]. Only when the symptoms included in the definition of ST are aggravated during the Valsalva manoeuvre or following changes in body position it is possible to classify patients as "True ST"; *Fodstad* et al suggest to rather defining patients as "Partial ST" when their symptoms are not affected by forceful at-

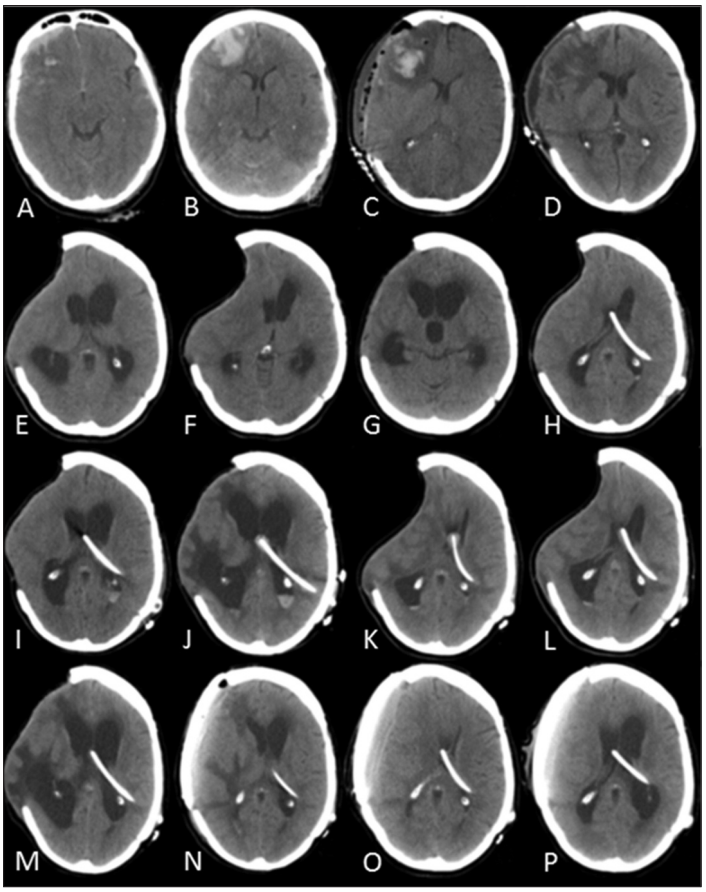

Figure 1. *Exemplificative case of TBI before (A-B) and after DC (C-E). ST was clinically evident since the beginning of the fourth postoperative week and lasted until restoration of CSF hydrodynamics (F-L) Note the lengthy process to treat HC optimising the setting of CSF shunt before (H-M) and after cranioplasty (N-P)*

tempts to raise the pressure in the intradural compartment[6].

Given the pathophysiology mechanisms outlined above, it is clear why EEG exploration in ST patients excludes epileptic activity, or again why older patients and/or those with more severe TBI, who also show less adaptability to the alteration of the pressure/volume relationship following DC, might have a higher occurrence rate of this complication[9, 10, 14].

Risk factors for ST

Interestingly most of the risk factors for ST and HC after DC overlap: *Stiver* et al identified ipsilateral contusions, abnormal cerebrospinal fluid circulation, and longer intervals to cranioplasty repair to be strongly associated with the development of ST following DC[15] while, according to Ding et al, the predictors of HC in patients operated for DC include distance from the midline, hygroma, age, injury severity, subarachnoid or intraventricular haemorrhage, delayed time to craniotomy, repeated operation, and duroplasty[16].

Surgical management

In light of the pathophysiology of the ST, it is useful to focus on some surgical tips to be considered at time of DC; those reported below are useful nuances which demonstrated to have potential in reducing the incidence of this late complication.

– The possible efficacy of a vascular protection during DC, has been highlighted to reduce the risk of secondary venous infarction due to the blocking pressure for venous outflow through bridging veins. This method may improve regional CBF after DC, and further impairment of CSF circulation even at a high level of ICP[17].

– The distance from the midline has been independently associated in logistic regression analysis with the development of altered CSF dynamics after DC. Patients with craniectomy whose superior limit is less than 25 mm from the midline have a markedly increased risk of developing HC (Odd Ratio = 17)[18]. This seems to be related to the altered venous outflow and the damage to the arachnoid villi along the sagittal sinus (known as „Pacchioni granulations") when the skull is removed too close to the midline.

– The use of advanced haemostatics and dural substitutes might also cause a microanatomical alteration of CSF flow over the cortex. During cranioplasty reoperation it has been observed the use of advanced dural substitutes for duroplasty at time of DC (such as polytetrafluoroethylene, etc) succeeds in creating a controlled dissection plane, and facilitating access to the epidural space by preventing peridural fibrosis which might play a role in CSF dynamics[19, 20].

In terms of surgical management of ST, all papers reviewed agree on the indication for a prompt cranioplasty and treatment of HC through shunt devices. Some particular points need to be retained and thoroughly considered at the time of designing the most appropriate surgical strategy to ensure the highest chances for a successful outcome.

– External CSF diversions (either ventricular or lumbar) are often not enough to treat the altered CSF dynamics, though they can be considered as temporary solutions while waiting for the optimal

timing for cranioplasty and insertion of definitive shunts. To this extent, programmable valves can be considered as a choice, because they give to the surgeon the chance to adjust the shunt setting to the CSF opening pressure, and to optimise it later according to the clinical or radiological findings[7]. A consensus is still lacking regarding the best timing (before or after cranioplasty) for insertion of permanent shunt.

– Cranioplasty is the single most important treatment option for ST. It has been recommended to perform in three to six months after the craniectomy, although the best timing is actually subject to high individual variability of each patient[21]. A moderate increase in venous outflow as well as a twofold increase in craniocaudal CSF systolic flow velocity has been clinically demonstrated after closure of skull defects in ST. The changes in the CSF oscillatory flow at the level of the craniovertebral junction could reflect changes in the compliance of the craniospinal system produced by closure of the cranial defect[22]. Furthermore, the increase in several parameters reflecting brain metabolism, such as cerebral metabolic rate of glucose or phosphocreatinine levels, detectable in ST patients after cranioplasty can confirm that restoration of CSF hydrodynamics is also pivotal in acting as a cascade on improvement of CBF[11, 23].

Conclusion

Following decompressive craniectomy patient should be monitored for the neurological, pshyhiatric and motor syndrome of trephined as a deleyed complication. The described deficit are usually reversible and could resolve after cranioplasty. The better understanding of pathophysiology the identification of early sign of clinical detorientation are fundamental to optimise the management of this often underestimated, yet poorly understood condition.

The timing of cranioplasty, the correction of HC and the initiation of an active physiotherapy represent a significant clinical challenge and required multimodality monitoring.

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