



Trigemino-cardiac reflex during chronic subdural haematoma removal: report of chemical initiation of dural sensitization

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TS and BS wrote the article; TS collected the data; BS interpreted and analysed the data; SK and CK performed the operation and the patient's treatment and provided substantial information regarding the patient's case; NS

The paper presents a new risk factor for the trigemino-cardiac reflex and goes deep into the reflex's physiology.

Introduction

The trigemino-cardiac reflex is a well-known clinical phenomenon described during different craniofacial or skull base surgery as well as neuroradiological interventions and defined as the sudden onset of parasympathetic dysrhythmia, sympathetic hypotension, apnea, or gastric hyper-motility during (intraoperative) stimulation of any of the sensory branches of the trigeminal nerve. According to strict and generally accepted diagnostic criteria, the occurrence of the trigemino-cardiac reflex is considered if there is observed a 20% or more decrease in heart rate and MABP as response to an adequate stimulus.¹

In the early 20th century, this phenomenon has gained increased clinical attention in the form of the oculocardiac reflex which represents the cardiac response associated with stimulation of the ophthalmic division of the trigeminal nerve during ocular surgeries.² In 1999, Schaller *et al.* have, for the first time, demonstrated that a similar reflex occurs after the stimulation of the intracranial (central) portion of the trigeminal nerve during skull base surgery¹ and has subsumed all these trigemino-depressor responses under the term 'TCR'. Later, Schaller's group has also described the occurrence of the trigemino-cardiac reflex during intraoperative stimulation

of the peripheral portion of the trigeminal nerve³ and has also shed light on the influence of trigemino-cardiac reflex on the surgical outcome. Since the late 1990s, there has been increasing interest and also discussion about the trigemino-cardiac reflex itself, its provoking factors, but also its treatment during intracranial or extracranial (neuro) surgical procedures. Several provoking factors for the intraoperative occurrence of trigemino-cardiac reflex have been described earlier^{1,3,4} and most attention is given to the mechanical stimulation of trigeminal afferents during surgical interventions. Currently, we are far away to define any specific risk profile for the intraoperative occurrence of the trigemino-cardiac reflex⁵ as there is a lack of detailed knowledge of the physiology of this reflex.

The current case report presents the occurrence of trigemino-cardiac reflex during a standard neurosurgical intervention for removal of giant chronic subdural hematoma and give therefore substantial evidence that temporary exposure of perivascular fibers to chemical agents alters their sensitivity to mechanical stimuli of the dura mater.

Case description

Preoperative history

A 67-year-old man was admitted to the Department of Neurosurgery, Tokuda Hospital, Sofia, Bulgaria with complaints of progressive memory loss and changes in the behavior. His relatives reported that over the last 10 years he gradually

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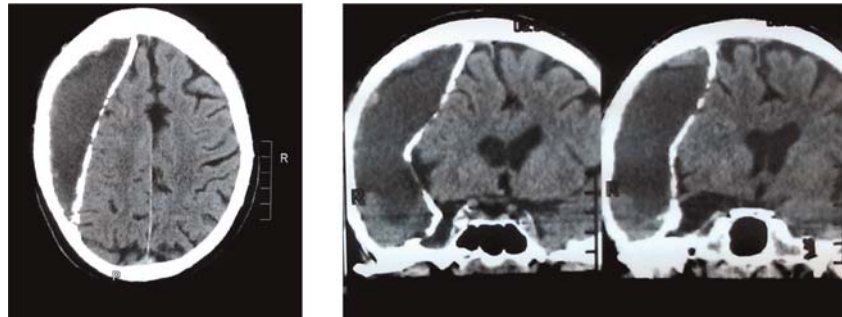
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Figure 1

Preoperative CT images indicating a large left fronto-temporo-parietal subdural haematoma with calcified capsule and liquefied content with extensive brain-shift



demonstrated a cognitive decline but his clinical symptoms had worsened in the last four days, when he '... drank 4 litres of water and felt really sick...'. At clinical examination, he presented with slight sensor aphasia and demonstrated 16 out of 30 points in the Mini-Mental Test, which indicated moderate dementia. A cranial CT scan was performed and showed large subdural haematoma with calcified walls that was located on the right side with a midline deviation of approximately 10 mm (Figure 1). There was no history for recent craniocervical trauma. However, the patient and his relatives reported a 'car accident 40 years ago'. Immediately after the accident, he was comatose for 10 days. After this period, he regained consciousness and presented without any neurological deficit. However, the patient had complained of constant temporal headache for years. No motor or sensory deficit developed over the years, except his further progressive cognitive impairment. There were no preoperative medications that the patient was taking.

After reviewing his CT scan and discussing the case, the patient was scheduled for an elective craniotomy for removal of the subdural haematoma content and extirpation of the haematoma capsule.

Anaesthetic technique

The patient fasted for 8 hours prior to surgery. Routine monitoring during surgery included electrocardiography (ECG), endtidal (ET) concentration of CO₂ and sevoflurane, pulse oximetry. An arterial line was placed in the left radial artery. All haemodynamic parameters were monitored continuously

and recorded throughout the neurosurgical procedure. Anaesthesia was induced with midazolam (1 mg – total dosage) and propofol (2 mg/kg) followed by suxamethonium chloride (1.1 mg/kg), atracurium (0.6 mg/kg) and fentanyl (100 µg – total dosage). After the trachea was intubated, the lungs were mechanically ventilated (S/5 Aespire Config; Datex-Ohmeda Ins, Madison, USA) with a mixture of air and O₂. Anaesthesia was maintained with Sevoflurane (1%). Additional 50 mg propofol and 1 mg midazolam were applied during the intervention when necessary. The anaesthesia was considered a 'deep' anaesthesia.

Surgical technique and trigemino-cardiac reflex occurrence

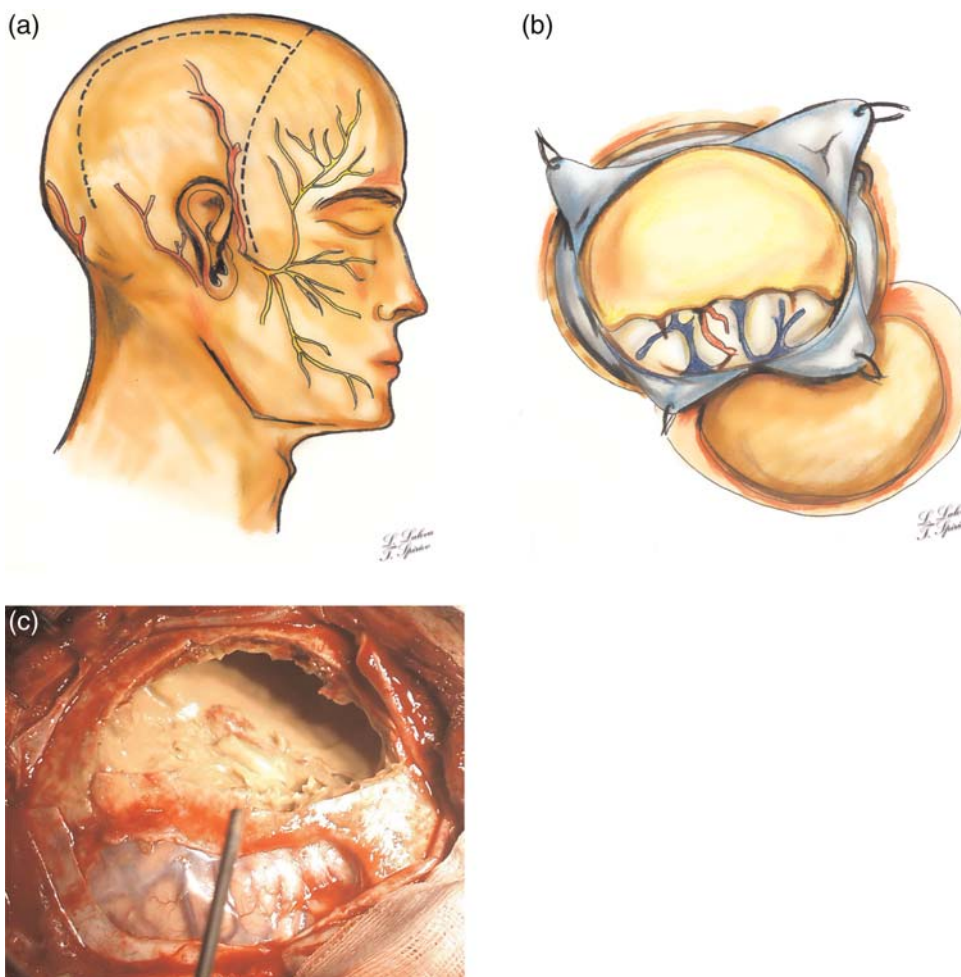
The patient was operated on with right fronto-parieto-temporal craniotomy. After opening the dura mater the calcified haematoma walls were clearly visible (Figure 2). Entering into the haematoma wall, a yellowish viscous fluid was found, probably liquefied blood. A material for microbiology testing was sent for further investigation, which proved to be negative afterwards.

The whole haematoma including the calcified walls were removed. Careful and meticulous microsurgical dissection was used, the capsule was removed in piecemeal fashion, with least possible traction. During the whole procedure the patient was with a tendency of hypertonia with maximal blood pressure of 185/95 mmHg.

However during the removal of the tumor capsule, due to the firm adhesions, although gentle tissue manipulation was applied, on

Figure 2

a. Schema of skin incisions and related superficial neuro-vascular anatomy. A large right fronto-temporo-parital craniotomy was made; **b.** Schema of the hematoma wall, after dural incision. The haematoma had clear margins and was separated from the surrounding brain (right temporal lobe is visualized); **c.** Intraoperative image after craniotomy and dural incision. The parietal hematoma wall was excised and the yellowish liquefied content is seen. The haematoma had clear margins and was separated from the surrounding brain



several occasions there were observed drops of the blood pressure and heart rate (HR).

When the whole capsule was removed, the haematoma cavity was irrigated with 3% diluted hydrogen peroxide and gauzes with this solution was administered in the cavity aiming to achieve haemostasis. At that time, the arterial blood pressure dropped from 95/60 mmHg to 60/40 mmHg and the HR dropped from 90 beats per minute (bpm) to 60 bpm. With this occurrence of

the trigemino-cardiac reflex, the gauzes with hydrogen peroxide were removed and the cavity was irrigated with normal saline. After this maneuver, the arterial blood pressure and HR returned to normal and no more concomitant drops in both parameters were recorded. Until the end of the procedure the patient remained haemodynamically stable and there was no change in the end tidal carbon dioxide volume, therefore the possibility of air embolism was excluded

The patient's postoperative period was uneventful, and he presented with no additional neurological or cardiologic deficits. The postoperative CT scan indicated some pneumocephalus, which lead to no additional symptoms. At the postoperative follow-up at 1 month after the operation, he presented with no further deterioration.

Discussion

Trigemino-cardiac reflex represents a phenomenon that is recognized in a considerable number of patients during neurosurgical interventions – several retrospective studies have shown an incidence of trigemino-cardiac reflex ranging from 8–18% using all the same inclusion criteria as defined earlier by our group.¹ However, until now, no neurosurgical routine operation was accompanied by the intraoperative occurrence of the trigemino-cardiac reflex. We present here the first report of the occurrence of a trigemino-cardiac reflex during a routine operation without any additional risk factors, possibly due to the mechanical stimulation of previously by H_2O_2 chemically activated and sensitized trigeminal primary afferent neurons of the dura mater. The microsurgical removal of the hematoma calcified capsule was associated with unavoidable traction, because of the dense adhesions between the hematoma wall and fronto-parietal dura, which is innervated by the first division of the trigeminal nerve. This routine surgical maneuver has led only to a trigemino-cardiac reflex because of the previous chemically induced expansion of the receptive field as laboratory and clinical studies point out that the nature of the stimulus is the most important risk factor in inducing the trigemino-cardiac reflex – abrupt and sustained traction is more reflexogenic than smooth and gentle traction. We are the first that describe and can prove such a chemical-induced sensitization in connection with the trigemino-cardiac reflex as the present case represents a routine neurosurgical operation without any other risk factor for trigemino-cardiac reflex.

Trigemino-cardiac reflex phenomenon was observed in this case during irrigation of the already removed haematoma wall with H_2O_2 – a manoeuvre that is often performed to clean the surgical field and achieve haemostasis. The cavity resulting from haematoma removal was large, the liberated oxygen from the H_2O_2 acted on a much

broader dural surface. We consider that liberated oxygen from H_2O_2 exerted a substantial concomitant chemical stimulation on a large dural surface innervated by V2 and V3. Stimulation of these trigeminal dural afferents might be the cause of central trigemino-cardiac reflex initiation. Other, already known risk factors like superficial anaesthesia or drugs could be excluded in this patient. However, a careful literature search revealed that complications related to hydrogen peroxide utilization in neurosurgery involve mainly venous embolism^{6–8} and postoperative pneumocephalus, some of them even fatal. According to the best of our knowledge, there are only three previous case reports in the neurosurgical literature describing the occurrence of dysrhythmias resulting by the irrigation of surgical field with H_2O_2 ,^{9–11} all published by Prabhakar *et al.* In two of these three cases^{9,11} the H_2O_2 irrigation was associated with bradycardia only, but not significant hypotension during trans-sphenoidal surgery and posterior cranial fossa intervention. These effects were thought to be related to the liberated oxygen from the H_2O_2 decomposition which was linked with possible stimulation of the cardiovascular centres in the brainstem.⁹ Another possibility was thought to be associated to exothermic reaction of H_2O_2 dissociation and the liberated energy to affect the vital centres.⁹ Similar possibilities were given in the other cases^{9–11} with mechanical and chemical stimulation of the anterior hypothalamus related with bradycardiac phenomena during transsphenoidal operation.¹¹ A true TRC, however, was only recorded in this third case¹⁰ where the phenomenon was associated with the action of H_2O_2 over the maxillary and ophthalmic divisions of the trigeminal nerve in the lateral wall of cavernous sinus during H_2O_2 irrigation of surgical wound during trans-sphenoidal pituitary adenoma surgery.

It is known that 1 mL of H_2O_2 produces 10 mL of oxygen and the volume expansion is most often related to the venous embolism reported in literature.⁹ However, this volume expansion is related with significant exothermic reaction and the release of reactive oxygen species.^{9–11} It has been shown experimentally that small quantities of H_2O_2 could initiate peripheral cardiovascular reflexes,^{12,13} an effect mediated by the reactive oxygen species. However, it has previously been shown in experimental and clinical situations that trigemino-cardiac reflex could be initiated in

mechanical, electrical and/or chemical stimulation of any of the branches of the trigeminal nerve.¹⁻³ However except experimental studies most of the published clinical trigemino-cardiac reflex cases are related to mechanical and electrical stimulations and there are only few related to chemical stimulation.¹¹

In the present case report the used concentration of H₂O₂ was much higher (3%) compared to the laboratory experimental concentrations used in the above-mentioned experimental studies (micromolar concentrations). The associated levels of liberated reactive oxygen species could be therefore expected to be high, respectively. Thus, we believe that possible mechanism of trigemino-cardiac reflex initiation is in this case by chemical stimulation (thermal and based on the release of large quantities of reactive oxygen species) on the trigeminal afferents located in the supratentorial dura. There has been proposed a chemical mode of activation of meningeal perivascular sensory fibres.^{14,15} Although the exact mechanism is unknown, it is generally accepted that temporary exposure of perivascular fibres to chemical agents, like H₂O₂ in the present case or inflammation in a previously described case¹⁴ alter their sensitivity to mechanical stimuli and leads to the sensation of the dura mater.¹⁵ Our current case supports this idea and shows for the first such a sensation that leads to the trigemino-cardiac reflex.

Conclusion

We present a case of clearly expressed form of trigemino-cardiac reflex, due to the chemical stimulation of dural trigeminal afferents by the action of hydrogen peroxide, a solution commonly used to achieve surgical hemostasis. The presented case is one of the few published clinical studies for trigemino-cardiac reflex initiation by chemical stimulation. Because of the routine operative procedure, the chemically-induced dural sensitization that lead to the trigemino-cardiac reflex could be described and proved for the first time. This report adds therefore an important feature to the previously identified risk factors for trigemino-cardiac

reflex occurrence. We consider that the usage of H₂O₂ should be regarded as a potential new risk factor for chemical sensitization of the dura mater and therefore indirectly also for occurrence of the trigemino-cardiac reflex.

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