

## CAS CLINIQUE / CASE REPORT

### REMISSION of CENTRAL FEVER with MORPHINE POST TRAUMATIC BRAIN INJURY

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Mendieta Zerón H, Arriaga García Rendón JC. Remission of central fever with morphine post traumatic brain injury. *J Med Liban* 2014 ; 62 (1) : 57-61.

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**ABSTRACT :** After a brain injury, raised temperature may be due to a regulated readjustment in the hypothalamic 'set-point' in response to inflammation. The purpose of this report is to mention possible implications related to temperature and homeostasis of morphine treatment in a patient with brain injury.

During the month previous to her hospitalization in our city she was treated for fever with paracetamol and metamizol without results. After 31 days with similar results, we changed to morphine IV considering the possibility of treating pain and fever. This option was successful and afterwards we changed to fentanyl patches, keeping fever absent. After 100 days of hospitalization, the patient was discharged to her home.

Keywords : brain damage, central fever, morphine

#### INTRODUCTION

Several areas of the hypothalamus, including the paraventricular hypothalamus, the ventromedial hypothalamus, the posterior hypothalamus and the dorsomedial hypothalamus have been implicated in thermogenesis. It has been also stated that maintenance of central temperature is determined by the balance between heat production and heat loss. Interesting studies on central drug effects and its different responses related to temperature and homeostasis have focused on opioids, which are known to inhibit the release of different neurotransmitters in the central nervous system and alter normal cerebral metabolism.

Raised temperature may be due to a regulated readjustment in the hypothalamic 'set-point' in response to inflammation and infection, or it may occur as a consequence of damage to the hypothalamus and/or its pathways. The mitochondrial respiratory chain-linked oxidative phosphorylation and calcium transport are compromised by traumatic brain injury (TBI) and support the idea that oxidative

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**RÉSUMÉ :** Après une lésion cérébrale, la température élevée peut être due à un réajustement régulé par l'hypothalamus en réponse à l'inflammation. Le but de ce rapport est de mentionner les implications possibles liées à la température et à l'homéostasie du traitement morphinique chez une patiente ayant une lésion cérébrale.

Au cours du mois précédant son hospitalisation dans notre ville, la fièvre avait été traitée avec paracétamol et métamisol, sans résultats. Après 31 jours de résultats similaires, nous avons opté pour la morphine IV envisageant la possibilité de traiter conjointement la douleur et la fièvre. Cette option a été un succès, et par la suite nous avons utilisé les patchs de fentanyl pour éliminer les accès de fièvre. La patiente a pu regagner son domicile après cent jours d'hospitalisation.

Mots-clés : fièvre centrale, lésion cérébrale, morphine

stress and perturbation of cellular calcium homeostasis play significant roles in TBI [1].

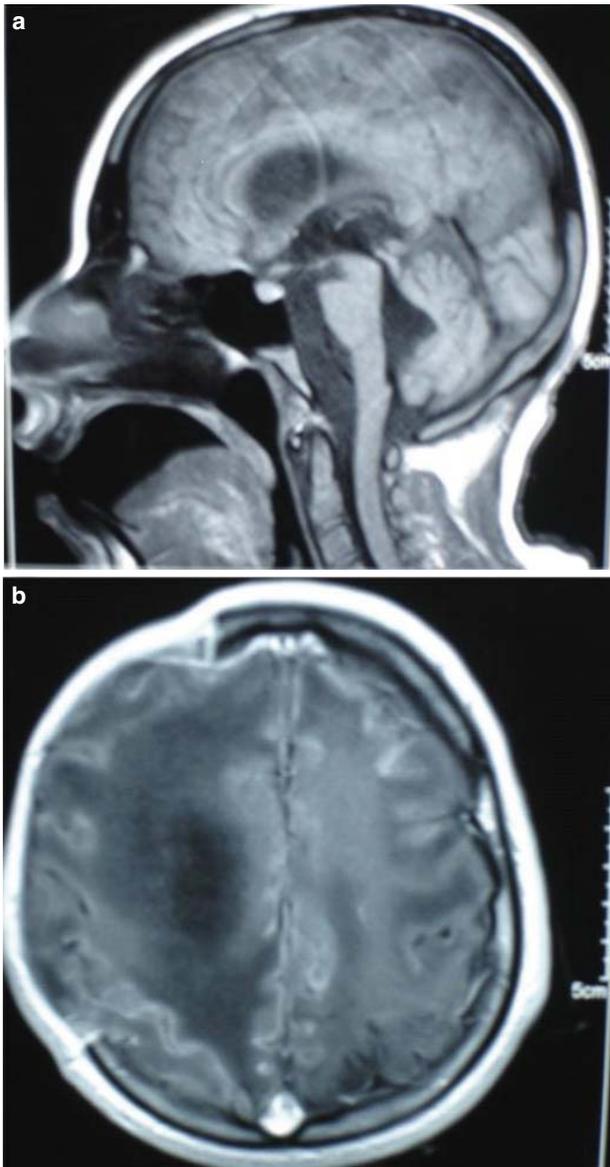
Fever in patients with severe head injury is a commonly-encountered diagnostic and management problem. Neurogenic fever is a noninfectious source of fever in the patient with head injury and, if untreated, can cause damage to the brain in many ways. Until recently, neurogenic fever was thought to be a relatively rare consequence of TBI, but other studies have reported that 4 to 37% of TBI survivors experience this sequela. Neurogenic fever is essentially a diagnosis of exclusion [2]. It is only when sepsis is excluded that neurogenic fever can be considered. Though brain temperature is indeed higher than the core temperature in the acute phase of severe TBI, that significance is uncertain with regard to outcome prediction, since there has been a paucity of work on the use of direct methods of brain temperature monitoring [3].

Hemodynamic data has shown that morphine increases intracranial pressure and decreases mean arterial blood pressure and cerebral perfusion pressure in patients with severe brain injury. Also, several changes observed in rats after morphine microinjection into the anterior hypothalamus showed a clear etiology of hypothermia as a central response to morphine. The purpose of this report is to mention possible implications related to temperature and homeostasis of morphine treatment in a patient with brain injury.

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**FIGURE 1.** Magnetic resonance imaging showing sagittal (a) and axial (b) slices of the brain.

#### CASE REPORT

A 23-year-old woman, who was victim of a car accident, was admitted to our institution on June 15, 2009. Due to the TBI (Figure 1), she had undergone decompressive craniectomy and subdural catheter placement for monitoring intracranial pressure. During one month she was treated in an Intensive Care Unit with esomeprazole, ferrous sulfate, metoclopramide, mannitol, sedation, relaxation, enteral diet based on alitraq, carbamazepine, tetrazepam, valproic acid, mechanical ventilatory support and finally gastrostomy.

On the physical examination she arrived to our hospital with persistent fever, weighing 40 kg, with a 7 (4-1-2) Glasgow Coma Score (GCS), spontaneous eyelid open-

ing, arreflectic right mydriasis, left eye with pupil diameter of 3 mm and papillary atrophy, meningeal signs were absent. She did not follow simple commands and after a painful stimulus she assumed decerebration position. There were no dysautonomias in addition to fever.

#### Clinical data

Electroencephalogram (Figure 2) on two occasions showed severe brain damage with slow waves. To exclude fever by infection, several studies were performed (axial computerized tomography of all the body, blood smear, chest X-ray, cerebrospinal fluid analysis, febrile reactions [Weil-Felix and Widal tests], hematic biometry, hemoculture, influenza A and B test, interleukin 1- $\beta$ , urine culture, etc.), all being normal. A tracheal aspiration culture was positive for *Pseudomonas aeruginosa* and was treated against this pathogen until being negative.

#### Treatment

Hemotransfusions were realized as required whenever euthermia occurred. Electrolyte disturbances were corrected and urinary flows closely watched. During the month previous to her hospitalization in our city she was treated for fever with paracetamol and metamizol without results.

After 31 days with similar clinical evolution, we changed to morphine IV, 0.05 mg/kg/h, considering the possibility of treating pain and fever. This option was successful with fever remission the following day (Figure 3). Afterwards, there was only one fever spike on day 33 with morphine and from day 34 we observed an absolute remission that allowed us to switch to fentanyl patches, keeping fever absent. After 100 days of hospitalization, she was discharged to her home with a 7 (4-1-2) GCS.

#### DISCUSSION

Even moderate temperature elevation soon after acute cerebral damage may markedly worsen initial brain injury. This effect may justify aggressive antipyretic treatment. An attempt to correct fever appears warranted in all patients with acute cerebral damage in order to obtain a better functional recovery and to limit maximally any further insult to the brain [4].

In the brain, energy metabolism is mainly oxidative. The oxidative metabolism and heat production are, therefore, strongly related. After major cerebral injuries, such as subarachnoid haemorrhage or traumatic brain injury, cerebral temperature can often exceed systemic temperature. Mitochondrial dysfunction is probably the cornerstone of these post-injury perturbations of brain temperature. Understanding this phenomenon remains, however, not complete [5]. It is hoped that earlier diagnosis and appropriate intervention for central fever will lead to improved outcomes [6].

It has long been recognized that opioids such as morphine can produce a range of effects on body temperature in a number of species including man [7-13], but only few

studies have analyzed the impact of this drug in central fever. Evidence has shown that hypothermia is certainly due to a central action of morphine since it occurs when morphine is applied by microinjection into the anterior hypothalamus. Within the last few years, a number of studies have been conducted to investigate whether morphine plays a role in temperature regulation, fever, and hypothermia [11,14]. Collected data has suggested that, according to the opioid/morphine receptor subtype that is stimulated, changes in temperature can be observed [12, 15]. Mu agonists have been an important component of pain treatment for thousands of years. The usual pharmacokinetic parameters (half-life, clearance, volume of distribution) of opioids have been known for some time. However, the metabolism has, until recently, been poorly understood, and there has been recent interest in the role of metabolites in modifying the pharmacodynamic response in patients, in both analgesia and adverse effects. A number of opioids are available for clinical use, including morphine, hydromorphone, levorphanol, oxycodone, and fentanyl [16].

In experimental studies, morphine pharmacokinetics is different in the brain compared with other tissues due to the properties of the blood-brain barrier and the action of efflux pumps. It has been reported in humans that the basal state in which morphine is administered to patients

may either obey an active efflux of morphine metabolism in a healthy brain tissue or on the other hand, follow an increase in permeability in damaged parenchyma. A recent explanation for this statement is based on the P-glycoprotein membrane protein which transports substrates across cerebral endothelial cells back to the blood stream and its permeability capacity to upstream morphine absorption in focal mass lesions and brain swelling.

Some studies have evaluated a down-regulation effect of Mu opioid receptors secondary to desensitization of Mu-Opioid-Receptor (MOR)-mediated G-protein activity due to levels of tolerance and relation to central nervous system mediated effects of morphine exposure. In an experimental study, MOR blockade resulted in inhibition of adenylyl cyclase activity and calcium channels and activation of potassium channels and several intracellular kinases. The final observed effect was the production of hypothermia. Other authors have suggested that nitric oxide (NO) has an antipyretic function, and that several neuronal and peripheral NO isoforms may interact with morphine doses, either to block or allow temperature changes.

Neuroinflammation hypotheses also have proposed that tendency of lowering central and peripheral body temperature after morphine administration can be linked to an immune system response suppressing natural killer cell activity, antibody responses, spleen and peripheral

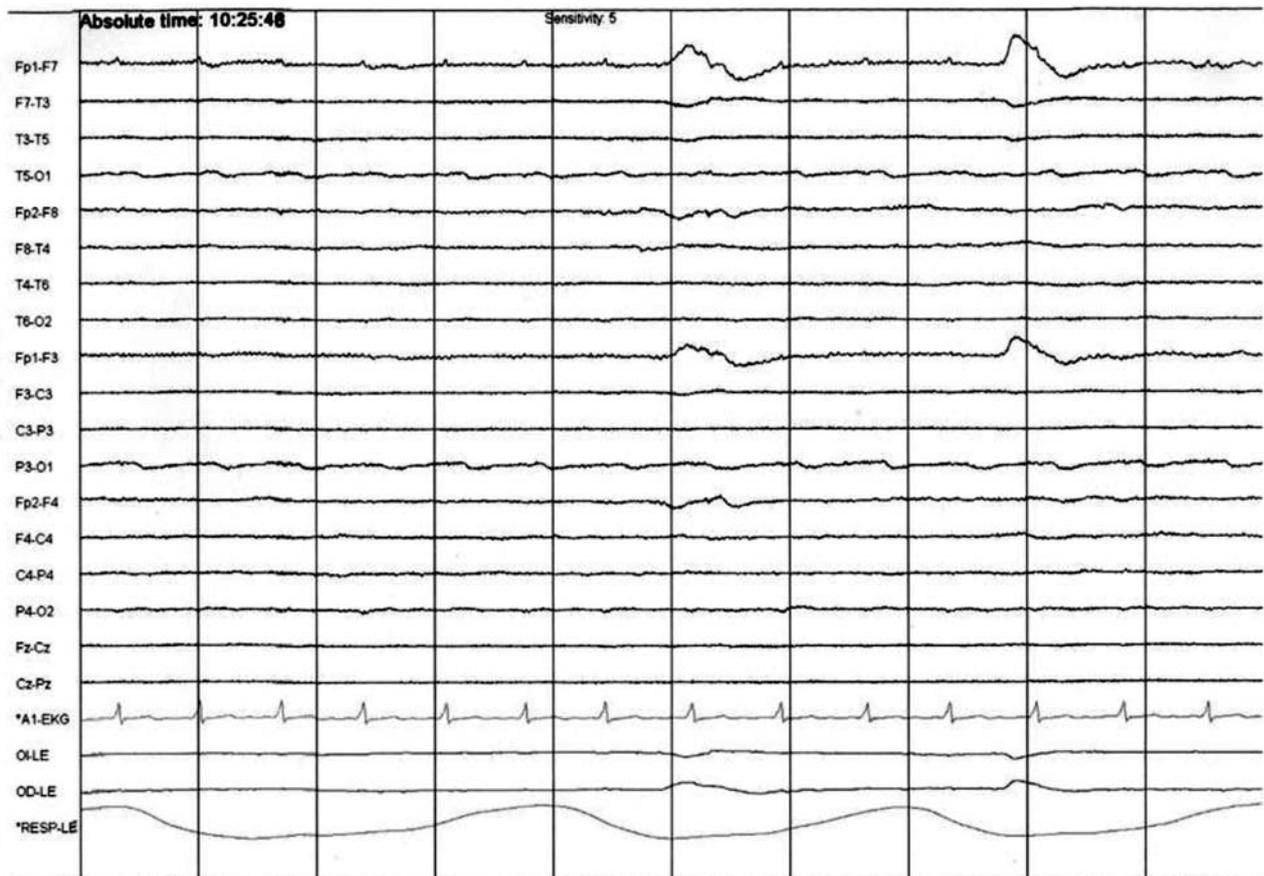


FIGURE 2. Electroencephalogram showing severe cortical brain damage.

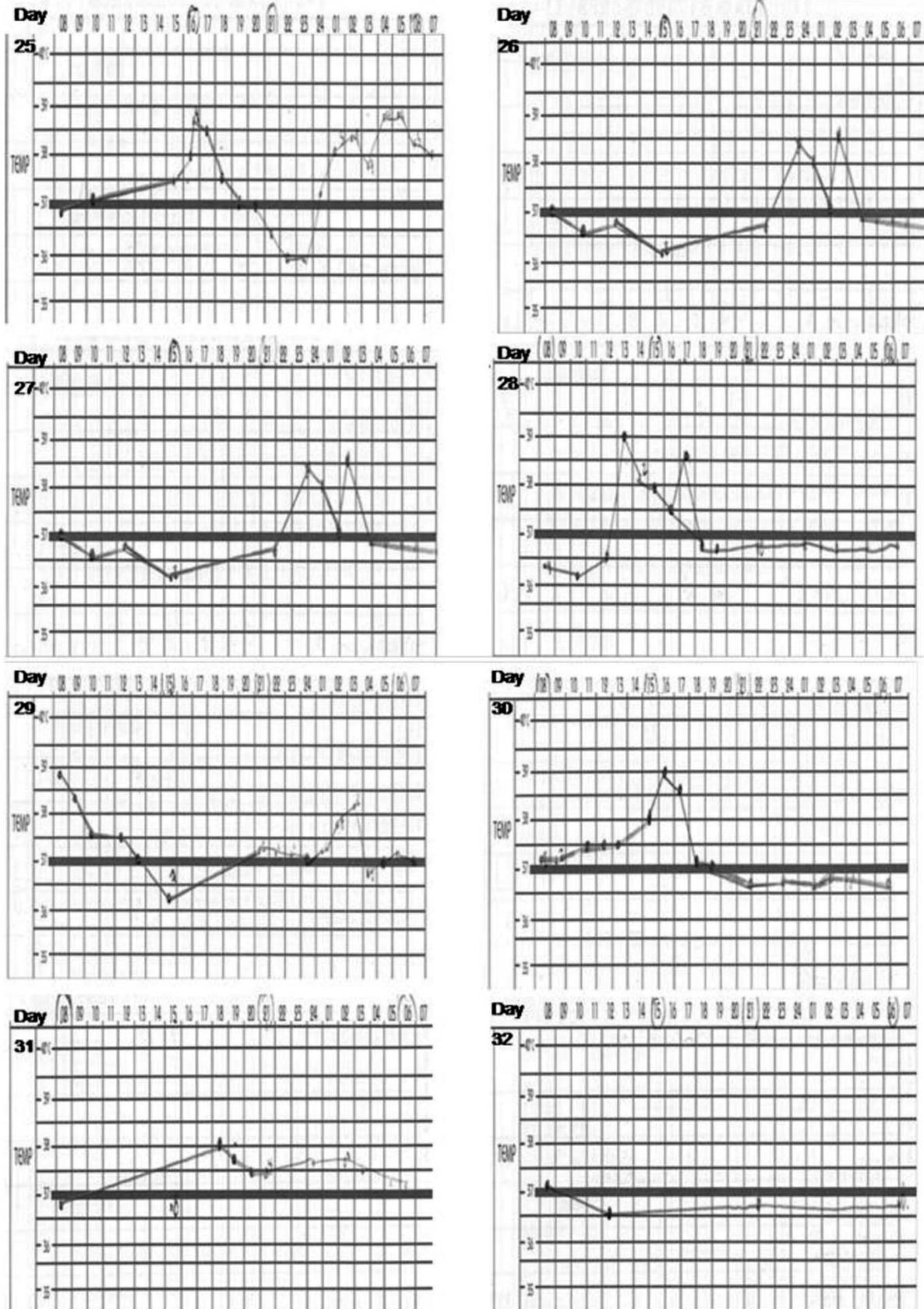


FIGURE 3. Thermic curves from day 25 to 32 of hospitalization. Day 32 was the beginning of I.V. morphine infusion. (Thermic curves of more days are available if requested to the corresponding author.)

blood cell responses to mitogens and macrophage function leading to a decrease of the inflammatory stimuli mainly within the preoptic anterior hypothalamus.

Available data indicate that ambient temperature, dose, specific opioid used and central or peripheral activity of receptors may greatly affect thermoregulatory responses to opioids. Tolerance is one of the undesired potential secondary effects of morphine administration and it has been suggested in experimental protocols that chronic exposure leads to a down-regulation of mu-opioid receptor mRNA in peripheral sensory ganglia supporting this fact.

Our patient had a chronic deficit in either sensing temperature elevations or activating heat dissipation mechanisms under thermal stress as was reported in another case [17].

Evidence obtained in clinical and experimental studies has demonstrated the importance and metabolic differences observed on a healthy brain exposed to morphine compared to a damaged tissue; this may lead to paradoxical changes related to morphine pharmacokinetics and potential intra- and extracranial effects. In rats, subcutaneous injection of morphine produces either a fall or a rise in body temperature according to dosage; future clinical evidence based on ethical support may lead to concrete explanation of this statement in humans.

Strong evidence related to temperature changes after morphine administration in humans with brain injury is limited, but the distinct roles of Mu and K receptor types may be important in understanding the mechanisms of opioid-induced effects on body temperature, and these receptors may also play specific roles in thermoregulation. As mentioned above, suggested links between the opioid and immune systems may lead to a better understanding of temperature regulation pathogenesis and future therapeutic approaches.

In summary, The pathophysiology and management of neurogenic fever is not well understood and needs more research and understanding for better management and a favorable outcome. We propose morphine as an antipyretic option in a context that justifies its other systemic and multiple effects as an advantage for patients with brain injury or trauma with no response to hyperthermia standardized treatment, and after excluding potential fever causes. Possible adverse effects of this treatment include behavioral and neuro-adaptive effects of morphine, like neural plasticity, dependence, withdrawal and antinociception, probably caused as a consequence of glutamatergic influence.

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CONFLICT OF INTEREST: None disclosed.

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## ANNONCES / ANNOUNCEMENTS

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