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Thermoregulation disorders of central origin — how to diagnose and treat

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Abstract

Fever is a common symptom in the Intensive Care Unit. At least half of febrile episodes are caused by infection. Excluding infectious etiology and other non-infectious causes of fever, especially in patients with central nervous system (CNS) disorders, attention should be paid to disturbances of thermoregulatory centre. In particular, subarachnoid haemorrhage, cerebral trauma, along with ischaemic or haemorrhagic stroke are strongly associated with the development of central fever. Proper, speedy diagnosis of the cause of fever makes it possible to implement preventive measures against the harmful effects of hyperthermia on the CNS and to avoid the consequences of inappropriate treatment. The aim of this review is to present the current treatment options for the management of central fever and to analyze recent recommendations for the treatment of hyperthermia, including the use of hypothermia. The recommendations of American and European associations are inconsistent, mainly due to the lack of randomized clinical trials confirming the effectiveness of such treatment. The diagnosis of central fever is still made by the exclusion of other causes. The authors of the review intended to present the characteristic features of central fever, differentiating this state from infectious fever and also analyze the presence of central fever in particular neurological diseases. It seems particularly important to establish diagnostic criteria for central fever or to find diagnostic markers. It is also necessary to conduct further randomized clinical trials evaluating the indications for treatment of hyperthermia.

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Key words: central fever, diagnosis, treatment

Fever is a common symptom in patients treated in intensive care units (ICUs); according to some sources, occuring even in 70% of ICU patients. In at least half of the cases, fever is caused by infection. Having excluded the infectious aetiology and other non-infectious causes of fever, especially in patients with central nervous system (CNS) disorders, thermoregulatory disturbances of central origin should be considered. Proper diagnosis of the causes of fever enables healthcare professionals to implement the management protecting one against the harmful effects of hyperthermia on the CNS and to avoid the consequences of inappropriate treatment [1].

THE SYSTEM OF THERMOREGULATION

During the course of evolution, human beings became warm-blooded (endothermic) organisms capable of maintaining a relatively constant core temperature despite environmental temperature fluctuations. Thermal homeostasis is maintained thanks to an efficient system of thermoregulation. The thermoregulatory mechanisms exist to adjust the amount of heat generated in the body (chemical thermoregulation) to the heat exchanged with the surroundings (physical thermoregulation).

The basic elements of thermoregulation include the centre of thermoregulation, thermoreceptors, thermosensors and effectors of the thermoregulatory system. The temperature fluctuations are received by the peripheral receptors and thermosensors. Peripheral thermoreceptors are mainly located in the skin, but also in the muscles, upper airway or venous walls. Thermosensors are located in the anterior hypothalamus and cervical spine. Thermoregulatory effectors are divided into the effectors of physical

thermoregulation (the cardiovascular system and sweat glands) and the effectors of chemical regulation (the skeletal muscles, liver and adipose tissue). The centre of thermoregulation is situated in the hypothalamus and consists of two parts: the centre of heat elimination regulating its loss and the centre of heat maintenance in the body [1, 2].

The centre of thermoregulation determines the thermoregulatory set point, i.e. the value of an adjustable variable (temperature) while the thermoregulatory system is to maintain "the set temperature " (temperature determined by the centre of thermoregulation). Any deviation from the core temperature is detected by specific receptors and the information is sent to the hypothalamus and further appropriate impulses are transmitted to the effectors.

An elevation in core temperature above "the set one" may be caused by the change in the thermoregulatory set point, exceeding the thermoregulatory abilities of the body in cases of uncontrollable production of heat (e.g. in malignant hyperthermia) or impairment of the thermoregulatory centre.

Changes in the set point, i.e. re-setting of a new elevated body temperature at proper thermoregulation, occur in fever. The increased "set temperature" is caused by the effects of endogenous pyrogens on the hypothalamus. Exogenous pyrogens, which are the constituent elements of pathogenic bacteria and viruses (e.g. endotoxin of Gram-negative bacteria) affect leukocytes, monocytes, macrophages and resident lymphoid cells, thus stimulating the release of endogenous pyrogens (interleukins 1 alpha, 1 and 6 beta, alpha and gamma interferons) that together with blood reach the hypothalamus triggering its production of neuromediators of inflammation, mainly prostaglandins. Once they get into the centre of thermoregulation in the brain, prostaglandins increase the set point, which leads to an increase in temperature. According to animal studies, the administration of IL-1 or IL-6 to the hypothalamus reduces the frequency of impulses from heat thermosensors and increases the frequency of impulses from cold thermosensors. Secondarily, thermoregulatory reactions are stimulated that decrease the loss of heat, such as constriction of skin blood vessels, as well as the reactions increasing heat production, such as by muscle shivering, and a new "set temperature" is determined, which does not exceed 41°C. When the exogenous pyrogens stop acting, the thermoregulatory mechanisms increasing the loss of heat are liberated and which last until the normal temperature of the "set point " is achieved.

A change in the thermoregulatory set point during fever has its merits. It is the adaptive mechanism developed during evolution, which aims at fighting pathogenic microorganisms [3]. At higher temperature, the protective mechanisms, such as the production of antibodies or proliferation of lymphocytes, markedly intensify (by about 10% per each degree) [3, 4].

The thermoregulatory capacities of the body can be exceeded, i.e. the abilities to lose heat are insufficient compared to the amount of heat obtained by the body in a given time unit, in various situations, including extreme atmospheric conditions. A special case of hyperthermia is malignant hyperthermia syndrome occurring during general anaesthesia in some genetically predisposed individuals.

When the system of thermoregulation is compromised at each level, thermoregulatory disorders develop [5]. Hyperthermia associated with impaired central mechanisms of thermoregulation is colloquially called "brain fever".

HYPERTHERMIA OF CENTRAL ORIGIN

Fever of central origin was first described by Ericson in "Brain" in 1939 [6]. The author defined this condition as a rapid increase in core body temperature at a low temperature of the integuments, occurring as a result of brain surgery [5]. However, the term of central hyperthermia remains controversial, especially that there are no diagnostic methods enabling the diagnosis at an early stage of the disease.

Disorders of central thermoregulation predominantly affect patients with severe CNS injuries associated with subarachnoid haemorrhage, brain trauma, ischaemic stroke, haemorrhagic stroke or CNS proliferative processes.

Hyperthermia of central origin is still diagnosed by exclusion of other causes. According to the retrospective study carried out by Hocker *et al.* [1] involving 526 neurological ICU patients with a fever exceeding 38.3°C, the incidences of systemic inflammatory response syndrome (a set of symptoms induced by systemic inflammatory response caused by various factors) and of isolated leukocytosis were comparable in patients with brain fever and in those with infectious fever. The above two groups differed in the percentage of neutrophils in blood tests, which was higher among patients with infectious fever and may suggest that although leukocytosis is not a reliable criterion for implementing empiric antibiotic therapy or withdrawing it prematurely, the left shifting observed in blood tests can prove useful [1].

According to Hocker *et al.* [1], patients with negative microbiological results and normal chest X-ray pictures, who developed fever within three days of hospitalisation, constitute the group that should be particularly suspected of central thermoregulatory disorders. The authors have reported that brain fever develops earlier and lasts longer than infection-related fever. Brain fever most commonly develops in patients with subarachnoid haemorrhage and /or intra-ventricular haemorrhage or brain tumour. In their study, patients with infectious fever were older and exposed to longer mechanical ventilation, as compared to patients with central fever (CF).

Table 1. Major characteristics of central fever

Resulting from an injury to the centre of thermoregulation
Diagnosis established by exclusion of other causes
Most common in severe brain damage cases
Is responsible for fever in 5–50% of patients with severe brain damage
Starts within the first three days following CNS injuries
Body temperature higher than that associated with infection
Resistance to antipyretic treatment
Lasts for several days or weeks

To facilitate the diagnosis of CF, it is necessary to determine the diagnostic criteria or find the diagnostic markers. Table 1 presents the major characteristics of CF.

CENTRAL FEVER IN VARIOUS CLINICAL CONDITIONS

HEAD INJURY

Central fever developing shortly after the disease onset is a common symptom in patients with head injuries. According to the sparse reports available in literature, its incidence ranges from 4–7% to 37%. Patients with CF have been found to have bradycardia, hypoidrosis, a lack of 24-hour temperature fluctuations for many days or even several weeks, and resistance to antipyretics; moreover, their body temperature is very high [7]. CF is more common in severely ill patients with diffuse white matter damage, brain oedema, hyperglycaemia, leukocytosis and hypotension [8].

CF in patients with head injuries can be caused by direct damage to the hypothalamus [7, 9]. According to Crompton [9], who performed autopsy studies on 106 patients who died due to severe brain injury, the features of damage to the hypothalamus were present in up to 42% of patients. Unfortunately, there are no other studies assessing the incidences of hypothalamus damage after head injury. An experimental study by Rudy *et al.* [7] has demonstrated that damage to the hypothalamus increases animal body temperature. The maximum temperature was observed about 1–1.5 h after injury with an elevated temperature maintained throughout the measurement period, i.e. 24 post-trauma hours. In another experimental study by Thomson *et al.* [10], brain damage resulted in CF in 27% of animals while acute hypothermia was observed in 69% of subjects. The development of CF was associated with the inflammatory changes within the hypothalamus. The role of acute phase response and interleukins has also been stressed by other authors [7]. The factors released due to injury activate thermosensitive neurones of the anterior hypothalamus leading to the development of fever. The clinical importance of cytokine-dependent fever involves the effects of increased production of glucocorticoids, increased secretion of aldosterone or shivering — the factors which may deteriorate a post-head injury prognosis [7]. Moreover, there is evidence that the passing of blood to the cerebrospinal fluid, especially its intraventricular presence, may stimulate the centre of thermoregulation in the hypothalamus and lead to CF [11].

SUBARACHNOID HAEMORRHAGE

Prolonged, drug-resistant fever occurring during the first 10 days after a subarachnoid haemorrhage (SAH) is associated with poorer prognosis and increased mortality [12]. Fever develops in about 70% of SAH patients, while its early occurrence supports its central origin [13]. Even half of patients with SAH can have central fever [14]. Rabinstein *et al.* [15], who studied 93 neurological ICU patients, have observed a higher percentage of non-infectious fever in SAH patients, as compared to those with head injury, i.e. in 48% of cases; moreover, it was particularly common in the group with concomitant vasoconstriction. Non-infectious fever developed most frequently during the first three post-SAH days. Beside the severity of the patient`s condition and the amount of blood in the subarachnoid space, a significant risk factor of non-infectious fever in patients with SAH was intraventricular haemorrhage [11, 12].

According to some researchers, increases in body temperature may also be caused by the products of heme decomposition, including carbon monoxide [13]. The experimental administration of carbon monoxide into the ventricles in rats induced an elevation in temperature by more than 1°C [16].

STROKE

In stroke, fever is common and usually results from infectious complications. When the cause of fever cannot be found and antibiotic therapy is ineffective, it is assumed that fever is likely to be associated with CNS damage [17]. In a retrospective study carried out by Morales-Irtiz [18] on 103 patients with stroke, fever developed in 23% of individuals while in 33% of patients the infection could not be documented (probably central fever). In this group, fever occurred earlier, reached the highest values and did not respond to antipyretics; the patients were severely ill and the mortality rate amongst them was higher. In another study by Georgillis *et al.* [17], patients with CF differed from those with infectious fever only in its earlier onset.

A vast majority of strokes are acute ischemic strokes (AIS). Hyperthermia is a common complication of AIS occurring in up to 50% of patients and is associated with a poorer prognosis [19]. The processes determining the brain temperature in AIS have not been fully elucidated [20, 21]. Animal studies have demonstrated that under normal health conditions, the balance between the generation of heat in various metabolic processes and cooling of the brain by

cerebral circulation is maintained [22]. In AIS this balance is impaired. Increases in temperature seem to be caused by local inflammatory response, including intracerebral synthesis of Il-6 and other proinflammatory cytokines and their effects on the hypothalamus [21]. Moreover, the temperature of an ischaemic area has been found to be higher than that in the remaining part of the brain [21, 23]. Whitley *et al.* [21] assessed the brain temperature using magnetic resonance spectroscopy in 44 patients with acute ischemic stroke. Their measurements were performed on the first and fifth day after stroke. The mean temperature in the ischaemic area was 38.4°C and 37.7°C in the remaining part, while the body temperature oscillated around 36.6°C. An increased concentration of interleukin 6 correlated with higher temperature of normal brain areas both on admission and after 5 days post-admission. No similar correlation was found with respect to the temperature in the ischaemic area [21].

Hemorrhagic stroke (HS) constitutes about 10–17% of all strokes and is associated with high mortality, which in the first 30 days is 35–52% [25]. According to a prospective study by Honig *et al.* [5] involving 95 patients with spontaneous intracerebral haemorrhage, central fever developed in 32% whereas infectious fever occurred in 9%. Analysis of the results revealed higher mortality and worse functional scores in the CF group assessed after 90 days using the modified Rankin scale. The development of CF increased with the extend of haemorrhagic stroke and in individuals with intraventricular haemorrhage. It should be noted that the peak fever was substantially higher in CF patients, as compared to patients with infectious fever. Additionally, the quicker the onset of fever, the higher its value was. The above results are consistent with the earlier findings demonstrating that earlier-onset fever is most commonly of central origin and reaches high values (40–42°C) [5].

CNS PROLIFERATIVE PROCESSES

The relationship between CNS proliferative processes and central fever has not been studied in detail. The literature contains descriptions of cerebral fever in cases of sellar, diencephalic and intraventricular tumours [25].

OTHER CNS INJURIES

Central fever in other CNS injuries is rare [26–28]. Only single cases have been reported, among them a patient with tuberculous meningitis whose fever persisted despite the effective treatment of tuberculosis. The patient was diagnosed with damage to the anterior hypothalamus [27]. Another example of central fever has been described in a patient with Angelman syndrome during myoclonic status epilepticus [26] and in a patient with gelastic epilepsy [28]. The above publications are case reports and do not allow one to draw definite conclusions.

An interesting, albeit rare symptom in patients with CNS damage is poikilothermia, i.e. the dependence of core body temperature on thermal conditions of the environment. Patients with poikilothermia can also develop symptoms of hyperthermia. The symptoms of poikilothermia have been described in a female patient with Devic`s syndrome and documented extensive damage to the diencephalon and periventricular region [29], in a 68-year-old female patient with ataxia suspected of vascular-derived damage to the hypothalamus [28], as well as in another female patient with left-sided germinoma of the basal and hypothalamic ganglia [30]. The mechanism of this phenomenon is most likely associated with damage to the hypothalamus.

CONSEQUENCES OF CENTRAL FEVER

Elevated temperature affects cerebral metabolism causing:

1) increased amounts of the end products of the energy metabolism, including CO_2,
2) increased consumption of oxygen,
3) acidosis,
4) elevated levels of glutamic acid, which is likely to result in higher concentrations of stimulating amino acids, exceeding toxic levels,
5) enhanced release of nitrogen oxide — a mediator of oxidative damage,
6) increased cerebral flow, which can secondarily lead to increases in intracranial pressure,
7) impaired performance of ion channels (some calcium and voltage-gated potassium channels are regulated by temperature),
8) damage to the endothelial cells and secondarily permeation of serum proteins across the blood-brain barrier and cerebral oedema [6].

Harmful effects of hyperthermia on the damaged brain, including increased activity of cytokines, enhanced vascular permeability or secondary damage to axons, have been demonstrated in numerous animal models [7, 31–33]. Moreover, a correlation has been found between increases in temperature and higher values of intracranial pressure in patients after SAH and head trauma [13]. A collective meta-analysis involving 14,431 patients with brain injuries has revealed that fever correlates with poorer prognosis and higher mortality [34].

THERAPEUTIC MANAGEMENT

In view of the harmful effects of hyperthermia on the brain observed in many experimental models, it would seem obvious that the treatment aimed at reducing fever should be initiated in all patients with central hyperthermia, as well as hyperthermia induced by other causes. Unfortunately, there are no large randomised clinical trials confirming the

beneficial impact of combating hyperthermia on prognosis. Furthermore, the decision to treat fever is mostly based on measurements of superficial or intravascular temperature. It has been shown that the brain temperature after severe brain injury is higher than the core body temperature and both values can change independently [13, 20, 35]. Rumana *et al*. [35], in a prospective study in 30 neurological ICU patients, evaluated temperatures of the brain, blood (measurements in the jugular vein) and body (rectal measurements). They found that the intracerebral temperature exceeded the body and jugular vein temperature by 1.1°C. Their findings have been confirmed by Rossi *et al.* [13], who measured simultaneously intraventricular and intra-pulmonary artery temperature in 20 patients with severe brain damage, demonstrating that the difference between them was even 2°C.

THE ADMINISTRATION OF ANTIPYRETICS

The administration of antipyretics (acetaminophen, nonsteroidal anti-inflammatory drugs) is the traditional treatment of choice for fever. These drugs block the synthesis of prostaglandin E, reducing "the set temperature " of the hypothalamus and subsequently activating the two major mechanisms dissipating heat, i.e. vasodilation and perspiration. The efficacy of antipyretics depends on the efficiency of the thermoregulatory system and is therefore lower in patients with CNS damage and impaired thermoregulatory mechanisms [36]. Moreover, possible side effects of such drugs should be born in mind, such as bleeding from the gastrointestinal tract, increased coronary symptoms or liver and kidney injuries. In the study carried out by Dippel [37] encompassing 65 patients with acute ischemic stroke from anterior vascularisation, the patients were randomly allocated to groups receiving 1000 mg of acetaminophen, 400 mg of ibuprofen or a placebo. The treatment was initiated within the first 24 hours after stroke onset and drugs were administered 6 times a day for 5 days. The body temperature was measured in 2-hour intervals during the first 24 hours and, subsequently, in 6-hour intervals. Although after 24 hours no significant inter-group differences in body temperature were observed, the administration of high doses of acetaminophen resulted in a decrease in body temperature by 0.3°C , as compared to baseline values. Acetaminophen did not substantially affect the body temperature during the next four days compared to the placebo while ibuprofen had no statistically significant effects throughout the study.

THE NON-PHARMACOLOGICAL METHODS

The non-pharmacological methods include non-invasive measures (air or ice cooling, e.g. ice bags, caps, water- or air-circulating cooling blankets, cooling blankets filled with hydrogel) and invasive procedures (rinsing the body cavities, urinary bladder or rectum, intravenous infusions of cold fluids into the peripheral or central veins, endovascular cooling) [36].

External cooling of the patient`s body is not superior to antipyretics and is additionally associated with high temperature fluctuations and rebound hypothermia [38]. Invasive methods are considered more effective than external cooling [36].

The disadvantage of non-pharmacological methods (physical) is the fact that they induce shivering. In the study by Mayer [39], shivering was present in 40% of patients undergoing physical cooling. The metabolic consequences of uncontrollable shivering may be severe and include increased resting energy expenditure, as well as oxygen consumption and the production of carbon dioxide. Monitoring of therapeutic cooling using computerised systems of thermoregulation can prevent shivering and optimise the treatment. Determinations of the intensity of shivering (e.g. using the bedside shivering assessment scale (BSAS) allow one to use appropriate management prior to the occurrence of adverse effects in the form of shivering (warming air, pharmacological treatment - buspirone, magnesium, meperidine) [36].

The above management algorithm does not prove effective in all patients with central hyperthermia. There are single literature reports demonstrating the efficacy of propranolol, growth hormone, baclofen and morphine [2, 40–44].

INTERNATIONAL GUIDELINES FOR HYPERTHERMIA MANAGEMENT

In the guidelines regarding the treatment of individual neurological diseases, the subject of hyperthermia is brought up to a variable extent and the recommendations for the treatment of hyperthermia are inconsistent. The recommended options of therapy do not depend on the cause of hyperthermia.

The guidelines of the Group of Experts from the Vascular Diseases Section of the Polish Neurological Society of 2012 stress that the body temperature of patients with acute ischemic stroke (AIS) may be elevated in the first hours after stroke onset, which increases the infarct focus and worsens prognosis. It is recommended to diagnose a possible source of infection. The experts stress that prophylactic antibiotic, antifungal or antiviral therapies are not indicated. Moreover, antipyretic treatment should be initiated at temperatures ≥ 37.5°C [24].

In view of the literature reports evidencing negative effects of hyperthermia on the brain, the guidelines of the European Stroke Organisation (ESO) of 2015 for the management of hyperthermia in patients with AIS might seem surprising. The researchers posed a question whether the treatment of hyperthermia, as compared to its abandonment, affected the functional status of patients and their survival.

Having analysed the available literature, they concluded that the treatment of hyperthermia cannot be recommended as a factor affecting the above-mentioned variables (recommendation grade: quality of evidence — low, strength of recommendation — poor). Nevertheless, it should be added that the authors found only 2 randomised clinical trials involving in total 42 patients. There was no statistically significant difference in mortality and functional status assessed using the Rankin scale between patients with hyperthermia treated with acetaminophen and controls. Another issue concerned the prevention of hyperthermia using antipyretics in patients with AIS and normothermia. As far as the functional status and mortality were concerned, the literature data were not sufficient to recommend the treatment of hyperthermia (recommendation grade: quality of evidence — moderate, strength of recommendation — poor. Therefore, further studies are needed [18].

The guidelines of the American Heart Association (AHA) and the American Stroke Association (ASA) of 2013 regarding the management of hyperthermia after ischaemic stroke did not change compared to their previous recommendations and are very general. In cases of hyperthermia (> 38°C), it is recommended to initiate antipyretic therapy (class I, grade C recommendation) [44]. The European and American guidelines seem different, yet they concern slightly different issues, i.e. the European ones focus on the effects of hyperthermia on one's functional status and survival while the American ones deal with general indications for temperature reduction [18].

The AHA/ASA guidelines of 2015 regarding intracerebral haemorrhage (ICH) are more cautious and state that the treatment of fever seems justifiable (class IIb, grade C recommendation) [46]. On the other hand, the European researchers admit that there is no sufficient evidence to definitely conclude whether, when and in which groups of patients with ICH, the prophylactic or early treatment of fever should be used [47].

The European guidelines for the management of subarachnoid haemorrhage advocate monitoring of temperature and the management of hyperthermia using both pharmacological and physical measures (conclusions based on the Principles of Evidence-Based Practice) [48]. Moreover, the guidelines of AHA/ASA concerning the management of non-traumatic subarachnoid haemorrhage are explicit. In the acute stage of subarachnoid haemorrhage, they recommend aggressive control of fever in pursuit of normothermia using standard or advanced forms of treatment (class IIa, grade B recommendation) [49].

APPLICATION OF HYPOTHERMIA

In the last two decades, beside the classic reduction of temperature to normal values, much attention was paid to the use of hypothermia as a form of management in patients with severe brain damage. The first reports about treatment with hypothermia can be traced in ancient 5000-year-old Egyptian descriptions with Hippocrates also recommending the use of packages with snow and ice in order to treat the cases in which intracerebral haemorrhage was suspected. Although therapeutic hypothermia has had beneficial effects in animal model, its use in clinical practice has been disputed. The early pre-clinical studies have demonstrated that a mild reduction in brain temperature after moderate or severe traumatic brain injury diminishes the extent of histopathological lesions and positively affects the severity of neurological deficits. Hypothermia suppresses the mechanisms of numerous secondary injuries, including excitotoxicity, the formation of free radicals, apoptotic cell death and inflammatory conditions. Although hypothermia has been successfully studied in many single clinical trials in patients after head injuries, larger, randomised multi-centre trials have not demonstrated any benefits associated with this form of treatment [50]. Moreover, the fourth edition of guidelines of the Brain Trauma Foundation on severe post-traumatic brain injury of 2017 does not recommend prophylactic hypothermia in patients with diffuse brain injury [51].

The AHA/ASA guidelines about AIS report the results of two small trials and one review paper, none of which demonstrated explicitly the efficacy of hypothermia in AIS. The positive effect of mild hypothermia for the management of AIS cannot be excluded yet further research is needed. Moderate hypothermia (32–33°C), as opposed to mild hypothermia (34–35°C), seems to lead to complications more commonly (hypotension, cardiac arrhythmias, pneumonia or thrombocytopenia) [45]. Likewise, the European Stroke Organisation does not recommend induced hypothermia as a measure either to improve the functional status or to lengthen the survival of AIS patients [19]. Moreover, there is no explicit answer to the question regarding temperature reductions in stroke patients; some issues are still unclear, i.e. the optimal moment of treatment institution, its duration, the rate of warming and the target temperature of cooling [52]. The AHA/ASA guidelines regarding ICH state only that hypothermia should be considered in ICH [46].

The statement of AHA is explicit. According to the current guidelines based on the review conducted by the International Liaison Committee on Resuscitation (ILCOR) of 2015, all adult comatose patients after sudden cardiac arrest (SCA) should be subjected to hypothermia of 32–36°C maintained for at least 24 hours [53]. In 2012, the European Society of Cardiology ranked therapeutic hypothermia in patients after SCA the highest grade of recommendation, namely I/B. The same kind of management has been recommended by the European and Polish Resuscitation Council [54].

In Poland, according to the protocol approved by the National Health Fund, treatment with hypothermia should also be used in newborns of ≥ 35 weeks gestation, who have sustained moderate or severe perinatal hypoxia. If a newborn fulfils the qualification criteria, he/she should be transported to an appropriate centre within 6 hours; there are two stages of qualification, which are based on clinical/biochemical evaluation of the newborn`s status and neurological examinations. The treatment is carried out using moderate selective head cooling (SHC) or whole body cooling (WBC) [55].

Hypothermia is a continuously developing method and its use requires further studies; numerous factors, such as the selection of patients and duration of treatment, seem essential for successful treatment outcomes [50].

SUMMARY

In clinical practice, monitoring of core temperature in patients with severe brain damage is recommended in intensive care. Since the CNS is highly sensitive to temperature fluctuations, it would seem that the prevention of fever should be a therapeutic element aimed at limiting the extent of neuron damage. The guidelines of the European and American Societies regarding this issue, however, are not consistent, which mainly results from the lack of randomised clinical trials confirming the efficacy of this kind of management. Although the beneficial effects of therapeutic hypothermia have been confirmed in animal models, its use in clinical practice is still open to dispute [4]. Further randomised clinical trials are required in order to assess indications for the treatment of hyperthermia and the application of hypothermia.

Despite intensive diagnostic procedures, in some cases the cause of fever cannot be found. In patients after severe brain injury, once other causes have been excluded, hyperthermia of central origin should be considered. Further studies regarding the therapeutic management in such cases are required. This is essential in order to determine the diagnostic criteria of CF or to identify its diagnostic markers.

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References

1. Hocker SE, Tian L, Li G, et al. Indicators of central fever in the neurologic intensive care unit. JAMA Neurol. 2013; 70(12): 1499–1504, doi: 10.1001/jamaneurol.2013.4354, indexed in Pubmed: 24100963.
2. Lee HC, Kim JM, Lim JK, et al. Central hyperthermia treated with baclofen for patient with pontine hemorrhage. Ann Rehabil Med. 2014; 38(2): 269–272, doi: 10.5535/arm.2014.38.2.269, indexed in Pubmed: 24855623.
3. Marik PE, et al. Fever in the ICU. Chest. 2000; 117(3): 855–869.
4. Jampel HD, Duff GW, Gershon RK, et al. Fever and immunoregulation. III. Hyperthermia augments the primary in vitro humoral immune response. J Exp Med. 1983; 157(4): 1229–1238, indexed in Pubmed: 6220108.
5. Honig A, Michael S, Eliahou R, et al. Central fever in patients with spontaneous intracerebral hemorrhage: predicting factors and impact on outcome. BMC Neurol. 2015; 15: 6, doi: 10.1186/s12883-015-0258-8, indexed in Pubmed: 25648165.
6. Erickson TC. Neurogenic hyperthermia (a clinical syndrome and its treatment). Brain. 1939; 62(2): 172–190.
7. Thompson HJ, Tkacs NC, Saatman KE, et al. Hyperthermia following traumatic brain injury: a critical evaluation. Neurobiol Dis. 2003; 12(3): 163–173, indexed in Pubmed: 12742737.
8. Young AB, Ott LG, Beard D, et al. The acute-phase response of the brain-injured patient. J Neurosurg. 1988; 69(3): 375–380, doi: 10.3171/jns.1988.69.3.0375, indexed in Pubmed: 3136234.
9. Crompton MR. Hypothalamic lesions following closed head injury. Brain. 1971; 94(1): 165–172, indexed in Pubmed: 5552160.
10. Thompson HJ, Hoover RC, Tkacs NC, et al. Development of posttraumatic hyperthermia after traumatic brain injury in rats is associated with increased periventricular inflammation. J Cereb Blood Flow Metab. 2005; 25(2): 163–176, doi: 10.1038/sj.jcbfm.9600008, indexed in Pubmed: 15647747.
11. Commichau C, Scarmeas N, Mayer SA. Risk factors for fever in the neurologic intensive care unit. Neurology. 2003; 60(5): 837–841, indexed in Pubmed: 12629243.
12. Fernandez A, Schmidt JM, Claassen J, et al. Fever after subarachnoid hemorrhage: risk factors and impact on outcome. Neurology. 2007; 68(13): 1013–1019, doi: 10.1212/01.wnl.0000258543.45879.f5, indexed in Pubmed: 17314332.
13. Rossi S, Zanier ER, Mauri I, et al. Brain temperature, body core temperature, and intracranial pressure in acute cerebral damage. J Neurol Neurosurg Psychiatry. 2001; 71(4): 448–454, indexed in Pubmed: 11561026.
14. Otawara Y, Ogasawara K, Yukawa H, et al. Brain and systemic temperature in patients with severe subarachnoid hemorrhage. Surg Neurol. 2003; 60(2): 159–164; discussion 164, indexed in Pubmed: 12900131.
15. Rabinstein AA, Sandhu K. Non-infectious fever in the neurological intensive care unit: incidence, causes and predictors. J Neurol Neurosurg Psychiatry. 2007; 78(11): 1278–1280, doi: 10.1136/jnnp.2006.112730, indexed in Pubmed: 17940175.
16. Steiner AA, Branco LG. Carbon monoxide is the heme oxygenase product with a pyretic action: evidence for a cGMP signaling pathway. Am J Physiol Regul Integr Comp Physiol. 2001; 280(2): R448–R457, indexed in Pubmed: 11208574.
17. Georgilis K, Plomaritoglou A, Dafni U, et al. Aetiology of fever in patients with acute stroke. J Intern Med. 1999; 246(2): 203–209, indexed in Pubmed: 10447789.
18. Morales-Ortiz A, Jiménez-Pascual M, Pérez-Vicente JA, et al. [Fever of central origin during stroke]. Rev Neurol. 2001; 32(12): 1111–1114, indexed in Pubmed: 11562838.
19. Ntaios G, Dziedzic T, Michel P, et al. European Stroke Organisation. European Stroke Organisation (ESO) guidelines for the management of temperature in patients with acute ischemic stroke. Int J Stroke. 2015; 10(6): 941–949, doi: 10.1111/ijs.12579, indexed in Pubmed: 26148223.
20. Mrozek S, Vardon F, Geeraerts T. Brain temperature: physiology and pathophysiology after brain injury. Anesthesiol Res Pract. 2012; 2012: 989487, doi: 10.1155/2012/989487, indexed in Pubmed: 23326261.
21. Whiteley WN, Thomas R, Lowe G, et al. Do acute phase markers explain body temperature and brain temperature after ischemic stroke? Neurology. 2012; 79(2): 152–158, doi: 10.1212/WNL.0b013e31825f04d8, indexed in Pubmed: 22744672.
22. Kiyatkin EA. Brain temperature fluctuations during physiological and pathological conditions. Eur J Appl Physiol. 2007; 101(1): 3–17, doi: 10.1007/s00421-007-0450-7, indexed in Pubmed: 17429680.
23. Karaszewski B, Wardlaw JM, Marshall I, et al. Measurement of brain temperature with magnetic resonance spectroscopy in acute ischemic stroke. Ann Neurol. 2006; 60(4): 438–446, doi: 10.1002/ana.20957, indexed in Pubmed: 16972284.
24. Wiszniewska M, Kobayashi A, Członkowska A: Postępowanie w udarze mózgu skrót wytycznych Grupy Ekspertów Sekcji Chorób Naczyniowych Polskiego Towarzystwa Neurologicznego z 2012 roku. www.ppn.viamedica.pl.
25. Clar HE. Clinical and morphological studies of pituitary and diencephalic space-occupying lesions before and after operation, with special reference to temperature regulation. Acta Neurochir (Wien). 1979; 50(3-4): 153–199, indexed in Pubmed: 517188.
26. Nicita F, Garone G, Papetti L, et al. Myoclonic status and central fever in Angelman syndrome due to paternal uniparental disomy. J Neurogenet.

2015; 29(4): 178–182, doi: 10.3109/01677063.2015.1091452, indexed in Pubmed: 26559560.
27. Alshahrani AM, Al-Said YA, Mamoun IA, et al. Central fever due to hypothalamic lesion in a patient with tuberculous meningitis. Neurosciences (Riyadh). 2002; 7(4): 301–303, indexed in Pubmed: 23978866.
28. Chaouki S, Boujraf S, Atmani S, et al. Gelastic seizures and fever originating from a parietal cortical dysplasia. J Pediatr Neurosci. 2013; 8(1): 70–72, doi: 10.4103/1817-1745.111433, indexed in Pubmed: 23772252.
29. Yildiz OK, Cevik S, Oztoprak I. Consciousness disturbance and poikilothermia revealing brain involvement in neuromyelitis optica. Acta Neurol Belg. 2012; 112(2): 213–215, doi: 10.1007/s13760-012-0029-x, indexed in Pubmed: 22426665.
30. Nakasu Y, Takeichi T, Takayama S, et al. Poikilothermia in a female patient with a germinoma in the basal ganglia. Acta Neurochir (Wien). 1993; 120(3-4): 190–192, indexed in Pubmed: 8460574.
31. Baena RC, Busto R, Dietrich WD, et al. Hyperthermia delayed by 24 hours aggravates neuronal damage in rat hippocampus following global ischemia. Neurology. 1997; 48(3): 768–773, indexed in Pubmed: 9065563.
32. Dietrich WD, Alonso O, Halley M, et al. Delayed posttraumatic brain hyperthermia worsens outcome after fluid percussion brain injury: a light and electron microscopic study in rats. Neurosurgery. 1996; 38(3): 533–41; discussion 541, indexed in Pubmed: 8837806.
33. Kim Y, Busto R, Dietrich WD, et al. Delayed postischemic hyperthermia in awake rats worsens the histopathological outcome of transient focal cerebral ischemia. Stroke. 1996; 27(12): 2274–80; discussion 2281, indexed in Pubmed: 8969793.
34. Greer DM, Funk SE, Reaven NL, et al. Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. Stroke. 2008; 39(11): 3029–3035, doi: 10.1161/STROKEAHA.108.521583, indexed in Pubmed: 18723420.
35. Rumana CS, Gopinath SP, Uzura M, et al. Brain temperature exceeds systemic temperature in head-injured patients. Crit Care Med. 1998; 26(3): 562–567, indexed in Pubmed: 9504587.
36. Scaravilli V, Tinchero G, Citerio G, et al. Participants in the International Multi-Disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage. Fever management in SAH. Neurocrit Care. 2011; 15(2): 287–294, doi: 10.1007/s12028-011-9588-6, indexed in Pubmed: 21755388.
37. Dippel DWJ, van Breda EJ, van der Worp HB, et al. PISA-Investigators. Effect of paracetamol (acetaminophen) and ibuprofen on body temperature in acute ischemic stroke PISA, a phase II double-blind, randomized, placebo-controlled trial [ISRCTN98608690]. BMC Cardiovasc Disord. 2003; 3: 2, doi: 10.1186/1471-2261-3-2, indexed in Pubmed: 12657165.
38. O'Donnell J, Axelrod P, Fisher C, et al. Use and effectiveness of hypothermia blankets for febrile patients in the intensive care unit. Clin Infect Dis. 1997; 24(6): 1208–1213, indexed in Pubmed: 9195084.
39. Mayer SA, Kowalski RG, Presciutti M, et al. Clinical trial of a novel surface cooling system for fever control in neurocritical care patients. Crit Care Med. 2004; 32(12): 2508–2515, indexed in Pubmed: 15599159.
40. Siefferman JW, Lai G. Propranolol for Paroxysmal Sympathetic Hyperactivity with Lateralizing Hyperhidrosis after Stroke. Case Rep Neurol Med. 2015; 2015: 421563, doi: 10.1155/2015/421563, indexed in Pubmed: 26167316.
41. Ünver Tuhan H, Anık A, Çatlı G, et al. Recovery of central fever after GH therapy in a patient with GH deficiency secondary to posttraumatic brain injury. J Clin Res Pediatr Endocrinol. 2015; 7(1): 77–79, doi: 10.4274/jcrpe.1639, indexed in Pubmed: 25800481.
42. Yu KW, Huang YH, Lin CL, et al. Effectively managing intractable central hyperthermia in a stroke patient by bromocriptine: a case report. Neuropsychiatr Dis Treat. 2013; 9: 605–608, doi: 10.2147/NDT.S44547, indexed in Pubmed: 23662059.
43. Mendieta Zerón H, Arriaga García Rendon JC. Remission of central fever with morphine post traumatic brain injury. J Med Liban. 2014; 62(1): 57–61, indexed in Pubmed: 24684128.
44. Huang YS, Hsiao MC, Lee M, et al. Baclofen successfully abolished prolonged central hyperthermia in a patient with basilar artery occlusion. Acta Neurol Taiwan. 2009; 18(2): 118–122, indexed in Pubmed: 19673364.
45. Jauch EC, Saver JL, Adams HP, et al. American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013; 44(3): 870–947, doi: 10.1161/STR.0b013e318284056a, indexed in Pubmed: 23370205.
46. Hemphill JC, Greenberg SM, Anderson CS, et al. American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, American Heart Association Stroke Council and Council on Cardiovascular Nursing. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2010; 41(9): 2108–2129, doi: 10.1161/STR.0b013e3181ec611b, indexed in Pubmed: 20651276.
47. Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke. 2014; 9(7): 840–855, doi: 10.1111/ijs.12309, indexed in Pubmed: 25156220.
48. Steiner T, Juvela S, Unterberg A, et al. European Stroke Organization. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis. 2013; 35(2): 93–112, doi: 10.1159/000346087, indexed in Pubmed: 23406828.
49. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. American Heart Association Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Clinical Cardiology. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke. 2012; 43(6): 1711–1737, doi: 10.1161/STR.0b013e3182587839, indexed in Pubmed: 22556195.
50. Dietrich WD, Alonso O, Halley M, et al. Delayed posttraumatic brain hyperthermia worsens outcome after fluid percussion brain injury: a light and electron microscopic study in rats. Neurosurgery. 1996; 38(3): 533–541; discussion 541, indexed in Pubmed: 8837806.
51. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery. 2017; 80(1): 6–15, doi: 10.1227/NEU.0000000000001432, indexed in Pubmed: 27654000.
52. Marehbian J, Greer DM. Normothermia and Stroke. Curr Treat Options Neurol. 2017; 19(1): 4, doi: 10.1007/s11940-017-0437-6, indexed in Pubmed: 28243991.
53. Donnino MW, Andersen LW, Berg KM, et al. ILCOR ALS Task Force, ILCOR ALS Task Force. Temperature management after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation. 2015; 132(25): 2448–2456, doi: 10.1161/CIR.0000000000000313, indexed in Pubmed: 26434495.
54. Klimczuk T, Kubica J, Kasprzak M, et al. Łagodna hipotermia terapeutyczna po nagłym zatrzymaniu krążenia. Folia Cardiologica. 2015; 10(1): 19–24.
55. Nowacka-Gotowiec M, Dunin-Wąsowicz D. Zastosowanie hipotermii leczniczej w encefalopatii niedotlenieniowo-niedokrwiennej noworodków. Neurol Dziec. 2012; 21(43): 11–17.

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