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THE PATHOPHYSIOLOGICAL MECHANISMS OF THE ONSET OF DEATH THROUGH ACCIDENTAL HYPOTHERMIA AND THE PRESENTATION OF „THE LITTLE MATCH GIRL" CASE

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Abstract

Hypothermia and death caused by hypothermia may be found in a number of fiction works, mainly in novels. In the well-known story "The Little Match Girl" by Hans Christian Andersen, one can notice that the descriptions of the phenomena occurring before the girl's death are in fact a literary presentation of the pathophysiological mechanisms of the onset of death through accidental hypothermia. This essay presents the medical aspects of the story written by Andersen.

Keywords: accidental hypothermia

Introduction

Hypothermia is defined as a clinical condition in which internal temperature (rectal, esophageal or tympanic) is less than 35°C [1]. The American College of Surgeons recognizes three degrees of hypothermia: mild (32-35°C), moderate (30-32°C), severe (below 30°C) [2]. The lowest recorded temperature in a pediatric survivor of accidental hypothermia is 14.4°C and the lowest in an adult survivor is 13.7°C [3].

Hypothermia can be classified according to etiology as: accidental (from exposure to cold), spontaneous (after trauma), iatrogenic hypothermia, therapeutic hypothermia [4]. Hypothermia may occur during any season of the year and in any climate [5].

The analgesic and hemostatic effects of cold have been recognized throughout the ages. Hippocrates used snow and ice to stop hemorrhage. Alexander the Great, during his campaign into India, is said to have become unconscious from cold. "Refrigeration" anesthesia was used during the Renaissance. Baron Larrey, Napoleon's surgeon, took advantage of the cold battlefield to carry out surgical repair on hypothermic soldiers. The concept of total hypothermia was tested by William Cullen in 1755, when he attempted to cool small animals to a state of suspended animation. In 1766 John Hunter tried, unsuccessfully, to revive carp after a period of induced freezing. Hypothermia was described frequently in militaries as a consequence of cold exposure during the wars [6-8].

Hypothermia may occur during open-water swimming events even in elite athletes competing in warm water [9]. Motion sickness may predispose to hypothermia by enhancing heat loss and attenuating heat production during exposure to a cold environment (study in human subjects); this might have implications for survival in maritime accidents [10].

The mortality from accidental hypothermia is approximately 600 deaths each year in the United States. Alcohol intake, activity level and type of clothing are among the modifiable factors associated with accidental hypothermia [11]. The persons at extremes of age and those who have certain underlying medical conditions are at greatest risk for accidental hypothermia [5,12]. It is estimated that 17 million newborns develop hypothermia annually in developing countries, with high mortality (poverty, home delivery, low birth weight, early bathing of babies, delayed initiation of breastfeeding and inadequate knowledge among health workers) [13,14].

In the well-known story "The Little Match Girl" by Hans Christian Andersen, I noticed that descriptions of the phenomena occurring before girl's death are a literary presentation of the pathophysiological mechanisms of installation of death through accidental hypothermia. The little match girl is a female child character from a family with low socioeconomic status. She was driven away from home *"bareheaded, and with naked feet"*, in bad weather conditions *("Most terribly cold it was; it snowed, and was nearly quite dark, and evening")* to sell a few boxes of matches.

Mild hypothermia (32-35°C)

The physiological adaptation of the body to cold temperatures is achieved through autonomic and somatic mechanisms, increasing thermogenesis and inhibiting thermolysis. In mild hypothermia, the normal thermoregulatory activity is present.

The somatic reaction consists in squatting position *("she seated herself down and cowered together. Her little feet she had drawn close up to her")*.

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Neurological signs. The patient has hyperreflexia, a slowness of ideation and dysarthria. Hypothalamic centers of thermoregulation have connections with the hunger and satiety centers. The decrease of intracranial blood temperature excites the hunger center and inhibits the satiety center *("She crept along trembling with cold and hunger – a very picture of sorrow, the poor little thing!")* [15].

Cardiovascular system. The patient presents:

A. Peripheral vasoconstriction with pale skin (blocked blood flow in the adipose tissue in order to reduce heat loss): the hypothalamus is stimulated through impulses from Krause receptors and the hypothalamus emits vasoconstrictor motor signals through adrenergic fiber [15] – *"her tiny naked* [...] *feet were quite red and blue from cold"*.

B. Tachycardia, increased cardiac output and increased blood pressure (through increase of the sympathetic tone) [16], increased secretion of the thyroid hormone (through hypothalamic TRH) [17], corticosteroids and catecholamines hormone increase (through feedback interrelationships between the endocrine glands which participate in thermoregulation [15]).

C. Atrial fibrilation at <33°C [18].

Respiratory system. The patient has tachypnea, bronchospasm and bronchorrhea.

Renal system. The cold determines the decrease of ADH secretion with subsequent onset of cold diuresis [19].

Muscular system. Muscle tone is increased and thermal shiver appears. The anterior hypothalamus coordinates the non-shivering heat conservation and dissipation mechanisms and the posterior hypothalamus coordinates shivering thermogenesis [20]. Shivering increases thermogenesis and replaces body heat losses, while peripheral vasoconstriction improves thermal insulation of the body and retards the rate of heat loss [21]. [A 28-year-old quadriplegic patient was admitted to the hospital with a core temperature of 24°C secondary to accidental hypothermia. Her neurologic disability was detrimental to thermoregulation by decreasing her ability to shiver actively and to vasoconstrict [22]]

General metabolic signs. The shiver produces a decrease of the glycogen reserve with installation of the hypoglycemia. ATP is used extensively, oxygen consumption increases and tachypnea occurs.

The somatic pain occurs due to the deficient outpouring of the catabolic products from the interstitial space into blood, they accumulate in the interstitial space and they irritate the free nerve endings.

Blood. The processes of coagulation and fibrinolysis are altered (experimental study in rabbits) with leading to an increased thrombotic and fibrinolytic tendency, which appears quite early in the course of temperature reduction [23].

[Mild induced hypothermia to 32–35 °C is effective in reducing elevated intracranial pressure and is a valid therapy in brain injury [24, 25]]

Moderate hypothermia (30-32°C)

In moderate hypothermia, cold adaptation mechanisms are exceeded *("but she grew colder and colder")*, glucose resources are depleted, major energy deficit occurs *("she seated herself down")*.

Neurological signs. The cerebral hypoxia causes hyporeflexia, pathological encephalographic trajectory, disorders of consciousness (obnubilation gradually worsening), disorders of sensitivity and perception (delusions, hallucinations) and thought (delirium) [15].

The disorders of sensitivity and perception begin in „The little match girl" case with a delusion episode (misperception of an existing object [26]): When *she lit* the first *match, "it was a wonderful light. It seemed really to the little maiden as though she were sitting before a large iron stove, with burnished brass feet and a brass ornament at top. The fire burned with such blessed influence; it warmed so delightfully. The little girl had already stretched out her feet to warm them too; but the small flame went out, the stove vanished: she had only the remains of the burnt-out match in her hand."*

A second psychotic episode follows, with hallucination (false perceptions without the presence of the object as perceptual stimulus [26]) after she lit the second match: *"She rubbed another against the wall: it burned brightly, and where the light fell on the wall, there the wall became transparent like a veil, so that she could see into the room. On the table was spread a snow-white tablecloth; upon it was a splendid porcelain service, and the roast goose was steaming famously with its stuffing of apple and dried plums. And what was still more capital to behold was, the goose hopped down from the dish, reeled about on the floor with knife and fork in its breast, till it came up to the poor little girl; when the match went out and nothing but the thick, cold, damp wall was left behind."*

It follows a third psychotic episode, with hallucinations, after she lit another match: *"Now there she was sitting under the most magnificent Christmas tree: it was still larger, and more decorated than the one which she had seen through the glass door in the rich merchant's house. Thousands of lights were burning on the green branches, and gaily-colored pictures, such as she had seen in the shop-windows, looked down upon her. The little maiden stretched out her hands towards them when the match went out. The lights of the Christmas tree rose higher and higher, she saw them now as stars in heaven; one fell down and formed a long trail of fire."*

The entry into delirium is described with emotion: *"‹Someone is just dead!› said the little girl; for her old grandmother, the only person who had loved her, and who was now no more, had told her, that when a star falls, a soul ascends to God."*

The ignition of the fourth match starts the fourth psychotic episode with unorganized delirium (serious disorder of thought, the patient lives in a system of false

ideas which she believes strongly [26]): *"She drew another match against the wall: it was again light, and in the lustre there stood the old grandmother, so bright and radiant, so mild, and with such an expression of love. ‹Grandmother!› cried the little one. ‹Oh, take me with you! You go away when the match burns out; you vanish like the warm stove, like the delicious roast goose, and like the magnificent Christmas tree!› And she rubbed the whole bundle of matches quickly against the wall, for she wanted to be quite sure of keeping her grandmother near her."*

Cardiovascular system. Hypothermia can be associated with a variety of electrocardiographic abnormalities: the presence of Osborne (J) waves, PR interval, QRS or QT prolongation, varied T-wave abnormalities, arrhythmias. But the hypothermia can simulate acute coronary ischemia or pericarditis [27-29].

The characteristic Osborn or J waves (these look like "delta" or "camel's hump" waves after regular QRS complex, at the QRS-ST junction) may be seen on the electrocardiogram at core temperatures below 32°C [30] in the precordial leads [31, 32]. The appearance of Osborn waves was considered to be due to the abnormalities during early ventricular repolarization, and this may be related to the altered action potential exaggerated outward potassium currently leading to repolarization abnormality [33]. The J wave is characteristic but not pathognomonic of hypothermia, as it may be observed in conditions of normothermia: patients with subarachnoid hemorrhage, myocardial ischemia or sepsis [34, 35], early repolarization syndrome (rare) [36], variant angina [37], intoxication by tricyclic antidepressants [38], cocaine abuse [39], hypercalcemia [40], encephalic lesion [41], Brugada syndrome [42], idiopathic ventricular fibrillation such as J waves prominent in the inferior wall [43], and the so-called concealed forms of arrhythmogenic ventricular dysplasia [44].

Hypothermia depresses the calcium-dependent ATPase by reducing the number of active calcium pump units, resulting in myocardial conduction delay [45]. The widening QRS complex is developed afterwards. Conduction delay can also cause PR prolongation and high-degree A-V blockage on the EKG. Increased calcium concentration extracellularly and decreased calcium concentration intracellularly in myocardial cells impairs the cardiac contractility and subsequently reduces the cardiac output [46]. The increasing acidosis in the cytosol further affects the enzyme activity, which forms a vicious cycle in the metabolism of myocytes during hypothermia [47]. Hypothermia depresses the pacemaker cells automaticity, affecting the transmembrane ion channel activity, resulting in lower calcium, higher potassium and higher hydrogen levels intracellularly [48].

Respiratory sistem. Respiratory rate decreases progressively [18].

Renal system. Renal blood flow is increased through the centralizing of the circulation (peripheral vasoconstriction). Antidiuretic hormone activity is inhibited. This results due to cold diuresis; intravascular volume begins to decrease [49].

Muscular system. The patient shivers, but he can have a paradoxical decrease in shivering [20].

General metabolic signs. After ATP depletion, anaerobic glycolysis occurs with development of secondary metabolic acidosis. Acidosis occurs due to respiratory depression and hypercarbia, and lactic acid production through shivering and poor tissue perfusion, hypoglycemia, respiratory or metabolic acidosis, and hyperkalemia.

Blood. There is a risk for intravascular thrombosis. Prominent laboratory abnormalities include leukopenia (from splenic sequestration), thrombocytopenia (during rewarming) [20].

Gastrointestinal system. Gastrointestinal motility decreases, and mild ileus may be seen at temperatures less than 32°C [50]. Splanchnic vasoconstriction, gastric erosions, hepatic necrosis, and pancreatitis may occur [20].

Severe hypothermia (below 28°C)

Severe hypothermia causes multiple organ dysfunction syndrome, coma and death.

Neurological symptoms. Cerebral metabolism is depressed 6-7% per 1°C decrease in core temperature. Cerebrovascular autoregulation remains intact until below 25°C, which helps maintain cortical blood flow. Electroencephalographic activity is abnormal below 33°C and it silences around 19-20°C [20]. The patient might attempt to undress (paradoxical undressing) [20].

Lack of oxygen to the brain causes a random activation of neurons in the occipital visual areas, creating the impression of bright lights [51]: *"The matches gave such a brilliant light that it was brighter than at noon-day: never formerly had the grandmother been so beautiful and so tall. She took the little maiden, on her arm, and both flew in brightness and in joy so high, so very high, and then above was neither cold, nor hunger, nor anxiety – they were with God."*

The patient is comatose, areflexic, with dilated pupils [52].

Cardiovascular system. Bradycardia is caused through a decrease in spontaneous depolarization of the pacemaker cell. The myocardium becomes irritable, predisposing it to bradyarrhythmias and hypotension. Atrial arrhythmias can occur with a slow ventricular response and they can precede ventricular arrhythmias and asystole at core temperatures below 25°C [49,53].

Respiratory system. At core temperatures below 28°C, minute ventilation is reduced; bronchorrhea may occur, with a loss of cough and gag reflexes leading to an increased risk for aspiration. Carbon dioxide production decreases, whereas oxygen consumption is reduced by 75% at 22°C. Apnea can then result [20].

Renal system. Acute renal failure.

Muscular system. No shivering, rigid muscles, pale gray skin [52].

Gastrointestinal system. Gastric mucosal erosions and ulcers, and haemorrhagic pancreatitis has been reported [54].

Death. The usual criteria of death do not apply to hypothermia [55]. In general, a normothermic patient should be pronounced dead without rewarming. The hypothermic patients should not be considered dead until they are "warm and dead." [56]

"But in the corner, at the cold hour of dawn, sat the poor girl, with rosy cheeks and with a smiling mouth, leaning against the wall frozen to death on the last evening of the old year." The little match girl's death occurred through overcoming the functional capacity of thermoregulatory mechanisms under prolonged exposure to low temperature. This simple story for children suggests the complexity of the psychosomatic structures of the body.

Experimental study in hypothermia

Nervous system. A study in cat cortex reported that the cooling to moderate temperature levels impeded the pump mechanisms exchanging Na^+/K^+ across the neuron membrane. Further cooling to lower temperatures blocked the passive exchange of Na^+/K^+ across membrane pores. These effects explain the association between hypothermia and seizures [57]. Hypothermia amplifies somatosensory evoked potentials in rats [58].

A study on cultured neuronal networks reported that the spatio-temporal pattern of networks survived in cold exposure [59].

Eye. There is a correlation between hypothermia-induced reductions in energy usage and neuroprotection. The hypothermia had reduced energy requirements more than energy production, therefore the hypothermia protects against retinal ischemic injury (study in rabbit retina in vitro) [60].

Respiratory system. With the fall in temperature the solubility of gases increases. In blood, with the fall in temperature the produced effects by change in the dissociation constant of buffers and displacement to the left of the haemoglobin dissociation curve are added to increased gas solubility. Clinical assessment of arterial oxygenation by examination for cyanosis is misleading because of the shift in the dissociation curve of haemoglobin. Cyanosis does not appear until arterial oxygen tension is very greatly reduced. Effect of hypothermia on lung function are: increase in conducting airway dead-space due to bronchodilation, the alteration of the alveolar-capillary metabolic exchanges, alteration of the mechanisms of control of respiration, the alterations in gas solubility and gas transport, the change in mechanical or other properties of the lung. Reduction of ventilation and depression of cough predispose to collapse of alveolar units and segments of lung [61].

There is a dysfunction of pulmonary surfactants due to acute respiratory distress and the activation of early-phase inflammatory mediators, with high mRNA expression levels of pulmonary surfactants in fatal hypothermia (cold exposure). These mRNAs can be used as molecular biological markers of pulmonary injury to assist investigations of the pathophysiology of drowning and fatal hypothermia in combination with other biochemical and biological markers [62].

Ventilation (VE) in hypothermic animals remains tightly coupled to oxygen consumption (VO_2) such that VE/VO_2 remains constant despite changes in body temperature [63].

The period during which the organism maintains viability in respiration arrest and disturbances in respiratory center are still reversible is prolonged under conditions of profound hypothermia (study in rats; they were cooled in water until attaining profound hypothermia and respiratory arrest, after removal from water, Na_2EDTA and Ca^{2+} was administered intravenously and promoted recovery of respiration following its arrest lasting 10.3±1.4 min) [64].

Blood. The effect of hypothermia on leukocyte migration was studied in pig blood. Neutrophil chemotaxis in vitro under agarose was significantly impaired at 29°C. Leukocytes isolated from hypothermic pigs and tested at 37°C migrated normally. Neutrophil and monocyte migration in vivo was markedly reduced at 29°C. Reduced inflammatory responses may contribute to increased infections during hypothermia [65]. Phagocytosis function of neutrophil in vitro was impaired at 29°C (conditions of moderate hypothermia) [66].

The thrombocytopenia of surface-induced deep hypothermia is due to completely reversible temporary sequestration of platelets in the liver and the mean survival of platelets exposed to this procedure is not shortened (the effects of surface-induced deep hypothermia (20°C), study in splenectomized dogs) [67]. Intravascular thrombosis has been reported as a complication leading to death [68].

Because of the depression of enzymatic activity of the activated clotting factors, clotting time (particularly partial thromboplastin time or PTT) is prolonged. Thrombocytopenia also commonly occurs because of bone marrow suppression along with splenic/hepatic platelet sequestration [20]. Hypothermia has a detrimental effect on the hemostatic mechanism.

Cellular and molecular biology. The Na^+/H^+ exchange function is affected by hypothermia, with delayed activation of the inward sodium current and more H^+ retained intracellularly [69,70].

The binding blood calcium ions with EDTA results in a reduction in Ca^{2+} concentration in the intercellular fluid and cytosol; thereby it can overcome the lower temperature limit at which cold shivering and respiration stop, by displacing it by 2–3°C (experimental study in rats) [71].

Hypothermia decreases HLA-DR expression [72].

The hypothermia inhibits cell proliferation and nitric oxide synthase expression in rats (study in rats; cold-water immersion for 5 min at 4°C suppressed the numbers of 5-bromo-2′-deoxyuridine-positive and nicotinamide adenine dinucleotide phosphate-diaphorase-positive cells in the

dentate gyrus, and these numbers were increased by warming for 30 min at 30°C) [73].

In severe hypothermia the suppression of the functional activity of the pineal gland occurred because of the exclusion of a proportion of pinealocytes from the process of active functioning (study in adult male Wistar rats exposed at 4 degrees C for 3 h) [74].

The effect of hypothermia on the phagocytic capacity of rat peritoneal macrophages for latex particles revealed growth of the superoxide anion production whereas the number of phagocytic cells decreased. In addition, the mean number of latex particles engulfed by each individual cell was lower [75].

Opioids and adenosine may play a role in hypothermia. In experimental conditions their role on hypothermia appears to be of minor importance because after treatment with opioids and adenosine antagonists, the changes in metabolic rate and temperature were only partially reversed [76].

Treatment of accidental hypothermia

Rough patient handling or sudden changes in posture may provoke ventricular fibrillation at any time in the severely hypothermic patient [77].

Immediately following removal from cold stress, the patient is in danger of a deteriorating condition that may be due to the collapse of arterial pressure and/or continued decrease of core temperature. Extra time should be taken to check for life signs [78].

Passive external rewarming (warm environment, blankets) is the method of choice for mild hypothermia and a supplementary method for moderate or severe hypothermia. Active external rewarming (immersion in warm water, electric blankets, environmental heaters, convective air blankets) is indicated for moderate or severe hypothermia or mild hypothermia that has not responded to passive rewarming. Active internal rewarming (warm pleural lavage, colonic lavage, peritoneal lavage, mediastinal lavage, inhalational gases, intravenous fluids) is indicated for hemodynamically stable patients suffering moderate or severe hypothermia [79,80]. In 1967, Lash reported peritoneal dialysis used in the treatment of hypothermia, in the treatment of patients with severe, prolonged depression of body temperature [81]. Today, the management of accidental hypothermia includes resuscitation and rewarming with extracorporeal circulation: hemodialysis centrifugal vortex pumps: veno-venous circulation, arteriovenous circulation, standard cardiopulmonary bypass, continuous arteriovenous rewarming [56,82].

Accidental hypothermia cases in the specialty literature

A 39-year-old man was brought to the emergency department with altered mental status and a core temperature of 27.6°C. The patient appeared to have had exposure to cold temperatures. He was known to have human immunodeficiency virus infection. His pulse was 40 beats per minute, his respiratory rate was 10 breaths per minute, and his blood pressure was 90/50 mmHg. A chest radiograph showed aspiration pneumonia. Electrocardiography revealed classic signs of hypothermia. After a long hospitalization, the patient was moved to a long-term care facility, where, after two months, he remained intubated [83].

On a January morning, an 87-year-old woman was found unresponsive in the fields, with fixed pupils and a respiration rate of about 6 per minute. Rectal temperature was recorded as <27°C (as no thermometer was available to read lower than <27°C). The electrocardiogram demonstrated atrial fibrillation with severe bradycardia and giant Osborn waves. The patient was successfully rewarmed and survived! [84].

A case of severe accidental hypothermia (core body temperature 23.2°C) was described to be successfully treated with hemodialysis in a diabetic patient with preexisting renal insufficiency [85].

In 2013 the case of patient which he survived 6 days in a crevasse was published. The patient conserved body heat in a crouching position, wrapping the rescue foil around his body, placing his hands under his armpits and exhaling into his shirt [86].

This study pays tribute to dead and abandoned children on the streets due to hypothermia in the world.

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