Neurogenic Fever

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Body Temperature Regulation

- The temperature within the deep tissues of the body (core temperature) is normally maintained within a range of 36.0°C to 37.5°C
- Within this range, there are individual differences and diurnal variations:
  - Internal core temperatures reach their highest point in late afternoon and evening and their lowest point in the early morning hours.
- Body temperature reflects the difference between heat production and heat loss.
  - Body heat is generated in the tissues of the body, transferred to the skin surface by the blood, and then released into the environment surrounding the body.

Body Temperature Regulation

- The thermoregulatory center is in the hypothalamus and functions to modify heat production and heat losses as a means of regulating body temperature.
  - The thermoregulatory center in the hypothalamus regulates the core body temperature, not the surface temperature.
- This center integrates input from cold and warm ***thermal receptors*** located throughout the body and generates output responses that conserve body heat or increase its dissipation = ***thermostatic set point.***
  - When body temperature begins to rise above the normal range, heat-dissipating behaviors are initiated;
  - When the temperature falls below the normal range, heat production is increased;
- A core temperature greater than 41°C or less than 34°C usually indicates that the body's ability to thermoregulate is impaired.

Body Temperature Regulation - Heat Gain

- Mechanism involved in regulation:
  - Vasoconstriction of the superficial blood vessels - confines blood flow to the inner core of the body;
  - Contraction of the pilomotor muscles that surround the hairs on the skin - reduces the heat loss surface of the skin;
  - Assumption of the huddle position with the extremities held close to the body - reduces the area for heat loss;
  - Shivering - increases heat production by the muscles. It is initiated by impulses from the hypothalamus;
  - Increased production of epinephrine - increases the heat production associated with metabolism;
  - Increased production of thyroid hormone - is a long-term mechanism that increases metabolism and heat production.

Body Temperature Regulation - Heat Loss

- Mechanism involved in regulation:
  - Dilatation of the superficial blood vessels - delivers blood containing core heat to the periphery where it is dissipated through radiation, conduction, and convection;
    - There are numerous *arteriovenous (AV) shunts* under the skin surface that allow blood to move directly from the arterial to the venous system.
    - When the shunts are open, body heat is freely dissipated to the skin and surrounding environment;
    - When the shunts are closed, heat is retained in the body.
    - The blood flow in the AV shunts is controlled almost exclusively by the sympathetic nervous system in response to changes in core temperature and environmental temperature.
  - Sweating - increases heat loss through evaporation.

Radiation

- Radiation involves the transfer of heat through the air or a vacuum.
- Heat from the sun is carried by radiation. The human body radiates heat in all directions.
- The ability to dissipate body heat by radiation depends on the temperature of the environment. Environmental temperature must be less than that of the body for heat loss to occur.

Conduction

- Conduction involves the direct transfer of heat from one molecule to another.
- Blood carries, or conducts, heat from the inner core of the body to the skin surface.
- The conduction of heat to the body's surface is influenced by blood volume.
  - In hot weather, the body compensates by increasing blood volume as a means of dissipating heat.
  - Exposure to cold produces a cold diuresis and a reduction in blood volume as a means of controlling the transfer of heat to the body's surface.

Fever

- Fever, or ***pyrexia***, describes an elevation in body temperature that is caused by a cytokine-induced upward displacement of the set point of the hypothalamic thermoregulatory center.
- Fevers that are regulated by the hypothalamus usually do not rise above 41˚C - safety mechanism.
- Fever can be caused by a number of microorganisms and substances that are collectively called ***pyrogens*** **(**many proteins, breakdown products of proteins, lipopolysaccharide toxins released from bacterial cell membranes, etc.).
  - Some pyrogens can act directly and immediately on the hypothalamic thermoregulatory center to increase its set point.
  - Other pyrogens, sometimes called *exogenous pyrogens*, act indirectly and may require several hours to produce their effect.

Causes of fever

- Central type fever= ***neurogenic fever***
- Non – central type fever:
  - Infectious disorders
  - Noninfectious disorders:
    - Myocardial infarction
    - Pulmonary emboli
    - Neoplasms (e.g. malignant cells in leukemia, Hodgkin's disease produce pyrogens)
    - Trauma
    - Surgery

Neurogenic fever

- It usually is caused by damage to the hypothalamus caused by:
  - central nervous system trauma;
  - intracerebral bleeding;
  - an increase in intracranial pressure
  - drugs (e.g. anesthetics)
- Neurogenic fevers are characterized by a high temperature that is ***resistant to antipyretic therapy*** and is ***not associated with sweating.***

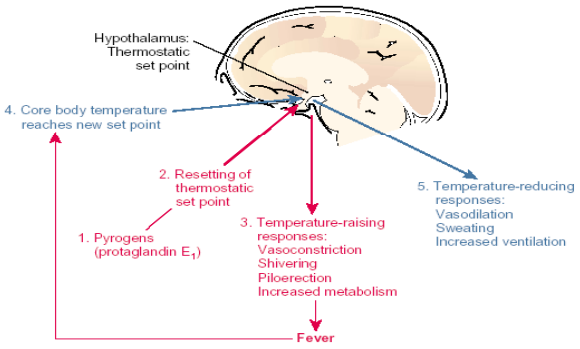
Mechanisms of fever

- (1) release of endogenous pyrogen from inflammatory cells;
- (2) resetting of hypothalamus thermostatic set point to a higher level (prodrome);
- (3) generation of hypothalamic mediated responses that raise body temperature (chill);
- (4) development of fever with elevation of body to new thermostatic set point;
- (5) production of temperature lowering responses (flush and defervescence) and return of body temperature to a lower level.

Mechanisms of fever

- Exogenous pyrogens induce host cells, such as blood leukocytes and tissue macrophages, to produce fever-producing mediators called *endogenous pyrogens* (*e.g.*, interleukin-1).
  - The endogenous pyrogens mediate a number of other responses. For example, interleukin-1 is an inflammatory mediator that produces other signs of inflammation, such as leukocytosis, anorexia, and malaise.
- The phagocytosis of bacteria and breakdown products of bacteria that are present in the blood lead to the release of endogenous pyrogens into the circulation.
- The endogenous pyrogens are increase the set point of the hypothalamic thermoregulatory center through the action of prostaglandin E2.
- In response to the sudden increase in set point, the hypothalamus initiates heat production behaviors (shivering and vasoconstriction) that increase the core body temperature to the new set point, and fever is established.

Mechanisms of fever



The effects of fever

- It enhance immune function;
  - Increases motility and activity of the white blood cells;
  - Stimulates the interferon production and activation of T cells;
- Inhibits growth of some microbial agents:
  - Many of the microbial agents that cause infection grow best at normal body temperatures, and their growth is inhibited by temperatures in the fever range (the rhinoviruses responsible for the common cold are cultured best at 33°C);
- Dehydration occurs because of sweating.

The effects of fever

- Metabolic effects:
  - Increased need for oxygen;
    - Increases the heart rate
    - Increases the respiration rate
  - Increased use of body proteins as an energy source;
  - During fever the body switches from using glucose (an excellent medium for bacterial growth) to metabolism based on protein and fat breakdown;
  - With prolonged fever, there is increased breakdown of endogenous fat stores;
  - If fat breakdown is rapid, metabolic acidosis may result.

Types of fever

- Intermittent
  - Temperature returns to normal at least once every 24 hours;
  - It is commonly associated with conditions such as gram - negative / positive sepsis, abscesses, and acute bacterial endocarditis;
- Remittent
  - Temperature does not return to normal and varies a few degrees in either direction;
  - It is associated with viral upper respiratory tract, legionella, and mycoplasma infections;
- Sustained or continuous
  - Temperature remains above normal with minimal variations;
  - It is seen in persons with drug fever;
- Relapsing
  - There is one or more episodes of fever, each as long as several days, with one or more days of normal temperature between episodes;
  - It may be caused by a variety of infectious diseases, including tuberculosis, fungal infections, Lyme disease, and malaria.

Manifestations of fever

- There are 4 successive stages - not all persons proceed through the four stages of fever development:
  - 1. Prodrome
    - nonspecific complaints, such as mild headache and fatigue, general malaise, and fleeting aches and pains;
  - 2. Temperature rises
    - generalized shaking with chills and feeling of being cold;
    - vasoconstriction and piloerection usually precede the onset of shivering;
    - skin is pale;
    - when the shivering has caused the body temperature to reach the new set point of the temperature control center, the shivering ceases, and a sensation of warmth develops.
  - 3. Flush
    - cutaneous vasodilation occurs and the skin becomes warm and flushed;
  - 4. Defervescence
    - the initiation of sweating.

Fever of unknown origin

- It is defined as a temperature elevation of 38.3°C or higher that is present for 3 weeks or longer.
- Among the causes are:
  - malignancies (lymphomas, metastases to the liver and central nervous system);
  - infections such as human immunodeficiency virus or tuberculosis, or abscessed infections;
  - drug fever;
  - cirrhosis of the liver.

Principles of treatment

- Because fever is a disease symptom, its manifestation suggests the need for ***treatment of the primary cause.***
- Actions:
  - modifications of the external environment intended to increase heat transfer from the internal to the external environment;
  - support of the hypermetabolic state that accompanies fever;
  - protection of vulnerable body organs and systems;
  - treatment of the infection or condition causing the fever.

Antipyretic drugs

- Antipyretic drugs, such as aspirin and acetaminophen, often are used to alleviate the discomforts of fever and protect vulnerable organs, such as the brain, from extreme elevations in body temperature.
- These drugs act by resetting the hypothalamic temperature control center to a lower level, presumably by blocking the activity of cyclooxygenase, an enzyme that is required for the conversion of arachidonic acid to prostaglandin E2.

Fever in children

- The mechanisms for controlling temperature are not well developed in the infant.
- In infants younger than 3 months, a mild elevation in temperature (*i.e.,* rectal temperature of 38°C) can indicate serious infection.
- Both minor and life-threatening infections are common in the infant to 3-year age group.
- The most common causes of fever in children are minor or more serious infections of the respiratory system, urinary system, gastrointestinal tract, or central nervous system. Occult bacteremia and meningitis also occur in this age group and should be excluded as diagnoses.

Manifestations

- Fever in infants and children can be classified as low risk or high risk, depending on the probability of the infection progressing to bacteremia or meningitis.
- Signs of toxicity (and high risk) include lethargy, poor feeding, hypoventilation, poor tissue oxygenation, and cyanosis.
- Blood and urine cultures, chest radiographs, and lumbar puncture usually are done in high-risk infants and children to determine the cause of fever.
- Febrile seizures can occur in some children.

Fever in the elderly

- In the elderly, even slight elevations in temperature may indicate serious infection or disease. This is because the elderly often have a lower baseline temperature.
- Normal body temperature and the circadian pattern of temperature variation often are altered in the elderly.
- The absence of fever may delay diagnosis.
- Unexplained changes in functional capacity, worsening of mental status, weakness and fatigue, and weight loss are signs of infection in the elderly.
- Confusion and delirium may follow moderate elevations in temperature.

Mechanisms

- Disturbance in sensing of temperature by the thermoregulatory center in the hypothalamus;
- Alterations in release of endogenous pyrogens;
- The failure to elicit responses such as vasoconstriction of skin vessels, increased heat production, and shivering that increase body temperature during a febrile response.
- Because of the increasingly poor oxygen uptake by the aging lung, pulmonary function may prove to be a limiting factor in the hypermetabolism that accompanies fever in older persons.
  - Confusion, incoordination, and agitation commonly reflect cerebral hypoxemia.

Neurogenic fever文獻回顧

- NF在臨床碰到的機會不高，但文獻報告中在頭部外傷(TBI)的存活者中發生率為4-37%
- 原因下視丘受傷，造成hypothalamic set point破壞所致
- 由屍體解剖的研究，TBI病人42.5%有下視丘病變，但沒有資料說明存活的TBI中有多少下視丘病變

Neurogenic fever：clinical

- relatively bradycardic
- absence of perspiration
- plateau-like temperature curve (no diurnal variation) that persists for days to weeks
- temperature being characteristically very high, and resistant to antipyretic medications
- may be associated with the presence of prolonged unawareness or coma state and diabetes insipidus
- exclude other diagnosis

Neurogenic fever：clinical consequence

- start of rehabilitation is often delayed
- increased local cytokine activity, increased infarct size
- increase intracranial blood volume, increase intracranial hypertension
- reduces compliance of brain
- Hyperthermia
  - high enough (>43°C) : neuronal injury in normal brain
  - lengthy periods of moderate (40°C) hyperthermia : alter brain structure and functioning
- in rodent models, hyperthermia significantly increased mortality and cellular damage.
- every 1°C rise in BT, 13% increase in the metabolic rate.

Neurogenic fever：treatment

- external cooling methods
- bromocriptine, amantadine, dantrolene, and propranolol
  - has significant potential side effects (for example, hypotension, gastrointestinal bleeding)
  - routine use without a relatively firm diagnosis of NF is not prudent
  - development of a predictive model to aid in the diagnosis of NF would be a valuable addition

Neurogenic fever after traumatic brain injury: an epidemiological study

J Neurol Neurosurg Psychiatry 2003;74:614-619

Objectives

- To determine the incidence of neurogenic fever (NF) in a population of patients in the acute phase following severe traumatic brain injury (TBI); to identify factors associated with the development of NF following severe TBI in adults

Methods

- Charts of patients admitted from 1996 to 1999 with severe TBI at a large, urban mid-Atlantic teaching hospital were retrospectively evaluated based on diagnostic criteria for each episode of hyperthermia to determine the diagnosis of NF. Data were collected regarding mechanism and area of injury, severity of injury, and demographic factors to determine potential predictors of NF

Results

- The incidence of NF in this population was 11.8% (9/76)
- Diffuse axonal injury (DAI) (OR 9.06, 95% CI 0.99 to 82.7) and frontal lobe injury of any type (OR 6.68, 95% CI 1.1 to 39.3) are independently predictive of an increased risk of development of NF following severe TBI. The presence of a skull fracture and lower initial Glasgow Coma Score (GCS) were individual predictors of development of NF, but did not contribute to the final model

Summary of Wald logistic regression analysis for variables predicting risk of development of neurogenic fever following severe traumatic brain injury (n=76)

Variable	Regression coefficient	SE	p value	Odds ratio (OR)	95% CI for OR
Diffuse axonal injury	2.2038	1.129	0.0508	9.0592	0.9921 to 82.7234
Frontal lobe injury	1.8998	0.9037	0.0355	6.6843	1.1371 to 39.2936

Attributes not independently predictive

- Glasgow Coma Score
- Skull fracture

結論

- 臨床醫師對於發生在嚴重頭部外傷病人身上的不明熱，必須檢視是否有DAI或frontal injury，若有任何一個因子存在必須將NF列入鑑別診斷