OUTCOME OF FEBRILE CASES ADMITTED IN A SPECIALIZED HOSPITAL IN RELATION TO THE DIAGNOSTIC AND THERAPEUTIC WORK UP

Thesis for the partial fulfilment of M.Sc degree in Endemic Medicine, Hepatology and Gastroenterology

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List of Tables

table	Title of table	Page
1	CSF findings in different forms of meningitis (diagnosis of meningitis)	60
2	Sheet used for data collection	75
3	Occupation of the studied patients	77
4	Provisional Diagnosis of The studied patients	79
5	Final diagnosis of the seven most common diseases	79
6	Mean age among the commonly reported febrile diseases	81
7	Sex distribution of common febrile diseases	82
8	Occupation of patients according to their final diagnosis	83
9	Residence of patients according to their final diagnosis	84
10	Findings in acute hepatitis cases	85
11	Brucella agglutination test results in brucellosis patients	86
12	Findings in pneumonia patients	86
13	Outcome of pneumonia cases by treatment	87
14	Test results of typhoid fever patients	88
15	Outcome of typhoid fever patients by their treatment	88
16	Outcome of meningitis patients according to the treatment	89
17	modified John's criteria in patients diagnosed with rheumatic fever	89
18	Hospital stay (in days) of commonly reported febrile diseases	90
19	Mortality among all febrile patients	91

List of figures

figure	Title of figure	page
1	Types of fever	5
2	Pathophysiology of fever	8
3	Diagnosis of hepatitis A	18
4	Meninges of the central nervous system	52
5	Resdience of the study patients	78
6	Most frequently reported final diagnosis in our study	80
7	Discharge status of all studied patients	81
8	Outcome of reported febrile illnesses	85

List of abbreviations

AFI	Acute febrile illness
NS	Non significant
SD	Standard deviation
FUO	Fever of unknown origen
PG	Prostaglandin
LPS	Lipopolysaccharide
IL	Interleukin
LBS	Lipopolysaccharide-binding protein
COX	Cyclooxygenase
POA	Pre optic area
Eif	eukaryote initiating factor
CDC	Centers for Disease Control
TLR	toll-like receptor
CFTR	Cystic fibrosis transmembrane conductance receotor
PCV	pneumococcal conjugate vaccine
NARST	nalidixic acid–resistant salmonella typhi
ALS	amyotrophic lateral sclerosis

CONTENTS

Acknowledgment.....I

List of tables II

List of figures.....III

List of abbreviations..... IV

-Introduction 1

-Aim of the work 3

-Review of literature

- Chapter 1 (Fever) 4

-Chapter 2 (Major infectious diseases in Egypt)

1- HA V 14

2- Brucellosis 22

3- typhoid fever 31

4- pneumonia 42

5- meningitis 52

6- T.B 72

- Patients and methods 74

- Results 78

- Discussion 93

- Summary and conclusion.....107

-Recommendations.....109

- References 110

-Arabic summary 148

Chapter-1

Fever

Fever (also known as pyrexia) is one of the most common medical signs and is characterized by an elevation of body temperature above the normal range of 36.5–37.5 °C (98–100 °F) due to an increase in the temperature regulatory set-point. This increase in set-point triggers increased muscle tone and shivering ***(Axelrod and Diringer, 2008)***

A morning temperature of >37.2°C (>98.9°F) or an evening temperature of >37.7°C (>99.9°F) is considered as fever while the normal daily temperature variation is typically 0.5°C (0.9°F) ***(Harrison's principles of internal medicine. 18th ed.)***

Fever differs from uncontrolled hyperthermia, in that hyperthermia is an increase in body temperature over the body's thermoregulatory set-point, due to excessive heat production and/or insufficient thermoregulation ***(Karakitsos and Karabinis, 2008).***

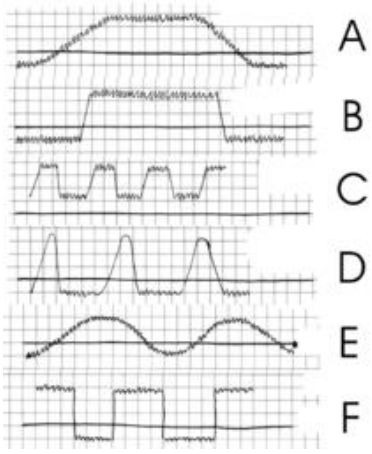
A wide range for normal temperatures has been found ***(Laupland, 2009).*** Fever is generally agreed to be present if the elevated temperature is caused by a raised set point and:

- Temperature in the anus (rectum/rectal) is at or over 37.5–38.3 °C (99.5–100.9 °F) ***(Axelrod and Diringer, 2008 and Laupland, 2009).***
- Temperature in the mouth (oral) is at or over 37.7 °C (99.9 °F) ***(Barone, 2009).***
- Temperature under the arm (axillary) or in the ear (otic) is at or over 37.2 °C (99.0 °F)

In healthy adult men and women, the range of normal, healthy temperatures for oral temperature is 33.2–38.2 °C (91.8–100.8 °F), for rectal it is 34.4–37.8 °C (93.9–100 °F), for tympanic membrane (the ear drum) it is 35.4–37.8 °C (95.7–100 °F), and for axillary (the armpit) it is 35.5–37.0 °C (95.9–98.6 °F) ***(Harrison's principles of internal medicine. 2011).***

Types

Figure (1): Types of fever



Performance of the various types of fever

a) Continuous fever
b) Fever continues to abrupt onset and remission
c) Remittent fever
d) Intermittent fever
e) Undulant fever
f) Relapsing fever ***(Schulman et al., 2010) and (Rantala et al., 2010)***

The pattern of temperature changes may occasionally hint at the diagnosis:

- Continuous fever: Temperature remains above normal throughout the day and does not fluctuate more than 1 °C in 24 hours, e.g. lobar pneumonia,

typhoid, urinary tract infection, brucellosis, or typhus. Typhoid fever may show a specific fever pattern (Wunderlich curve of typhoid fever), with a slow stepwise increase and a high plateau. (Drops due to fever-reducing drugs are excluded) ***(U.S. National Library of Medicine, 2010)***.

- Intermittent fever: The temperature elevation is present only for a certain period, later cycling back to normal, e.g. malaria, kala-azar, pyaemia, orseptic emia. It includes the following types:
  - Quotidian fever, with a periodicity of 24 hours, typical of Plasmodium falciparum or Plasmodium malaria
  - Tertian fever (48 hour periodicity), typical of Plasmodium vivax or Plasmodium ovale malaria
  - Quartan fever (72 hour periodicity), typical of Plasmodium malariae malaria ***(U.S. National Library of Medicine, 2010)***.
- Remittent fever: Temperature remains above normal throughout the day and fluctuates more than 1 °C in 24 hours, e.g., infective endocarditis.
- Pel-Ebstein fever: A specific kind of fever associated with Hodgkin's lymphoma, being high for one week and low for the next week and so on. However, there is some debate as to whether this pattern truly exists.
  - A neutropenic fever, also called febrile neutropenia, is a fever in the absence of normal immune system function. Because of the lack of infection-fighting neutrophils, a bacterial infection can spread rapidly; this fever is, therefore, usually considered to require urgent medical attention. This kind of fever is more commonly seen in people receiving immune-suppressing chemotherapy than in apparently healthy people ***(Loscalzo et al., 2008, Fischler et al., 2009 and U.S. National Library of Medicine, 2010)***.

Hyperpyrexia:

Hyperpyrexia is a fever with an extreme elevation of body temperature greater than or equal to 41.5 °C (106.7 °F). Such a high temperature is considered a medical emergency as it may indicate a serious underlying condition or lead to significant side effects ***(Stephen et al., 2012)***.

Infections are the most common cause of fevers, however as the temperature rises other causes become more common Infections commonly associated with hyperpyrexia include: roseola, rubeola and enteroviral infections. Immediate aggressive cooling to less than 38.9 °C (102.0 °F) has been found to improve survival. Hyperpyrexia differs from hyperthermia in that in hyperpyrexia the body's temperature regulation mechanism sets the body temperature above the normal temperature, then generates heat to achieve this temperature, while in hyperthermia the body temperature rises above its set point due to an outside source ***(Harrison's Principles of Internal Medicine 17 ed.).***

Hyperthermia:

Hyperthermia is an example of a high temperature that occurs from a number of causes including heatstroke, neuroleptic malignant syndrome, malignant hyperthermia, stimulants such as amphetamines and cocaine, idiosyncratic drug reactions, and serotonin syndrome. **:** ***(Walter and Boron. 2003)***.

Signs and symptoms:

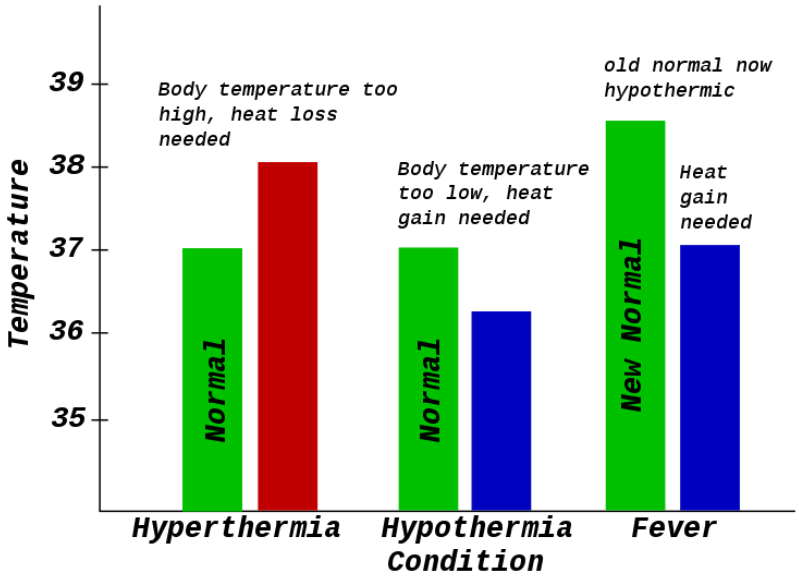
A fever is usually accompanied by sickness behavior, which consists of lethargy, depression, anorexia, sleepiness, hyperalgesia, and the inability to concentrate ***(Schulman CI.et al., 2005)***.

Differential diagnosis:

Fever is a common symptom of many medical conditions:

- Infectious disease, e.g., Brucelosis, typhoid fever, meningitis, acute infective hepatitis, Rheumatic fever, Pneumonia.
- Various skin inflammations, e.g., boils, or abscess
- Immunological diseases, e.g., systemic lupus erythematosus, sarcoidosis, inflammatory bowel diseases, Kawasaki disease.
- Tissue destruction, which can occur in hemolysis, surgery, infarction, crush syndrome, rhabdomyolysis, cerebral hemorrhage, etc.
- Reaction to incompatible blood products
- Cancers, most commonly kidney cancer, leukemia and lymphomas
- Metabolic disorders, e.g., gout or porphyria
- Thromboembolic processes, e.g., pulmonary embolism or deep venous thrombosis ***(Schulman et al.,2005).***

Pathophysiology: Figure (2):



Hyperthermia: Characterized on the left. Normal body temperature (thermoregulatory set point) is shown in green, while the hyperthermic temperature is shown in red. As can be seen, hyperthermia can be conceptualized as an increase above the thermoregulatory set point ***(Byrne and J.H, 2013 and Marx and John 2011).***

Hypothermia: Characterized in the center: Normal body temperature is shown in green, while the hypothermic temperature is shown in blue. As can be seen, hypothermia can be conceptualized as a decrease below the thermoregulatory set point ***(Karakitsos and Karabinis, 2010).***

Fever: Characterized on the right: Normal body temperature is shown in green. It reads "New Normal" because the thermoregulatory set point has risen. This has caused what was the normal body temperature (in blue) to be considered hypothermic ***(Axelrod and Diringer, 2008)***.

Temperature is ultimately regulated in the hypothalamus. A trigger of the fever, called a pyrogen, causes a release of prostaglandin E2 (PGE2). PGE2 then in turn acts on the hypothalamus, which generates a systemic response back to the rest of the body, causing heat-creating effects to match a new temperature level. In many respects, the hypothalamus works like a thermostat. When the set point is raised, the body increases its temperature through both active generation of heat and retaining heat. Vasoconstriction both reduces heat loss through the skin and causes the person to feel cold. If these measures are insufficient to make the blood temperature in the brain match the new setting in the hypothalamus, then shivering begins in order to use muscle movements to produce more heat. When the fever stops, and the hypothalamic setting is set lower; the reverse of these processes (vasodilation, end of shivering and nonshivering heat production) and sweating are used to cool the body to the new, lower setting ***(Laupland, 2009).***

This contrasts with hyperthermia, in which the normal setting remains, and the body overheats through undesirable retention of excess heat or over-production of heat. Hyperthermia is usually the result of an excessively hot environment (heat stroke) or an adverse reaction to drugs. Fever can be differentiated from hyperthermia by the circumstances surrounding it and its response to anti-pyretic medications ***(Rantala et al., 2009)***.

Pyrogens:

A pyrogen is a substance that induces fever. These can be either internal (endogenous) or external (exogenous) to the body. The bacterial substance lipopolysaccharide (LPS), the cell wall of some bacteria, is an example of an exogenous pyrogen. Pyrogenicity can vary: In extreme examples, some bacterial pyrogens known as superantigens can cause rapid and dangerous fevers. Depyrogenation may be achieved through filtration, distillation, chromatography or inactivation ***(Manson's Tropical Diseases, 2011)***.

Endogenous pyrogens:

In essence, all endogenous pyrogens are cytokines, molecules that are a part of the innate immune system. They are produced by phagocytic cells and cause the increase in the thermoregulatory set point in the hypothalamus. Major endogenous pyrogens are interleukin 1 (α and β), interleukin 6 (IL-6). Minor endogenous pyrogens include interleukin-8, tumor necrosis factor-â, macrophage inflammatory protein-α and macrophage inflammatory protein-β as well as interferon-á, interferon-â, and interferon-ã.[1] Tumor necrosis factor-á also acts as a pyrogen. It is mediated by interleukin 1 (IL-1) release.

These cytokine factors are released into general circulation, where they migrate to the circumventricular organs of the brain due to easier absorption caused by the blood–brain barrier's reduced filtration action there. The cytokine factors then bind with endothelial receptors on vessel walls, or interact with

local microglial cells. When these cytokine factors bind, the arachidonic acid pathway is then activated ***(Manson's Tropical Diseases, 2011).***

Exogenous pyrogens:

One model for the mechanism of fever caused by exogenous pyrogens includes LPS, which is a cell wall component of gram-negative bacteria. An immunological protein called lipopolysaccharide-binding protein (LBP) binds to LPS. The LBP–LPS complex then binds to the CD14 receptor of a nearby macrophage. This binding results in the synthesis and release of various endogenous cytokine factors, such as interleukin 1 (IL-1), interleukin 6 (IL-6), and the tumor necrosis factor-alpha. In other words, exogenous factors cause release of endogenous factors, which, in turn, activate the arachidonic acid pathway ***(Manson's Tropical Diseases, 2011).***

PGE2 release:

PGE2 release comes from the arachidonic acid pathway. This pathway (as it relates to fever), is mediated by the enzymes phospholipase A2 (PLA2), cyclooxygenase-2 (COX-2), and prostaglandin E2 synthase. These enzymes ultimately mediate the synthesis and release of PGE2.

PGE2 is the ultimate mediator of the febrile response. The set point temperature of the body will remain elevated until PGE2 is no longer present. PGE2 acts on neurons in the preoptic area (POA) through the prostaglandin E receptor 3 (EP3). EP3-expressing neurons in the POA innervate the dorsomedial hypothalamus (DMH), the rostral raphe pallidus nucleus in the medulla oblongata (rRPa) and the paraventricular nucleus (PVN) of the hypothalamus. Fever signals sent to the DMH and rRPa lead to stimulation of the sympathetic output system, decrease heat loss from the body surface. It is presumed that the innervation from the POA to the PVN mediates the

neuroendocrine effects of fever through the pathway involving pituitary gland and various endocrine organs ***(Manson's Tropical Diseases, 2011)***.

Hypothalamus:

The brain ultimately orchestrates heat effector mechanisms via the autonomic nervous system. These may be:

- Increased heat production by increased muscle tone, shivering and hormones like epinephrine
- Prevention of heat loss, such as vasoconstriction.

In infants, the autonomic nervous system may also activate brown adipose tissue to produce heat (non-exercise-associated thermogenesis, also known as non-shivering thermogenesis). Increased heart rate and vasoconstriction contribute to increased blood pressure in fever ***(Lewis.et al., 2007 and U.S National Library of Medicine, 2009).***

Usefulness:

There are arguments for and against the usefulness of fever, and the issue is controversial. There are studies using warm-blooded vertebrates and humans in vivo, with some suggesting that they recover more rapidly from infections or critical illness due to fever. Finnish study suggested reduced mortality in bacterial infections when fever was present ***(Craven and Hirnle, 2011).***

In theory, fever can aid in host defense. There are certainly some important immunological reactions that are sped up by temperature and some pathogens with strict temperature preferences could be hindered ***(Lewis et al, 2009).***

Research has demonstrated that fever assists the healing process in several important ways:

- Increased mobility of leukocytes