Fever of Unknown Origin in Childhood

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KEYWORDS

• Fever of unknown origin • Diagnostic evaluation • Cancer • Infection • Inflammation

KEY POINTS

- Evaluation of fever of unknown origin (FUO) in children requires documentation of fever in the medical setting and repetitive reassessment of history and physical evaluation.
- Most childhood FUOs have an infectious cause, but in some cases, underlying neoplastic, rheumatologic, or inflammatory conditions are diagnosed.
- Diagnostic evaluation of childhood FUO should be performed in a staged manner, leaving expensive imaging and invasive procedures for last.
- Molecular genetic techniques are playing an increasingly important role in the diagnosis of childhood FUO.

INTRODUCTION

Elevation of body temperature beyond the normal range is characteristic of a wide variety of abnormal conditions in adults and children. Body temperature is maintained within a normal range through a complex interactive array of physiologic processes. Derangement of these processes, frequently induced by a wide variety of infectious agents, leads to elevation in body temperature beyond the normal physiologic range, called "fever." In addition to infectious agents, a variety of autoimmune, metabolic, oncologic, neurologic, developmental, and inflammatory conditions also produces fever. Diagnostic assessment of a persistently febrile child may become daunting when the child's clinical and laboratory findings do not match one of the common causes of febrile disease. Evaluation of such children, especially when the child manifests persistent or progressive illness, calls upon the physician to construct a comprehensive, sometimes unfamiliar, differential diagnosis. A persistently febrile child, lacking an obvious source of fever, can be one of the most perplexing and worrisome puzzles encountered in clinical pediatrics and can be highly stressful for the child, his parents, and his physician.

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TEMPERATURE CONTROL AND HUMAN DISEASE

Elevation of body temperature beyond the normal range is an ancient weapon in the armamentarium of complex multicellular organisms against microbial invasion and other disease processes. Despite a high metabolic cost, fever, as a response to an invasive microbial attack, has been retained as a basic host defense mechanism through hundreds of millions of years of natural selection. Its preservation speaks to its fundamental importance in host defense.[1,2]

Endothermal ("warm blooded") vertebrates establish their own internally maintained temperature-controlled environments via a variety of physiologic and behavioral mechanisms.[1,2] Endogenous pyrogenic cellular cytokines released in response to an inflammatory process have the capacity of advancing upward the central thermoregulatory "set point." Constant monitoring of blood temperature by thermosensitive cells within in the anterior hypothalamus serves as a biologic thermostat. Body temperature is regulated through a centrally controlled efferent system of physiologic responses to a negative disparity (blood temperature below set point) between blood temperature and central set point that includes increased heat production due to motor activity (shivering) and brown fat catabolism, augmented by increased heat retention secondary to peripheral vasoconstriction.[1–3] In the presence of a positive disparity between blood temperature and set point, body temperature is reduced through vasodilation and perspiration.[1–3] Behavioral activities, such as adjusting room temperature, clothing selection, body positioning, and ingestion of warm or cool liquids, play a secondary role in temperature control.

Currently, the mammalian thermoregulatory system remains a black box from a molecular point viewpoint. However, it is clear that tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), in conjunction with interleukin-1Aβ (IL-1Aβ) are major contributors in the upregulation of the central nervous system's thermoregulatory set point.[4,5] No single cytokine seems to efficiently increase the central set point. Both IL-1 and IL-6 seem to be required for greatest effectiveness, perhaps in conjunction with other agents.[4,5] The major effect of IL-1 and IL-6 in thermoregulation is on the elaboration of prostaglandin E in the cyclooxygenase-2 and STAT3 metabolic pathways.[6] Inhibition of prostaglandin E synthesis is the mechanism of action through which most antipyretics, including acetaminophen and nonsteroidal anti-inflammatories (NSAIDs), reduce the central set point.[7]

Fever is an important sign in alerting parents and physicians that the child is experiencing an infection or other significant cause of upregulation of the hypothalamic set point. Parents, and to a lesser degree, professional caregivers, are often concerned about the potential harm that fever may have upon the health of the febrile child. Such concern can reach a crescendo, dubbed "fever phobia," describing the exaggerated fear about the height to which fever can spiral in an otherwise physiologically intact child.[8]

Ironically, the most available evidence leads to the conclusion that elevated body temperature is a major host defense mechanism, evolved and conserved through the eons by natural selection. Fever appears to play a nonspecific, but significant role in protection of the host against microbial invasion. Studies have repeatedly demonstrated that critically ill patients in intensive care units, whose body temperatures are aggressively maintained at normothermic levels by suppressing fever through pharmacologic or external environmental means, are significantly more likely to expire than matched patients whose body temperatures are allowed to increase freely.[9,10] At least one study had to be terminated for ethical concerns because death rates in the fever-controlled group so significantly exceeded that of the unsuppressed fever group.[10]