

APPROACH TO FEVER OF UNKNOWN ORIGIN IN CHILDREN

Adriana ONDRUŠOVÁ

Faculty of Healthcare, Alexander Dubček University of Trenčín, Študentská 2, 911 50 Trenčín, Slovak Republic

Abstract

Fever is a common problem for children and outpatient general practitioner febrile children with a third of examinations. Febrile illness of children can be divided into categories fever with localized signs of where the diagnosis is established based on history and physical examination; and fever without source; fever without adequate explanation despite a detailed history, physical examination and laboratory screening. Fever of unknown origin (FUO) in children is defined as a fever higher than 38.3°C, at least 14 days, at which it is diagnosed, despite a thorough medical history, physical examination and laboratory screening in the clinic or family doctor for at least a week-long hospitalization. In most cases, the responsible FUO infection, then systemic diseases, cancers are less common. The basis for clarifying the causes is the medical history, physical examination and laboratory screening. In fever of unknown origin empirical antibiotic treatment or anti-inflammatory treatment is not recommended. However, in many cases, notwithstanding realized examinations fail to establish a definitive diagnosis and fever subsides over time and children are in good clinical condition

Key words: fever of unknown origin, children, diagnosis

1 Introduction

Under physiological conditions, the body temperature of healthy individuals maintain a small temperature range, notwithstanding temperature changes, and physical activity. The normal body temperature is considered the temperature of the body to 37 and the aim of the thermoregulatory mechanisms of the body to maintain the temperature within this range. The body temperature varies during the day, with a peak in the afternoon. Temperature measured in the rectum with a value of more than 38°C is generally considered to be increased, particularly if accompanied by other symptoms.

Character temperatures in children depends on their age and the nature of the disease, e.g. newborns do not have to observe a fever despite severe infections, and they may even be hypothermic. Children under 5 years of age can in turn reacts with an exaggerated fever 40.6°C even on the non-serious viral infections. For older children such fever is unusual, and if fever occurs, usually indicative of serious diseases. According to the nature of the temperature curve cannot distinguish infectious from non-infectious cause.

Febrile disorders could by divided as:

- The fever with localized signs, at which diagnosis can be established based on history and physical examination.
- Fever without source: fever lasting a week or less, without adequate explanation, despite a thorough medical history and physical examination.
- Fever unknown origin: fever greater than 38.3°C; lasting at least 14 days, at which it is diagnosed after the initial screening in the clinic, including medical history, general physical examination and basic laboratory tests, or for at least a week-long hospitalization [1].

2 Fever in children younger than 3 months

Fever of infants is associated with a higher risk of serious bacterial infections compared to older children. While the majority of febrile events in this age group due to a viral infection, there may be a serious bacterial infection, which include:

- Bacteremia (caused by group *B streptococci*, *E. coli*, *L. monocytogenes* in newborns or *Pneumococcus*, *H. influenzae*, *N. meningitidis*, *Salmonella* in older children).
- Urinary tract infection (*E. coli*).
- Pneumonia (*Streptococcus pneumoniae*, group *B streptococci*, *Staphylococcus aureus*).
- Meningitis (*H. influenzae*, *Str. pneumoniae*, *N. meningitis*).
- Gastroenteritis (*Salmonella*, *Shigella*, *E. coli*).
- Osteomyelitis (*St. aureus*, *Streptococcus* gr. B).

All newborns with fever should be hospitalized and should be started empirical antibiotic therapy, which should be adjusted on the base of the results of examinations. Also infant under 3 months with fever should be admitted to hospital when clinical deterioration started.

The children older than one month, with fever, but good-looking, identified without clear focus of infection have a lower risk of infection that they develop severe bacterial infections. (0.8% and 2% bacteremia severe localized infection) [1].

In general, among children at low risk of developing a serious infection may include:

- children older than one month,
- agile, thriving, good looking,
- born in the term,
- without prior antibiotic treatment,
- a leukocyte less than 15 000,
- negative urinalysis,
- normal chest X-ray (refers to children with respiratory symptoms).

These children may be monitored as an outpatient, without empirical antibiotic treatment, but over 72 hours should be checked by pediatrician

3 Fever of unknown origin

A specific disease entity - fever of unknown origin (FUO) has taken an important place in infectology at the very beginning of its defining Petersdorf and Beeson 50 years ago, in the 1961th [2]. Although the original definition has been amended several times, a wide variety of spectrum diseases (including infections, malignancies systemic diseases) as possible causes of FUO has its place in the diagnosis remains. In practice it is appropriate to distinguish between fever of unknown causes and fever without a clear source for several reasons:

- Differential diagnosis and the most common causes of both units are different.
- Children with FWS (fever without source) usually require prompt investigation and assessment of the state, as opposed to children with FUO, where it is not so urgent.
- Children with FUO usually no antibiotic treatment is indicated, which in turn is generally recommended some children with FWS [3].

Many classic case series of FUO in children was published before the availability of sophisticated conventional methods now commonly available [4]. So improving investigation methods and their availability is a big part FUO diagnosed earlier, during disorder [5].

4 Diagnosis

FUO diagnosis usually begins in the office of the pediatrician. Thus, except when the severity of the child's clinical condition requires immediate hospitalization. If tests in the office of the pediatrician not reveal the cause of FUO, hospitalization is an opportunity to re-take a thorough medical history, repeated physical examination, laboratory tests and supplement what is equally important, traceability of the child in the department. Even then, it may happen that

the parents of adding new data, or a history of new symptoms appear, which were not clear in the initial phase of the disease. For the correct diagnosis it is important to indicate the correct tests.

4.1 History

Firstly, it is extremely important to take a detailed medical history. It is understood that the majority of children not cause abnormal cause, rather to the atypical course of common diseases [6]. When taking the medical history should be addressed to:

- Duration, fever value, characteristics (parents may confuse normal body temperature variations - e.g. fever after exercise in the afternoon).
- How the temperature was measured. By touch? Thermometer? If a thermometer, which kind was used? Rectal temperature is the most accurate. In older children temperature measured orally is right as well.
- Whether fever was confirmed by someone else (other than parents).
- How does the child look during fever? The presence of other symptoms. If the child is calm, without any generalized symptoms, may be an artificially induced fever.
- As the temperature response to a given antipyretics or other symptoms (headaches, muscle pain, nausea) persist even after resolution of fever. If they persist, it is worrying. If the fever does not respond to NSAIDs (nonsteroidal anti-inflammatory drugs), given antipyretics, FUO may be non-inflammatory etiology (dysautonomia, ectodermal dysplasia, thalamus failure, diabetes insipidus [6]).
- Whether a fever accompanied by sweating. Patients with fever, sweating and heat intolerance may have hyperthyroidism. If a fever accompanied by intolerance of heat without sweating, it may be an ectodermal dysplasia.

4.1.1 Characteristics of fever

Characteristic temperature curve the temperature and duration in general usually do not help to decide the specific diagnoses, but in some cases (e.g. malaria) may be beneficial temperature monitoring.

Types of fever:

- Intermittent fever - fever, significant fluctuations during the day (by more than 1°C) and transient with normal values (Sepsis, tuberculosis, lymphoma, juvenile idiopathic arthritis JIA).
- Remittent fever - significant fluctuations in temperature elevations during the day (more than 1°C) without a decrease in the normal range. It can be confused with intermittent administration of antipyretics (Viral and bacterial infections, endocarditis, sarcoidosis, lymphoma, atrial myxoma).
- Continuous fever - high fever lasting for days and weeks (Typhoid fever, typhus, brucellosis, pneumonia, sepsis).
- Biphasic fever - a temperature increase within 1-2 days, then decrease and increase again (Viral infections.)
- Fever undulans - not high, with slowly increasing, lasting several weeks with afebrile intervals (Morbus Hodgkin, Cancer, autoimmune disease).
- Recurrent fever - more days lasting high fever recurring at regular intervals, lasting more than six months (Metabolic disorders, CNS regulation called. Periodic disease - cyclic neutropenia syndrome hyperimmunoglobulinemia D, immunodeficiencies) [7].

Related problems:

- redness of the eyes - which can resolve spontaneously - Kawasaki disease,

- runny nose – sinusitis,
- recurring pharyngitis with ulceration - periodic fever with aphthous stomatitis, pharyngitis,
- gastrointestinal disorders - salmonellosis, intra-abdominal abscess, inflammatory bowel disease,
- pain in the limbs or bones - leukemia, osteomyelitis, infantile cortical hyperostosis.

Exposure:

- Contact with infectious sick people.
- Contact with the animal (domestic, wild living).
- Travel history going back to the perinatal period. Many diseases become apparent until many years after exposure - *histoplasmosis, coccidioidomycosis, blastomycosis*, malaria. It should contain:
 - the place of residence,
 - prophylaxis,
 - preventive measure (food, water),
 - various artifacts, merchandise, rocks, soils from different geological regions - brought from roads and placed in the home.
- Tick bite (Lyme disease, tick-borne encephalitis, tularemia, ehrlichiosis).
- Eating raw meat, game meat, shellfish (brucellosis, toxoplasmosis, tularemia, hepatitis).
- Pica syndrome (toxocariasis, toxoplasmosis).
- Taking medicines or supplements.
- Surgery in history (intra-abdominal abscess).

4.2 Physical examination

Though the details collected history is significantly contributes to the correct diagnosis, in any case cannot be underestimated physical examination of the child. On physical examination, it proceeds systematically through organs from head to toe.

Status praesens generalis: Patients with FUO should be investigated during an episode of fever. On examination the patient is evaluated appearance, sweating, heart rate, respiratory rate and other accompanying symptoms. E.g. skin rash at JIA is fleeting and occurs only during episodes of fever. It is also necessary to record any drop in weight growth. They are indeed non-specific symptoms, but may be accompanied by e.g. inflammatory bowel disease or disorder associated with pituitary intracranial injury results in a disproportion growth retardation.

Status praesens localis: Examination every part of body.

4.3 Laboratory investigation

Laboratory and imaging tests should be carefully planned. The intensity of the examination depends on the overall clinical condition of the child. Sometimes it happens that the fever subsides before invasive examinations of the child.

4.3.1 Screening

All children with FUO should have realized the following tests:

- a complete blood count,
- ESR, CRP,
- blood cultures,

- urine analyses,
- X-ray of chest,
- PPD, tuberculin skin test,
- serum minerals, creatinine, urea, liver enzymes,
- serology.

4.3.2 Additional testing

ANA (antinuclear antibody) levels - should be investigated in children older than five years with a positive family history of rheumatic diseases. Positive ANA upon connective tissue disease (SLE). Immunoglobulins: The serum concentration of IgM, IgG and IgA should be investigated in children with recurrent or persisting infections and even fever. Low concentrations suggestive of immunodeficiency conditions. Elevated concentrations may draw attention to chronic infection, autoimmune disease or other immune system deficiency.

Examination of IgE is important in allergic and parasitic diseases,

Examination of IgD is done in children with intermittent but recurring fever.

4.4 Imaging methods

One of difficult decisions is to determine when to implement complementary imaging examination of children with FUO. On the one hand examination of the sinuses, procesus mastoides or digestive system now in the initial stage of the investigation has meaning only in certain specific situations, on the other hand should be implemented for children with persistent fever without an explainable cause.

- Examination of abdomen should be indicated in children with persistent fever, faster ESR, CRP increased, anorexia, weight decreased the elimination of IBD, especially if the children and gastrointestinal problems, either with or without anemia or anemia. USG, CT and MRI can detect abdominal abscesses, tumors and lymphadenopathy.
- Examination of the brain - CT and MR, either with or without EEG EEG have in children with FUO importance rarely.
- PET - positron emission tomography is another diagnostic options.
- Immunoscintigraphy.
- Whole-body MR. This examination can be used to assess the extent of multisystem diseases of childhood cancer patients.

5 Treatment

It is generally recommended to reduce body temperature when it exceeds 38,5°C.

In children with FUO it is good to avoid the use of empirical anti-inflammatory and antibiotic treatment as a diagnostic test. The exception is the use of NSAIDs in children with JIA and antituberculotics predicted in children with possible disseminated tuberculosis.

The use of anti-inflammatory drugs does not help to differentiate fever of infectious or non-infectious causes.

The use of broad-spectrum antibiotics may mask or delay the diagnosis of serious infections - meningitis, endocarditis, and osteomyelitis. Makes it more difficult respectively. Prevents isolation of microorganisms from blood cultures or other places of culture.

6 Conclusion

Unlike adults, most children with FUO is treatable or spontaneously cleared. In most cases, fever or resolve with time out the specific diagnosis. Despite these facts, however, the overall prognosis is not favorable. In earlier studies from 1970, mortality was 9% in the group of 100 children and 6% in the group of 54 children [8, 9]. In later studies, mortality was lower [10].

A special feature is that it may be more favorable prognosis in children, where despite extensive examinations failed to establish a diagnosis. Many of these children to be good, although episodes of fever may return [11].

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