

Unexplained Recurrent Fever in Review

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Abstract

Background: Recurrent fever occurs due to diverse disorders concerning different organ systems or by repeated unrelated infections of the same organ system. In some cases, recurrent fever could be result of a single condition wherein fever and some other signs or symptoms rise and decline in the illness trajectory. The etiology of recurrent fever comprises infectious and noninfectious causes. Many patients present to physician asymptomatic as each episodes of recurrent fever is relatively of short duration.

Aim: The main objective of this article is to overview the causes and diagnosis of unexplained recurrent fever.

Conclusion: Unexplained recurrent fever has variety of etiologies which must be covered carefully during diagnosis. Diagnosing recurrent fever should consider age, family history, duration of breaking periods, and associated symptoms. Physicians should be aware of accompanying symptoms of each differential diagnosis and laboratory tests must be used to confirm the right diagnosis to reach a right management of the case.

Keywords: Unexplained Recurrent Fever; Fever; Causes of Fever; Causes of Recurrent Fever

Introduction

Fever is a physiologic condition in which the temperature is raised over natural [1]. A raised body temperature can associate any disorder in which endogenous or exogenous heat gain exceeds of heat dissipation such as develops with physical activity, exposure to a warm temperature, or use of drugs can cause excess heat output or restrict heat dissipation [2].

Knockaert., *et al.* identified recurrent fever as a cyclical fever with apparent reduction of the disease with break intervals of at least 14 days [3]. Recurrent fever is relatively prevalent and can be the most conspicuous symptom of many diseases [4]. Recurrent or periodic fevers are defined by three or more episodes of mysterious fever in a six month period for at least seven days separately. Recurrent fever is problematic to be diagnosed due to the intermittent nature of the fever that results in unfinished investigations [5]. Breaks between fever attacks are irregular in some cases and regular in others. Fevers usually resolve unexpectedly without antibiotic, anti-inflammatory or immunosuppressive treatment [6].

Recurrent fever occurs due to diverse disorders concerning different organ systems or by repeated unrelated infections of the same organ system. In some cases, recurrent fever could be result of a single condition wherein fever and some other signs or symptoms rise

and decline in the illness trajectory [7]. To evaluate recurrence, some physicians necessitate at least three episodes of unexplained fever during six months, with a least interval of 7 days between two episodes [8]. Other physicians require minimum interval of only 48h for diagnosis [9]. In adults; recurrent fever is common representing 18% - 42% of fevers of unknown origin [5].

Fever periods often have a normal “clockwork” regularity, such as cyclic neutropenia and intermittent or periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome (PFAPA syndrome); in other cases, the recurrent cycle might be less common [10].

The key difference between classical fever and recurrent fever is how frequently it occurs and how it lasts for a few days, gets stronger, stronger, disappears and reappears after duration of time [11]. Classic fever is usually associated with an infection or virus. With a recurrent fever, body temperature may be higher than classic fever without any virus or bacterial infection [12].

The etiology of recurrent fever comprises infectious and noninfectious causes. Many patients present to physician asymptomatic as each episodes of recurrent fever is relatively of short duration [13]. A diversity of bacterial infections can cause recurrent fever which may be easily identified through culture or require serological or molecular tests for identification. Also, many viral, parasitic and fungal infections can cause recurrent fever [14].

Since differential diagnosis remains complicated, there are no structured recommendations for the management to patients with recurrent fever [15]. Acute recurrent fever need proper diagnosis and management as it affects particular morbidity and decreases the quality of life of patients and their families, and it can also reduce long-term complications which can contribute to mortality [16].

The main objective of this article is to overview the causes and diagnosis of unexplained recurrent fever.

Participants and Methods

Study design: Review article.

Study duration: Data were collected between 1 September and 30 November 2020.

Data collection: Medline and PubMed public database searches have been carried out for papers written all over the world on unexplained recurrent fever. The keyword search headings included “unexplained recurrent fever, fever, causes of fever, causes of recurrent fever” and a combination of these were used. For additional supporting data, the sources list of each research was searched. Criteria of inclusion: the papers have been chosen on the basis of the project importance, concerning study objective in English language due to lack of translation resources. Criteria for exclusion: all other publications that did not have their main purpose in any of these areas or multiple studies and reviews were excluded.

Statistical analysis

No predictive analytics technology has been used. In order to evaluate the initial results and the methods of conducting the surgical procedure, the group members reviewed the data. The validity and minimization of error were double revised for each member’s results.

Causes

Many inflammatory and also non-inflammatory disorders can cause a recurrent which increase body core temperature. Recurring fevers tend to develop without a trigger or explanation [17]. It is also referred to as the primary symptom of multiple periodic fever syndromes. Often these syndromes are caused by a genetic disorder. When recurrent fever is associated with periodic fever syndrome, elevated body temperatures can be the consequence of one of these genetic problems [18].

Bacterial or mycobacterial causes include brucellosis, dental abscess, endocarditis, nontuberculous mycobacteria (e.g. *Mycobacterium chelonae*), occult bacterial infection, recurrent bacterial infections, relapsing fever (*Borrelia* spp other than *Borrelia burgdorferi*), and *Yersinia enterocolitica*. Parasitic causes like Malaria (e.g. *Plasmodium vivax*, *Plasmodium ovale*). Viral causes include Epstein-Barr virus (infectious mononucleosis), hepatitis viruses, and recurrent viral infections [19].

Inflammatory or immunologic causes such as Behçet syndrome, inflammatory bowel disease (e.g. Crohn disease), sarcoidosis, systemic lupus erythematosus, vasculitis (e.g. polyarteritis nodosa), and PFAPA syndrome are also causes of recurrent fever. Familial Mediterranean fever (FMF), Tumor necrosis factor receptor associated periodic syndrome (TRAPS), Hyper-immunoglobulin D syndrome (HIDA) (also called mevalonate kinase associated periodic fever syndrome), Neonatal onset multisystem inflammatory disease (NOMID), Muckle-Wells syndrome and familial cold auto inflammatory syndrome, Periodic fever, Aphthous-stomatitis, Pharyngitis, and Adenitis (PFAPA) syndrome [20]. Autoimmune disorders prompt antigen-specific proinflammatory processes resulting in fever. Intermittent phases, particularly at onset of illness, are often observed and must therefore be addressed in patients with recurrent fever of unknown cause [21].

Leukemia and lymphoma are within malignant causes. In malignancies, a diversity of mechanisms to induce recurrent fever are suggested as cytokines production and release by necrotic material and batch-wise growing tumor cells. Especially in lymphomas and leukemia, which often present with B symptoms, elevated levels of the endogenous pyrogens IL-1 β and IL-6 are observed [22].

Other causes as benign giant lymph node hyperplasia (Castleman disease), CNS abnormalities (e.g hypothalamic dysfunction), drug fever, factitious fever and IgG4-related disease were also identified as causes of recurrent fever [18].

Diagnosis

Fever recurrence, absence periods and associated symptoms all guide the physician to diagnose the case correctly. History and physical examination are critical to make a diagnosis to the cause of fever as each case may be distinguished through number of tests and the accompanied symptoms [23,24]. Careful travel history, exposure to individuals with fever or with other known infectious disease as well as animals, ticks, unprocessed foods or toxins should all be obtained within history. Also, sexual history and family history provide important points in diagnosis [25].

Recurrent minor illnesses are typically diagnosed with moderate symptoms only; malignancies are also preceded by signs of B (in addition to fever weight loss, night sweating) and autoimmune disorders often include multiple organs. Associated signs can also suggest some auto-inflammatory conditions [26].

The medical worth of fever configurations is questioning, although there are some distinguished exceptions. Intermittent, remittent, sustained, and relapsing are all fever configurations. With intermittent fever, the fever is raised but drops to normal every day, while in a remittent fever the fever drops every day but not to normal [27]. In these two configurations; fever changes more than 0.3°C and less than 1.4°C. Sustained fever is a configuration in which there is a slight change (0.3°C or less) in the raising fever during a day. In relapsing fever, an irregular of the intermittent configuration, fever confounds are separated by days or weeks of intervening normal temperature [28].

During infection, fever ordinarily varies with brief non-pyretic rests during the day, but the appearance of a single infectious disease with distinct fever occurrences parted by days of regular temperature is much less common [29]. It could be informative to inquire if other family or friends have the same conditions. The incidence and characteristics of infections, inability to survive and family history of immune deficiencies should be taken into consideration in order to rule out potential immunodeficiency [30].

Recurrence of febrile episodes over the year, during the summertime, periods of full health, symptoms-related fever and similar physiological signs, duration of episodes and comparable intervals, sudden recovery of symptoms, would indicate periodic fever. Inflammatory markers (ESR, CPR, SAA) and the level of WBCs rise during the fever cycle and begin to stabilize with fever resolution [32].

Recurrent fevers at periods of a few to a few days indicate a diagnosis of relapsing fever. If it is followed by a crisis phenomenon, hepatomegaly or splenomegaly, cranial neuritis also in case of tick-borne relapsing fever, or jaundice and petechiae in the case of louse-borne relapsing fever, and epidemiological possible exposure to lice or soft-bodied ticks, then relapsing fever is highly possible [33].

PFAPA syndrome is commonly concomitant with cervical lymphadenitis, pharyngitis and mouth aphtas. In cyclic neutropenia; decreased neutrophils, pharyngotonsillitis and aphtas are larger than those of PFAPA, and severe bacterial infections. CBC must be done every seven days for at least one month to make the right diagnosis of PFAPA and prognosis is benign with spontaneous resolution within ten years [34].

If a clinical history associated with one of the auto-inflammatory disorders may be detected, families and doctors also obtain evidence from genetic tests. Genetic diagnosis should be pursued in a logical way that acknowledges the expense and limits of research [35]. Relapsing fevers may be seen in rat-bite fever, malaria, cholangitis, infections with *Borrelia recurrentis*, Hodgkin's disease (Pel-Ebstein fever) and other neoplasms [36]. Autoinflammatory diseases are triggered by a weakness in the innate immune system, which leads to irregularly increased inflammation. Fevers often go above 39°C, although in CAPS, low-grade fever is more typical. In breaks between fever episodes, which is of variable duration, symptoms are only rarely present, but subclinical inflammation may easily be detected [37].

Brucellosis also has large number of different symptoms but is typically concerned with undulant fever, arthralgia or arthritis and hepatosplenomegaly. *Brucella* species, both melitensis and suis, have been believed to be found for recurrent fever in older adults [38].

Regarding parasitic infections; malaria, with typical fever configurations, and visceral leishmaniasis are the parasitic causes of recurrent fever. Residence in endemic areas can direct medical scepticism in both pathologies [39]. For one case, repeated outbreaks of fever arising at 1-, 3- and 6-weeks of age combined with neurological and ocular defects is due to hypothalamic thermoregulatory failure secondary to congenital toxoplasm infection. Chills, sweats, fatigue and splenomegaly with malaria fever [40].

In Crohn's, fever can accompany other common symptoms of inflammatory bowel disease, including abdominal pain or diarrhea, in weeks or even months. Microcytic hypochromic anemia and growth dysfunction are useful medical signs [41].

Management

Management generally varies according to the case state and diagnosis, but fever generally must be managed by initial steps as drink water or fluids, getting sufficient rest, administrating anti-pyritic drugs, avoiding heavy blankets or cloths that cause overheat and voiding cold water baths.

Antibiotics inefficacy is a clear evidence of an auto inflammatory disorder. Steroids must be administrated as it show benefit in many of the auto inflammatory diseases, although in general it is only very effective in PFAPA, so JIA and AOSD and to a lesser extent in HIDS [42].

Conclusion

Unexplained recurrent fever has variety of etiologies which must be covered carefully during diagnosis. Diagnosing recurrent fever should consider age, family history, duration of breaking periods, and associated symptoms. Physicians should be aware of accompanying symptoms of each differential diagnosis and laboratory tests must be used to confirm the right diagnosis to reach a right management of the case.

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