

Unmasking an Obstinate Fever

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A 14 year old girl was evaluated in our outpatient department because of intermittent fever, partly responsive to antipyretics, which started 4 weeks earlier. Fever spikes occurred daily, exceeding 39.0°C, and were associated with frontal headache and nausea without any apparent explanation. Neither neck stiffness nor chills were present during the fever spikes, and no weight loss had been observed by her parents during that time. She did not smoke or use illicit drugs, and no medication had been administered before fever onset. The patient was perfectly healthy until 1 month earlier, when her parents noted a decrease in her activity level and refusal to attend school.

Fever is the prominent non-specific symptom of many different disorders, and febrile diseases in children and adolescents are the most common reason for seeking advice or clinical evaluation from general practitioners [1]. Many articles on the risk stratification of fever were based on clinical and laboratory characteristics, but no meta-analysis has been performed to create a widely shared protocol for the investigation of fevers in children. Fever above 38.3°C for a period of 3 weeks without any identified etiology after 1 week hospitalization conventionally suggests the so-called fever of unknown origin [2]. Durack and Street [3] have proposed that nosocomial, neutropenic, and human immunodeficiency virus-associated FUO1 be considered as distinct groups different from classic FUO in order to reduce the

investigative phase from 1 week to 3 days before a prolonged unexplained fever could qualify as FUO. The history reported in this patient seems like a case of FUO. The initial strategy of FUO investigation requires a full comprehensive history, repeated physical evaluations, and graded laboratory tests. All localizing signs, symptoms and abnormalities that potentially point to a diagnosis must be sought, and all medications should be discontinued early to rule out a drug-induced fever [4].

The patient was born after a full-term gestation and had jaundice in the neonatal period with no consequence. She had otherwise been well and had received all childhood immunizations. The girl was a high school student, lived in an urban area in central Italy with her parents, one sibling and a cat, was inactive outdoors, had not travelled outside Italy in the past year, and had had no recent contact with a sick person. Her parents were successful construction engineers. In the last month the girl had been evaluated in the emergency departments of three hospitals; initially the first suspected origin of fever was infection. Hematologic and serum chemical laboratory data were normal at each hospital admission. In addition, inflammatory parameters evaluated during fever spikes were within the normal range. Urine and blood cultures were obtained only on the first evaluation, and amoxicillin/clavulanic acid had been administered empirically for 7 days. Infectious mononucleosis screen also demonstrated no evidence of Epstein-Barr virus infection. The parents were distressed about the possibility of an occult infection and requested a trans-thoracic echocardiography, which was performed on an outpatient basis and showed a left ventricular ejection fraction of 74% with no valvular abnormalities. She had

no known allergies and there was no family history of autoinflammatory disorders.

Pediatric acute febrile infections exert a significant burden on pediatric emergency departments. Most of these illnesses are due to bacteria or viruses. Infectious diseases should be excluded in patients with FUO, and the many possible infectious conditions should be considered one by one. The patient lived with a cat, and cats can transmit *Bartonella henselae*, the agent of cat scratch disease, though these patients usually present a typical papular lesion at the site of Bartonella inoculation, with regional lymph node enlargement. Many viral diseases may start with a combination of fever, headache, and nausea. Infectious mononucleosis is a common and usually self-limited disease in adolescents, characterized by fever with a long lasting course. If fever fails to resolve during a period of 2 to 4 weeks, even in the absence of pharyngitis and lymphadenopathy, a real-time polymerase chain reaction or IgM antibodies test to verify Epstein-Barr virus infection should be performed. Tick-borne diseases and arbovirolosis could be disregarded given the girl's hesitancy to be involved in any outdoor activities. The consideration of systemic autoinflammatory syndromes is also correct given the 4 week history of persistent fever with no localizing signs. Among these many disorders, the most likely condition fitting with the reported history is tumor necrosis factor receptor-associated periodic syndrome, an autosomal dominant inherited disease, caused by mutations in the *TNFRSF1A* gene. This condition manifests as recurrent febrile episodes of prolonged duration, 3–4 weeks, and an

FUO = fever of unknown origin

initial good response to corticosteroids. Febrile attacks in TRAPS are associated with variable inflammatory signs involving joints, muscles, skin, or eyes, presence of a gastrointestinal tube, with many variations among patients, and an acute-phase response during attacks, though subtle or mild clinical pictures have been described [5]. Since headache and nausea are commonly observed in many pediatric conditions, they were not helpful in narrowing the diagnostic focus. Several strategies for identifying febrile patients with a severe disease have been tested, but the strengths and limitations of these observations are controversial [6]. A painstaking thorough history remains essential to elucidate a hidden infection; the history should address all associated symptoms and behaviors, exposure to sick contacts (siblings, babysitters, day caregivers) and any previous illness or medication use. Nevertheless, whatever drug administered, previous exposure to insect bites, prior surgery, or travel to tropical countries must be known, as well as previous contacts with infected animals. An acquired or congenital immunologic defect should be considered a possible cause of a persistent infection, including humoral defects (e.g., hypogammaglobulinemia, hyper-IgM or hyper-IgE syndrome), phagocytic defects (e.g., chronic granulomatous disease), or defects in cellular immunity (e.g., infection with human immunodeficiency virus). Surprisingly the inflammatory parameters were completely normal. The complete absence of inflammatory symptoms in this girl and the lack of inflammatory parameters made a diagnosis of TRAPS rather unlikely.

At our first examination in the outpatient department, the girl was alert. Her temperature was 37.0°C, blood pressure 108/76 mmHg, pulse 85 beats/minute, respiratory rate 20 breaths/minute, and oxygen saturation 100% while breathing ambient air. Her weight was 52 kg (50th percentile). She did

not have dental caries, gingivitis or evidence of abscesses in the oral cavity. Heart sounds were normal, and there were no murmurs, rubs, or gallops. The lungs were clear. The abdomen was soft with no organomegaly. The extremities were warm and well perfused, while deep tendon reflexes in the legs were brisk and symmetric. No pain and discomfort in her joints, no thyromegaly or lymphadenomegaly were noted. The conjunctivae were clear and fundoscopic examination was negative. Complete blood count was fairly normal. C-reactive protein and erythrocyte sedimentation rate were 1.5 mg/L (reference range < 5 L) and 6 mm/hr (reference range < 18) respectively. The levels of glucose, creatinine, alanine and aspartate aminotransferases, total and direct bilirubin, alkaline phosphatase, amylase, total protein, albumin, uric acid, lactate dehydrogenase, and clotting test were normal, as was urinalysis. Plain-film radiograph of the chest was normal, and an abdominal echography showed a large amount of air in the gut. No other abnormalities were noted. Toxicologic analysis of the urine and serum was negative. Testing for antibodies to HIV was negative. We believed it necessary to hospitalize the girl for a short time to verify the febrile peaks and the girl's general condition during fever spikes. However, we suggested the possibility of a non-organic disease to the parents and minimized further testing or instrumental checking.

Unrevealing blood tests are a frustrating occurrence in pediatric patients with FOU, and all rarer causes of FOU must be investigated in these cases. Many seasonal tick-borne diseases should be considered in the differential diagnosis, such as Lyme disease, caused by the bacterium *Borrelia burgdorferi*, or ehrlichiosis and anaplasmosis, caused by different ehrlichial species. Some collagen vascular diseases might start with FOU, requiring an assessment of immune status, with the inclusion of antinuclear antibodies and serum immunoglobulin levels. Patients with malignancies might

also display persistent low grade fever, though frequent red flags that merit attention are unexplained weight loss, systemic visceral lymph node enlargement, palpable splenomegaly, and highly increased serum levels of lactate dehydrogenase. Other miscellaneous diseases that can display FOU at their onset are often accompanied by illuminating clinical signs, such as Behçet's disease, inflammatory bowel diseases, and Fabry-Anderson disease [7]. The frequency of FOU in thyroid disorders is unknown, and the diagnosis may be frequently overlooked since many patients do not have a history of clinically overt thyroid hyperfunction. Thyroid-stimulating hormone testing might lead to early recognition of thyrotoxicosis or subacute thyroiditis in patients with FOU showing persistent negative results for any infectious diseases [8].

On repeat physical examination the girl did not appear ill. There were no new symptoms. Her level of consciousness did not decline at any time, and her appetite remained normal. Fever was never noted during the observation in our department, although the girl claimed to be feverish at least twice, reading 38.4°C on the thermometer. She never appeared tachycardic on either of these occasions, and nurses revealed a normal body temperature with an infrared thermometer, always less than 37.0°C. Further laboratory tests were performed: tuberculin skin test was negative, as were an immunoglobulin screen and cytomegalovirus and Mycoplasma tests. Levels of free thyroxine and thyrotropin were normal. The biochemistry panel was again unremarkable and neutrophil burst test was negative. The girl's parents were distressed that no diagnosis had been made, but the girl, asymptomatic and without fever, was discharged from hospital after 3 days. No empiric treatment was begun. The family was hopeful regarding the definite disappearance of fever, but 2 days after discharge the fever returned and the girl could not go to school. Temperatures peaking at over 39.0°C (102.2°F) persisted for one week, despite regular antipyretics, and disappeared during the Easter holidays during which she went to a dance party.

TRAPS = tumor necrosis factor receptor-associated periodic syndrome

HIV = human immunodeficiency virus

Fever disappearance during the hospital stay was discriminating in this case, as unusual trends of fever or unusual peak frequency, which skip holidays, and the absence of objective clinical points related to the high temperature should drive the suspicion of a factitious disorder [9]. In this case, the symptoms “appeared” through thermometer manipulation and fever simulation when caregivers were present in the patient’s room. The non-plausibility of the fever pattern and dissociation between the presumed fever and fever-related clinical signs must always be considered, as well as the negative laboratory investigations, which are crucial to corroborating the hypothesis of factitious disorders. Ward nurses are often the first to unmask the suspected behavior during temperature measurement. Otherwise, the association of fever with weight loss, sweating, shivers, tachycardia or palpitation, heart murmurs, gastrointestinal complaints, osteoarticular signs, severe anemia, and low platelet count dictates the exclusion of organic causes of fever and refutes the diagnosis of factitious disorders.

At the umpteenth clinical evaluation in the outpatient department, after the Easter holidays, apart from fever claimed by the girl, the physical examination was unremarkable and fever was not present. The diagnosis of factitious fever was communicated to the parents. A neuropsychiatrist was recruited to help in the management of the girl and to revive a dialogue between the parents and their daughter. No hospitalization was required.

Factitious disorders are based on the intentional production of feigned symptoms in an attempt to assume the “patient” role. Referrals of factitious disorders might come from almost all clinical departments, including the emergency care unit, surgery, endocrinology, neurology, dermatology, and gastroenterology. In the histories of these patients it is usual to see a number of outpatient evaluations or even hospitalizations across different

hospitals, intricate clinical sceneries with prolonged symptoms and signs associated with negative laboratory test results and ineffective treatments, combined with the willingness to undergo further medical diagnostic procedures. These patients are usually wily in their deception and represent a challenging dilemma for the pediatrician. Clinical findings might be more complex than fever alone and might include dramatic complaints related to all medical specialties. The differential diagnosis should always include all the common causes of FUO in children. A striking feature that must be emphasized is the crucial role of the nursing personnel in the disclosure of a factitious fever, as nurses are directly involved in checking and recording patients’ body temperature. The socio-environmental milieu of these patients should also be carefully investigated to disclose intrafamilial conflicts and help achieve a full recovery of factitious disorders.

COMMENT

We emphasize the multiple causes that can be concealed behind patients with FUO. It is important to maintain a broad differential diagnosis, including infections and non-infectious causes of FUO, even when preliminary laboratory results or clinical details may point toward a specific disease entity. Long lasting fevers might be related to specific bacterial diseases – such as typhus fever, malaria, or tuberculosis – and confuse pediatricians. Immune-mediated diseases such as systemic onset-juvenile idiopathic arthritis, systemic lupus erythematosus, or thyroid gland disorders may also cause a persistent fever of varying intensity in children. Cancers such as Wilms’ tumor and neuroblastoma may sometimes result in chronic fevers. Discriminating between patients requiring an extensive evaluation and those whose care can be managed conservatively is not simple. The missed demonstration of fever by nurses and the negative laboratory tests, including inflammatory markers, can signal the diagnosis of factitious fever. Ever since factitious disorders entered the official

psychiatric nomenclature in DSM-III and DSM-IV-TR, there has been a proliferation of reports. The prevalence of factitious fever in pediatric patients is currently not available, but the disease appears more common in females than in males (occurring at a ratio of approximately 3:1 for adult patients) [10]. The differential diagnosis of factitious fever requires an interdisciplinary team to help discard, one-by-one, any potential organic disease. Early detection of this disorder is possible only with the strict cooperation of the nursing staff with the aim of snapping the vicious circle of ongoing hospitalizations and unnecessary treatments. Many of these patients wander as “frequent flyers” across different hospitals, reject the medical assessments of their fever, and ask for unnecessary medical acts or prolonged hospital stay. They should be referred to the psychosomatic-psychotherapeutic consultation service.

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