

PEDIATRIC RHEUMATOLOGY FOR THE GENERALIST

Fever: A Pediatric Rheumatologist's Perspective

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Abstract

Unexplained fever is one of the most common conditions evaluated by the pediatric rheumatologist. Indeed, fever is the predominant symptom of certain rheumatic diseases, and 5-20% of fevers of unknown origin (FUOs) are caused by collagen vascular diseases (1-5). Arthritis is simply the presence of swelling in a joint. Like fever, it is a non-specific finding. The presence of arthritis narrows the differential diagnosis of an unexplained fever, but the list of potential etiologies is still extensive. While an exhaustive review of this topic is beyond the scope of a single article, a systematic approach to diagnosis of the child with fever and arthritis is presented, including a discussion of the more common conditions resulting in these symptoms. The approach is based on a thorough history and physical exam, combined with an understanding of the clinical presentation of rheumatic diseases, and the recognition of patterns of signs and

symptoms that guide in the selection and evaluation of laboratory tests, and ultimately in establishing the diagnosis.

Conditions that mimic a collagen vascular disease ([see Diagnostic Considerations #1](#))

Most large case series of FUEOs divide the causative diagnoses into four major disease categories: infections, malignancies, collagen vascular diseases, and miscellaneous. When evaluating an unexplained fever in the context of symptoms suggestive of a collagen vascular disease, it is still necessary to systematically consider diagnoses for all four disease categories. It is well known that some rheumatic diseases can mimic other conditions; and the reverse is also true. One of the more difficult problems facing the rheumatologist is the distinction between conditions that mimic a rheumatic disorder and that may require prompt and specific treatment such as antibiotics, and actual collagen vascular diseases that require immunosuppression. Some rheumatic disorders will evolve over weeks or even months before a definitive diagnosis can be established; some remain both clinical diagnoses as well as diagnoses of exclusion. Thus, it is important to first consider other possible etiologies.

Infection

Infections represent the most frequent cause of fever in children (1-5). A thorough search for infectious etiologies which include cultures of blood and urine as well as any additional testing indicated by the history or physical examination should be conducted prior to consulting the rheumatologist. Musculoskeletal complaints associated with active infection usually occur in three settings (6): 1) localized infection of a joint or bone, 2) arthritis occurring as a manifestation of a systemic infection, or 3) arthritis following an acute infection as the result of immunologic cross-reactivity to an epitope present on the infecting organism.

Localized Infection.

A single joint with the acute onset of unexplained pain and swelling in a febrile patient must be considered a septic joint until proven otherwise. Typically, the fever pattern is high grade, between 100-104 F, (37.8- 40 C), consistent with a closed space bacterial infection (6). The involved joint is usually warm, swollen, sometimes erythematous and very painful to palpation and range of motion testing. Septic arthritis most commonly affects the knees, hips, ankles or elbows and is usually monoarticular, but can involve several joints (7). Septic arthritis may be a component of a more systemic infection; therefore, blood cultures should be drawn in all patients. Cultures of other sites may also be indicated. Prompt aspiration and evaluation of the synovial fluid for infection is essential since considerable morbidity is associated with a delay in treatment.

Fever associated with bone pain should suggest osteomyelitis, which may be associated with a septic joint or arise as an isolated condition. A prior history of trauma is present in some patients. Typically the infection is located in the metaphysis and pressure over the affected area elicits pain. Two thirds of patients have involvement of the lower extremity (8). Fever associated with gait abnormalities and hip or groin pain may represent pelvic osteomyelitis (9). Bone scans, although non-specific, may be useful in localizing the infection, especially if the axial skeleton is involved. Biopsy and culture of bone is necessary to accurately identify an organism. Recurrent episodes of culture negative osteomyelitis with fever and lytic bone lesions may represent chronic recurrent multifocal osteomyelitis (CRMO), a benign idiopathic inflammatory condition.(10)

Systemic Infection

Gonococcal arthritis usually occurs in the context of a systemic illness manifested by fever, chills, rash and arthritis. It occurs most commonly in adolescent girls during or just after menstruation. The arthritis is initially migratory and may result in a purulent arthritis in several joints. Wrist involvement with associated tenosynovitis is characteristic as it is a sparse vesiculopustular rash. Most patients deny genitourinary symptoms. Cultures of both blood and synovial

fluid may be negative, so it is important to culture multiple sites including the vesicle, genital tract, rectum, and pharynx. Prompt response to antibiotic therapy is typical (11).

In endemic areas, Lyme disease should be considered in patients with fever, flu-like symptoms and migratory arthralgia or arthritis, especially if followed by an erythema chronicum migrans rash (12, 13). False positive results are common with the enzyme-immunoassay, so clinical characteristics consistent with Lyme and a confirmatory Western blot are important in establishing this diagnosis.

Rare in North America, Brucella is more commonly seen in Europe and South America. It is associated with the ingestion of unpasteurized milk and its products. Fever, arthralgia or arthritis, and hepatosplenomegaly are the most common presenting features.(14) Younger children most often have involvement of a hip or knee. Older adolescents usually have spondylitis or sacroiliitis (15).

Bartonella (cat scratch disease) can also mimic a collagen vascular disease. Cases of arthritis and myositis associated with fever have been reported in several children (16, 17).

Although many viruses cause arthralgia with fever, true viral arthritis is relatively rare. The most common organisms associated with viral arthritis are parvovirus B-19, rubella and hepatitis B. Viral arthritis is generally migratory, self-limited and non-deforming, although the arthritis associated with parvovirus can last for months in some cases. HIV has been associated with a variety of rheumatic syndromes including reactive arthritis, Reiter's, and psoriasiform arthritis in adults, but appears to be much less common in children (6, 11).

Post-Infectious Causes.

Arthritis is the most common major manifestation of Acute Rheumatic Fever (ARF), occurring in approximately 70% of patients (7). ARF should be considered in the diagnosis of any acute onset arthritis associated with fever. Initially, the arthritis of ARF may resemble a septic joint. Typically a single large joint such as a knee, ankle, elbow or wrist becomes acutely painful, red, warm,

and swollen. Pain is the predominant symptom. As that joint spontaneously improves over hours to a week, a different joint becomes involved. The arthritis then follows a migratory and often additive pattern (6). Fever occurs in most patients, but is variable in duration and intensity (18). Many patients will recall a pharyngitis two or three weeks prior to the onset of the arthritis. The most feared complication of ARF is rheumatic heart disease; this underscores the importance of a complete physical exam in any patient with fever and arthritis. The detection of a new cardiac murmur may provide the clue that allows the diagnosis of an acutely swollen knee. Diagnosis is based on clinical criteria, and the demonstration of prior streptococcal infection is required.

Not all children developing articular symptoms and fever after a Group A streptococcal infection will fulfill the modified Jones criteria for the diagnosis of acute rheumatic fever. Post streptococcal reactive arthritis is characterized by a shorter latency period (<10 days) after strep infection than ARF, as well as a distinctive non-migratory, persistent arthritis which is poorly responsive to salicylates or non-steroidal inflammatory medications. The need for penicillin prophylaxis in this group is controversial. (19)

Reactive arthritis refers to an inflammatory arthritis that appears to be secondary to an immunologic response to infection, typically of the gastrointestinal or genitourinary tract. The presence of a certain genetic background, specifically the haplotype HLA-B27, increases the likelihood of developing this condition. These patients may present with fever, weight loss, arthralgia, myalgia, and arthritis several weeks after an infection with *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter* or *Chlamydia*. Other common symptoms include mucocutaneous involvement such as oral or genital ulcers, and ocular inflammation (11). Reiter's syndrome, one possible presentation of reactive arthritis, is the triad of arthritis, conjunctivitis, and urethritis. Patients usually have low-grade fever, and involvement of a few lower extremity large joints in an asymmetric pattern, although multiple small joint involvement can occur. Enthesitis and dactylitis also may be present. Most patients resolve within a few

months, but some will have recurrent episodes and may evolve into a chronic spondyloarthropathy (7).

Malignancy

As with infection, malignancy must always be considered in the differential diagnosis of fever with musculoskeletal complaints. In leukemia, the fever is usually low grade, although as many as 30% of children will have high fevers (20). The arthritis typically involves fewer than 5 joints, and may be migratory or transient. Pain is typically out of proportion to the swelling. Other features that suggest malignancy are non-articular bone pain, back pain, and night sweats (20, 21). The initial CBC may be normal in these patients, but a discordant ESR and platelet count (i.e., highly elevated ESR with a normal platelet count) may be present. Elevated uric acid or lactic dehydrogenase levels are also suggestive (22).

Inflammatory bowel disease

The presence of overlapping symptoms may make it difficult to distinguish the initial presentation of inflammatory bowel disease (IBD) from that of a collagen vascular disease. Patients often display non-specific signs of inflammation such as fever, weight loss, anemia and elevated acute phase reactants. Arthritis is a common extra intestinal manifestation occurring in 10-20% of patients, and may precede the onset of gastrointestinal symptoms (7). Usually the arthritis is episodic, lasting a period of weeks, and is most commonly oligoarticular, involving the large joints of the lower extremity (23, 24). Other extra-intestinal features suggestive of IBD include uveitis, erythema nodosum, pyoderma gangrenosum, and oral or perianal ulcers (23). A detailed history of gastrointestinal symptoms is very important in this context and if negative, may need to be reassessed over time. Diagnosis is based on consistent clinical features in conjunction with compatible endoscopic and radiographic findings.

Collagen vascular diseases ([see Diagnostic Considerations #2](#))

The most common collagen vascular diseases cited in pediatric FUO case series are systemic onset juvenile arthritis (SOJA) and systemic lupus erythematosus (SLE) (1-5). As with most collagen vascular diseases, diagnosis for these conditions is based on a set of criteria rather than a single definitive test. In rheumatic diseases, any single piece of information is almost never diagnostic. Serologic testing is very non-specific, and must be interpreted with caution since the likelihood of false-positive results is extremely high, unless tests are ordered in the context of symptoms suggestive of a *specific* disorder. A complete history, a thorough and skilled physical examination, and familiarity with and recognition of rheumatic disease patterns are essential in the diagnosis of collagen vascular diseases. Close clinical follow-up and re-evaluation are sometimes necessary to establish a diagnosis.

Systemic onset juvenile idiopathic arthritis

Systemic onset juvenile arthritis is the collagen vascular disease most likely to present as an FUO. In 4 large pediatric FUO reviews, systemic onset juvenile arthritis represented over half of all patients with collagen vascular disease presenting as fever (1-4). Indeed, high spiking fever is the predominant symptom seen in of this type of onset. Characteristically the fever is high grade, reaching 39 C, (102.2 F), or higher once or twice daily before returning to baseline. Spikes of fever often occur in the afternoon or evening. This quotidian fever pattern is quite distinct from the usual more hectic fever seen in most infectious conditions which has less predictable spikes and which may not return to baseline. During afebrile periods the child with SOJA may appear surprisingly well. An evanescent salmon pink macular rash frequently accompanies episodes of fever. The rash is most frequently seen on the trunk and proximal extremities. It exhibits the Koebner phenomenon, and may be pruritic. Patients may also have hepatosplenomegaly, lymphadenopathy, or pericarditis (8). Uveitis is rare in systemic onset juvenile arthritis, and its presence should prompt a review of other possible etiologies, including sarcoidosis or Chronic Infantile Neurologic

Cutaneous and Articular syndrome (CINCA) /Neonatal Onset Multi-system Inflammatory disease (NOMID). (25). The arthritis that allows the definitive diagnosis of SOJA may be present at onset, but can take months and even years to evolve (7).

Systemic onset juvenile arthritis cannot be diagnosed by serologic means and remains both a clinical diagnosis and a diagnosis of exclusion. Typical laboratory results (leukocytosis with a neutrophilic shift, anemia, thrombocytosis, and highly elevated erythrocyte sedimentation rate) reflect the systemic inflammation, but are non-specific. Rheumatoid factor and antinuclear antibody tests are usually negative. If the patient has atypical features, it is extremely important to pursue differential diagnosis including infectious etiologies, acute rheumatic fever, malignancy, and other forms of collagen vascular disease, particularly vasculitis.

Fever is unusual in other forms of juvenile idiopathic arthritis, although polyarticular onset patients may have low-grade fever.

Systemic lupus erythematosus

The majority of lupus patients will experience fever and other constitutional symptoms, especially at onset. The fever of active lupus is typically mild to moderate, 99.5-101.5 F, (37–38.6 C), and can be either persistent or intermittent. Occasionally fevers can be high grade, 102-105 F, (39- 40.6 C), and rarely SLE may present as an FUO (6). Systemic lupus is much more common in girls and has a peak childhood onset between 11-15 years. It is rare below the age of 5 years (26). The clinical manifestations of lupus are protean. Although SLE can present with a single affected organ system, multisystem disease is more characteristic and is one of the features that should suggest this diagnosis. Most children will have cutaneous findings with approximately half exhibiting a malar erythema. Photosensitivity, alopecia, and oral ulcers are also seen. Arthritis and arthralgia are common (26, 27). The arthritis can be transient, migratory or persistent, and is usually painful. Small joints of the hand, wrists with an accompanying tenosynovitis, elbows, shoulders, knees and ankles are the

most commonly involved joints (7). Nephritis is more common in children with SLE than in adults, involving at least 80% of patients, usually early in the course. CNS disease is another major source of morbidity and mortality in lupus (26). Its manifestations vary widely, ranging from psychosis and seizures to cerebrovascular accidents and headaches. Serositis, Raynaud's, hepatosplenomegaly, myositis, and lymphadenopathy are also seen.

The diagnosis of SLE is clinical with confirmatory lab tests. The importance of having a clinical picture consistent with lupus prior to drawing immunologic serology must be emphasized. The yield of serologic tests such as ANA, rheumatoid factor, Anti-Neutrophil Cytoplasmic Antibodies (ANCA), Extractable Nuclear Antigen (ENA), and antibody to double-stranded DNA is relatively low, and false positive results are common, unless the tests are drawn in a context of symptoms suggestive of a specific disorder (28). However, having said this, laboratory testing is essential in the diagnosis of SLE.

Routine laboratory tests such as the CBC and urinalysis are usually abnormal and may suggest the diagnosis with findings of leucopenia, lymphopenia, anemia, thrombocytopenia, proteinuria, hematuria, or red blood cell casts. A positive ANA is the hallmark of SLE, and is present in virtually all active patients (7). A negative ANA indicates that the diagnosis of SLE is very unlikely. Anti-DNA antibodies are present in most patients and are quite specific. A whole host of other autoantibodies, including rheumatoid factor and antiphospholipid antibodies may be present. Other tests that should suggest the diagnosis are coagulation abnormalities, and depressed complement levels.

Other systemic connective tissue diseases

Fever is present to some degree in the onset of juvenile dermatomyositis (JDM) in about two thirds of patients, but rarely dominates the clinical picture (29). Muscle weakness and pain are usually present, but if not specifically sought, may be missed, particularly in a younger child in whom these symptoms may be misinterpreted as clinginess or irritability. Fortunately, most children with inflammatory myositis will exhibit typical rash: heliotrope, Gottron's and periungal

erythema. Periorbital, facial, or more generalized subcutaneous edema without proteinuria should also suggest this diagnosis. Elevation of transaminases without evidence of liver disease should prompt assessment of muscle enzymes. It is best to check a panel of muscle enzymes (CPK, aldolase, LDH, AST and ALT) since any one enzyme may be normal in the presence of active myositis (30). Diagnosis is based on a combination of clinical and laboratory findings.

Mixed connective tissue disease (MCTD) is characterized by the clinical features of rheumatoid arthritis, scleroderma, SLE, and dermatomyositis and a positive antibody titer to the ribonuclear protein (RNP) component of extractable nuclear antigen (ENA). Fever is common at onset and MCTD has been reported as a cause of FUO (6).

Vasculitis [\(see Diagnostic Considerations #3\)](#)

Vasculitis is relatively rare. Nevertheless, it is very important to consider it in the differential diagnosis of unexplained fever, since failure to diagnose and treat vasculitis in a timely manner may have catastrophic consequences for the patient. Invasive procedures such as angiography or biopsy may be required to establish the diagnosis in some types of vasculitis, so pattern recognition is especially important to guide investigations.

Kawasaki Disease

The most common childhood vasculitis that presents with fever is Kawasaki Disease (KD). This condition occurs primarily in young children with 80% of cases presenting under the age of 4 years. Fever is a predominant feature and is required for diagnosis. It is typically present at onset, high grade, >39 C (>102.2 F), and remittent. Untreated, the fever usually lasts 1-2 weeks, but may persist up to a month. Rarely, persistent fever may be almost the sole manifestation of KD, with diagnosis later revealed by the finding of coronary aneurysms on echocardiography (31). Other symptoms typically seen during the initial stages of illness include bilateral conjunctival injection without exudate, often associated with an anterior uveitis, dry swollen cracked lips, erythema of

the oral cavity, and a strawberry tongue. The child's hands and feet become diffusely swollen, painful and erythematous on the palms and soles followed several weeks later by periungual desquamation. Rashes on the trunk, often in the perineal area, can be maculopapular, scarletinaform or erythema multiforme. The adenopathy of KD is typically a solitary node >1.5 cm in the anterior cervical chain. Other characteristic features include extreme irritability, aseptic meningitis, diarrhea, and otitis media (31). Arthralgia, myalgia, and more rarely arthritis can occur. The arthritis usually develops during the second week of illness and involves the large joints of the lower extremity. Small joints in the hand may also be involved, but are difficult to distinguish from the edema in the digits (7).

Lab findings reveal systemic inflammation, but are nonspecific. The acute phase is characterized by a leukocytosis with a neutrophilic predominance, mild anemia, and elevated acute phase reactants. Mildly elevated liver enzymes and a sterile pyuria can also be seen. Thrombocytosis typically develops in the second week (7). Antinuclear antibody tests and rheumatoid factors are negative.

Diagnosis is based on clinical criteria. The differential diagnosis includes a variety of infections, toxic drug reactions, systemic onset juvenile arthritis and polyarteritis nodosa (31). Not all patients with KD will fulfill the diagnostic criteria. It is therefore important to consider this diagnosis even in incomplete or atypical cases, since the failure to administer IVIG in a timely fashion may result in very serious cardiac consequences. Unfortunately, incomplete KD appears to be more common in infants, the group with the highest risk of developing coronary aneurysms (32). Fever generally responds to treatment with IVIG within 1-2 days (31). If the fever recurs or persists despite IVIG, or if the presentation is atypical, differential diagnosis must be reconsidered and the involvement of a pediatric rheumatologist is recommended.

Other Forms of Vasculitis

The other common form of vasculitis in childhood is Henoch-Schonlein purpura (HSP). Although low-grade fever is not unusual in this condition, fever is

seldom a major symptom. Typically the clinical picture is dominated by purpuric rash, abdominal pain, arthritis, and renal involvement.

Polyarteritis nodosa is very rare, but may present insidiously with high or low-grade fever in a remittent pattern; arthritis, diffuse muscle pain, abdominal pain, and cutaneous findings are common. Other suggestive findings include nephritis, testicular pain and peripheral neuropathy.

Fever can also be a symptom in most other forms of vasculitis. Microscopic polyarteritis nodosa is characterized by pulmonary hemorrhage, a rapidly progressive pauci-immune nephritis and a perinuclear staining pattern of antineutrophil cytoplasmic antibodies (p-ANCA) with specificity for myeloperoxidase (MPO). In contrast, Wegener's Granulomatosis typically has ANCA in a cytoplasmic pattern (c-ANCA) specific to proteinase 3 (PR3) as well as a granulomatous vasculitis of the upper and lower respiratory tracts and a pauci-immune nephritis. Churg-Strauss vasculitis typically develops after a long history of asthma and is characterized by eosinophilia, shifting pulmonary infiltrates, and neuropathy. Takayasu's Arteritis is most common in young women and may have a subtle and insidious presentation. The aorta and its major branches are typically affected and loss of brachial pulse, and claudication of extremities may result. Hypersensitivity vasculitis usually begins a week or two after exposure to a medication and is characterized by rash (palpable purpura, urticaria or nodules), arthritis/arthralgia and myalgia.

Features that suggest vasculitis include unexplained constitutional symptoms such as fever, fatigue and weight loss associated with skin lesions, neurologic symptoms, pain or inflammation of the joints or muscle, hypertension and pulmonary infiltrates or hemorrhage. Suggestive lab findings include evidence of inflammation (leucocytosis, anemia, elevated acute phase reactants), eosinophilia, hematuria, and the presence of antineutrophilic cytoplasmic antibodies (ANCA) (7).

Behcet's Disease

Behcet's Disease, a vasculitis of unknown etiology, was originally described as the triad of recurrent aphthous stomatitis, genital ulcerations, and uveitis. Fever is a common symptom and Behcet's disease has been occasionally reported as the cause of FUO. Other clinical features include erythema nodosum, arthritis, neurologic involvement and pathergy (the development of a pustular rash at the site of needle injection). Bowel disease virtually identical to that seen in IBD can occur in Behcet's Disease, making the differentiation between these two conditions difficult (33, 34).

Sarcoidosis

Sarcoidosis is a rare multisystem inflammatory disease of unknown etiology characterized by the presence of non-caseating granulomas. Age of onset appears to affect the clinical presentation. Older children have similar features to adult onset disease, with prominent pulmonary involvement, especially hilar adenopathy and lymphadenopathy, and usually have a milder course (35). Children presenting under the age of four more typically have the triad of uveitis, rash, and arthritis. They often have significant fever, and may be misdiagnosed as systemic onset juvenile arthritis. The arthritis is initially very boggy, and painless with prominent tenosynovitis and minimal limitation. Over time it may become more destructive and painful. Uveitis can be severe and can result in blindness. The presence of uveitis is a feature that helps distinguish juvenile onset sarcoid from systemic onset JA. Another distinguishing feature is the rash, which is usually papular, or nodular in sarcoidosis, in contrast to the salmon pink macules seen in SOJA. Pulmonary disease is seldom seen in the early onset patients. Angiotensin converting enzyme (ACE) levels are also less likely to be positive (35-37). Diagnosis is clinical and supported by histologic evidence of non-caseating granulomas in affected tissues.

Recurrent Episodic Fevers [\(see Diagnostic Considerations #4\)](#)

Some children with unexplained fever present with a prolonged course of episodes of high grade fever lasting several days to several weeks separated by fever free intervals of variable duration. Children with this fever pattern tend to present at an earlier age and to have higher maximal temperatures than those presenting as classic FUO (38). Although the term “periodic fever syndromes “ has been used to describe this presentation, most of the disorders classified in this group have fevers that occur at irregular and unpredictable intervals (39). An exception to this rule is the PFAPA syndrome (periodic fever, aphthous ulcers, pharyngitis and adenopathy) which has episodes of high fever lasting an average of 3 days, and recurring at regular intervals of 21-28 days, especially in the first year of disease. The majority of cases occur in children less than 5 years of age. The most common associated manifestations are cervical adenopathy, pharyngitis and aphthous stomatitis. This condition is non-familial and diagnosis is based on clinical criteria (40, 41).

Cyclic neutropenia also exhibits regular intervals of fever and should be considered in the differential diagnosis (40).

The identification and characterization of the genes responsible for several of the familial periodic fever syndromes has created an explosion of knowledge in this area. A brief overview of these conditions is provided, and the interested reader is directed to several excellent reviews (39-44).

Familial Mediterranean Fever (FMF) is an autosomal recessive disease occurring primarily in people of eastern Mediterranean ancestry (40). Most cases develop prior to the age of 20 years. The classic presentation is fever with serositis, especially peritonitis. Attacks typically last 1-3 days and are almost always associated with pain in the abdomen, joints or chest (39).

Hyper IgD syndrome (HIDS) is an autosomal recessive disease most commonly seen in people of Dutch or French ancestry. The classic triad of features is fever, cervical adenopathy and diarrhea. A distinguishing feature of this condition is the early age of onset, usually below the age of 1 year and it is frequently triggered by immunization. IgD levels are typically greater than 100 during attacks, but diagnosis is based on genetic analysis (40, 43).

Tumor necrosis factor (TNF) receptor associated periodic syndrome (TRAPS) is an autosomal dominant disease. Distinguishing features of TRAPS include the longer duration of fever episodes, some lasting weeks, periorbital edema, and localized myalgias (39, 40).

Mutations in a single gene, CIAS1, appear to be responsible for the auto-inflammatory syndromes of familial cold urticaria (FCU), Muckle-Wells syndrome, and Chronic Infantile Neurological Cutaneous and Articular Syndrome (CINCA)/Neonatal Onset Multisystem Inflammatory Disease (NOMID). FCU is characterized by cold induced episodes of fever, urticaria, arthralgias, and conjunctivitis. Muckle-Wells syndrome is similar, but is not triggered by cold, and patients eventually develop sensorineural hearing loss (40). CINCA/NOMID is characterized by very early onset of rash (often at birth), a characteristic arthropathy, and involvement of the central nervous system including the sensory organs accompanied by recurrent fever and inflammation. (44)

Both Bechet's Disease and Inflammatory Bowel Disease can present with a recurrent fever pattern (39, 40)

Evaluation of the patient

History

A thorough history and physical are essential in the evaluation of the patient with unexplained fever. *Multiple pediatric FUO series indicate that the history and physical suggested the final diagnosis in the vast majority of patients (1, 2, 5).* A detailed history of the present illness should be elicited including the duration, intensity, and pattern of the fever as well as associated symptoms. A complete review of systems should be performed with particular attention to musculoskeletal symptoms, mucocutaneous manifestations, ocular problems, and gastrointestinal symptoms. A history of prior illness, particularly streptococcal infection or a severe diarrhea before the onset of symptoms may be an important

clue. Travel history, exposure to pets, a complete list of medications, family and social history may also provide pertinent information.

Physical Examination

Physical examination should include vital signs, including blood pressure, height and weight plotted on a growth curve and a general gestalt of the patient (does the patient appear acutely or chronically ill?). Although weight loss was not found to be either a differential or prognostic feature in Pizzo's FUO series (2), in cases of very prolonged or periodic fevers its absence can be reassuring. Eyes should be carefully checked. Formal ophthalmologic evaluation, especially slit lamp, is non-invasive and may provide diagnostic clues. The presence of palatal vasculitis or aphthous ulcers of the nose, mouth, or genital area should be noted. Lymphadenopathy and hepatosplenomegaly are non-specific but suggest a systemic process. Localized findings such as a new heart murmur may be extremely useful in directing further workup. The skin should be carefully assessed for petechiae, purpura, nodules, and edema, as well as rashes including those distributed on the hand or in photosensitive areas. Each peripheral joint should be assessed for swelling, heat, redness, tenderness and range of motion. The child's gait should be observed and the spine checked for tenderness and range of motion. Long bones should be palpated for areas of tenderness. Muscle weakness is often mistaken for generalized debilitation. Formal muscle testing as well as observation of the patient's ability to get on the exam table or sit up from a supine position may detect specific abnormalities.

Laboratory and Radiology

Complete Blood Count (CBC)

Although a CBC does not provide diagnostically specific information, it is still a useful screening test in the evaluation of a patient with fever and arthritis. Leucocytosis, anemia, and thrombocytosis all may indicate systemic inflammation, and are commonly present in patients acutely ill with collagen

vascular diseases (CVD). The exception to this is SLE, with which an active patient often has leucopenia, and thrombocytopenia. Differential counts are also helpful since most patients with CVD will have a neutrophilic predominance (2). Eosinophilia is suggestive of Churg-Strauss vasculitis. A low white blood cell count, or thrombocytopenia in a patient without lupus, or neutropenia should prompt consideration of leukemia.

Urinalysis

Urinalysis should always be performed since evidence of nephritis is an important clue suggesting SLE or other forms of vasculitis.

Erythrocyte Sedimentation Rate (ESR)

An elevated ESR is present in most CVD patients with fever (3). This is a highly non-specific test, but a normal result in an acutely ill patient makes the diagnosis of an inflammatory condition much less likely. If a patient has a high ESR but a normal platelet count, leukemia should be considered.

Serum Protein Analysis

A low albumin and elevated globulin are another non-specific indication of inflammation and have been found to be of use in suggesting CVD in some FUO series (2, 3).

Immunologic Serology

As previously discussed, the diagnostic yield of autoantibody tests is low unless drawn in the context of findings suggestive of a *specific* collagen vascular disease (28). The ANA is very non-specific and can be positive both in infections and in malignancy.

Other

Additional testing such as muscle enzymes, LDH, uric acid, infectious antibody titers or additional cultures should be directed by specific indications.

Plain films of joints are rarely helpful, and in one FUO series, all such studies were negative, including those in patients with active juvenile arthritis (3). The diagnostic yield of abdominal ultrasound, gallium scans, indium scans, and bone marrow biopsies have been shown to be low, except when directed by specific indication (4, 45, 46).

Conclusion

Five to twenty percent of FUOs in childhood are ultimately determined to be caused by a collagen vascular disease. The most common rheumatic diseases to present with fever in childhood are systemic onset juvenile arthritis, systemic lupus, and Kawasaki Disease. In evaluating unexplained fever in the context of symptoms suggestive of a rheumatic disorder, detailed history and a thorough physical examination yield the most significant information. Familiarity with the clinical presentation of rheumatic diseases and recognition of typical disease patterns is essential in guiding laboratory and radiographic investigation and in the interpretation of serologic studies. Conditions which may mimic rheumatic disorders, such as infection or malignancy, must be considered in the differential diagnosis. Close clinical follow-up and re-evaluation of the patient over time may be necessary to establish the diagnosis.

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