



ORIGINAL ARTICLE

Fever of Unknown Origin Among Children in Two Private, Urban, Tertiary Hospitals: A 27-year Retrospective Study

Robert Dennis J. Garcia, M.D., M.H.S.A.

Makati Medical Center
Cardinal Santos Medical Center

Correspondence:
Dr. Robert Dennis J. Garcia
Email: rdgarcia59@yahoo.com

The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

ABSTRACT

Introduction: Fever of unknown origin (FUO) is a problem commonly encountered by infectious disease specialists, and even general pediatricians, in spite of the improvement in diagnostic modalities. There is no local study on childhood FUO from a private hospital. Thus, there is a need to determine the etiology of FUO seen in private practice, which may be different from those encountered in government or teaching hospitals.

Objectives: The purpose of this study is to identify the etiologies of childhood FUO from two private, urban, tertiary hospitals, as evaluated by a single pediatric infectious disease physician; and to discuss epidemiologic, clinical and diagnostic clues for the most common etiologies.

Methods: Childhood FUO cases were compiled from 1993 to 2020. Each consecutive, inpatient, admission or referral of a patient, 18 years or younger, was logged into a personal computer, and the discharge diagnosis for the FUO was recorded. Clinical, epidemiologic, diagnostic and therapeutic data, relevant to the FUO diagnosis were likewise recorded. FUO was defined as daily fever of 38°C for ten consecutive days, or more, with no etiology identified after being admitted for seven days.

Results: Of 171 cases of childhood FUO, the etiology was an infection in 68%, collagen-vascular disease in 13%, miscellaneous cause in 8%, malignancy in 6%, and no diagnosis in 5%. The most common infections were Epstein Barr Virus (EBV) mononucleosis, tuberculosis, enteric fever, sinusitis, pneumonia and incomplete Kawasaki disease. The most common collagen vascular diseases were juvenile idiopathic arthritis and systemic lupus erythematosus. Hemophagocytic lymphohistiocytosis was the most common miscellaneous cause. Lymphoma was the most common malignancy.

Conclusion: This study found EBV mononucleosis, sinusitis, pneumonia, incomplete Kawasaki disease, lymphoma, HLH and Kikuchi-Fujimoto disease to be FUO etiologies not reported previously in other local reports.

INTRODUCTION

Fever of unknown origin (FUO) is defined as fever of 8-21 days or more, according to different authors, with no diagnosis being evident after a careful history, physical examination and preliminary diagnostic evaluation.¹⁻⁶ This problem is encountered commonly by infectious disease specialists, and occasionally, by general pediatricians, in spite of improvement in diagnostic modalities. Locally, FUOs are due to infections in 44-54%, collagen-vascular disease in 6-39%, malignancies in 14-21%, histiocytosis in 0-7%, and are without a diagnosis in 4-18%.⁴⁻⁶

Studies from the Philippine General Hospital, Philippine Children's Medical Center and the University of the East-Ramon Magsaysay Medical Center showed that infections that most commonly cause FUO are enteric fever, tuberculosis (TB), and septicemia. The most common non-infectious causes are juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), leukemia, lymphoma and histiocytosis.⁴⁻⁷ There are no reports from private, non-teaching institutions.

There is a need to be aware of the most common causes of FUO in private hospitals, where patients and hospital resources are less constrained by economic factors, so that clinicians who practice outside of urban centers, where diagnostic tests and radiographic imaging are not readily available, may be guided on the appropriate evaluation and treatment of FUO. When access to a good laboratory is hampered, even infectious disease specialists may not be able to provide the appropriate evaluation and treatment. Thus, there is a continuing need to identify the most common causes of FUO in both private and government hospitals, in order to provide efficient care and decrease morbidity and mortality.

The purpose of this study is to identify the etiologies of childhood FUO, as seen and evaluated by a single pediatric infectious disease physician, in two private, urban, tertiary hospitals, over a 27-year period. Secondly, epidemiologic, clinical and diagnostic clues to the diagnosis of the most common causes of childhood FUO will be presented.

MATERIALS AND METHODS

Cases in this study of childhood FUO were compiled from 1993 to 2020. Each consecutive, inpatient admission or referral of a patient 18 years or younger,

was logged into a personal computer and cases in which a discharge diagnosis of FUO, together with the eventual identified diagnosis to explain the FUO (if any such was arrived at), were included in this study. Clinical, epidemiologic, diagnostic and therapeutic data, relevant to the FUO diagnosis, were recorded in each patient's account. The inclusion criteria for FUO were: fever of 38°C, or more, at any time during a 24-hour period, for ten consecutive days, or more, before the hospital admission, and during the hospital admission; with no etiology identified for the fever, after being admitted and evaluated as an inpatient for seven days, or more.

As the cases were compiled over 27 years, diagnostic tests to determine illness etiology evolved over time. The etiologic diagnosis was made, with the following criteria:

1. Epstein Barr Virus (EBV) mononucleosis: clinical findings, with a positive result for a serum heterophile antibody test; or EBV IgM and/or IgG; or/and an EBV polymerase chain reaction (PCR) test.
2. TB disease: clinical findings, a positive 5 TU PPD test or a serum TB Quantiferon result, characteristic radiographic findings, epidemiology, and laboratory findings (positive AFB smear, TB GeneXpert, and/or *Mycobacterium tuberculosis* culture). In addition, for TB lymphadenitis, pathologic findings of caseation necrosis, or a positive AFB smear, or *M. tuberculosis* culture of tissue; for TB meningitis, characteristic cerebrospinal (CSF) results and computerized tomography (CT) or magnetic resonance imaging (MRI) findings of hydrocephalus, basal cistern enhancement and/or presence of CNS tuberculomas; for vertebral TB osteomyelitis, typical radiographic findings of anterior vertebral body collapse, anterior paraspinal abscess, and disc narrowing between affected vertebrae.
3. Enteric fever: clinical findings, and a blood culture growth of *Salmonella typhi* or *Salmonella paratyphi*; or a positive Typhi IgM, if the child was previously treated with antimicrobials, and had no growth in a blood culture.
4. Paranasal sinusitis: clinical findings, confirmed by a paranasal sinus radiograph or a CT scan.
5. Pneumonia: clinical findings, confirmed with a chest radiograph or CT scan. Bacterial organisms were identified using standard laboratory methods; mycoplasma disease was identified using the

Immunocard Mycoplasma IgM test; *Pneumocystis jirovecii* was identified by a methenamine silver stain of Gomori, direct fluorescent antigen staining, or by PCR testing.

6. Herpes simplex virus (HSV) encephalitis: clinical findings, and a positive serology for HSV-1 or HSV-2 IgM or IgG, or a positive CSF HSV PCR result, and cranial CT or MRI findings compatible with the disease.
7. Anti-NMDA encephalitis: clinical findings, and a positive result for anti-NMDA receptor antibody.
8. Juvenile idiopathic arthritis (JIA): clinical findings, with the concurrence of the rheumatology service fulfilling the criteria for JIA.⁸
9. Kikuchi-Fujimoto disease: characteristic lymph node biopsy findings.⁹⁻¹⁰
10. Malignancies: based on biopsy, or bone marrow aspirate pathology, in conjunction with an oncology referral.
11. Hemophagocytic lymphohistiocytosis (HLH): based on standard criteria.⁸⁻¹¹

Excluded were cases of patients who have chemotherapy-associated febrile neutropenia, HIV-related FUO, and infants born in the study institutions, who have not been discharged from the nursery after their neonatal stay.

This study was approved by each hospital's Institutional Review Board. As all the cases were obtained from the author's personal files in a password-protected, personal computer, no medical records were accessed from the hospitals' medical records department. The author declares no conflict of interest in the conduct of this study.

RESULTS

Table 1: FUO causes from two private, urban, tertiary hospitals, 1993-2020: (n=171)

Infections	116 (68%)
Mononucleosis	25
Tuberculosis	22
Enteric fever	16
Sinusitis	11
Pneumonia	7
Incomplete Kawasaki disease	5
Endocarditis	4
Rheumatic fever, with arthritis and no carditis	2
<i>Clostridium difficile</i> colitis	2

Urinary tract infection	2
Cervical lymphadenitis	2
HSV meningoencephalitis	2
Anti-NMDA encephalitis	2
Post-meningitic <i>Escherichia coli</i> frontal subdural abscess	1
<i>Staphylococcus aureus</i> bacteremia	1
<i>Brevundimonas spp.</i> sepsis	1
<i>Pseudomonas aeruginosa</i> tonsillitis	1
Retroperitoneal abscess secondary to a femoral vein perforated by a Broviac catheter	1
Multiple liver abscesses	1
Ruptured Appendicitis	1
Acute hemorrhagic pancreatitis	1
Ventriculo-peritoneal shunt infection	1
Leptospirosis	1
Bronchitis, cold-agglutinin-positive	1
Cryptococcal meningitis	1
HyperIgE eosinophilia syndrome with pneumonia and pyoderma	1
Systemic viral illness, clinical	1
Collagen Vascular Diseases	23 (13%)
Juvenile idiopathic arthritis	13
Systemic lupus erythematosus	5
Erythema nodosum	1
Henoch-Schonlein purpura	1
Takayasu's arteritis	1
Behcet's syndrome	1
Vasculitis, unspecified	1

Miscellaneous	13 (8%)
Hemophagocytic lymphohistiocytosis	7
Kikuchi-Fujimoto disease	3
Inflammatory bowel disease	3
Malignancies	11 (6%)
Lymphoma	7
Leukemia	2
Craniopharyngioma	1
Dysgerminoma	1
No diagnosis	8 (5%)
Total	171

Table 2: Epidemiologic, clinical and diagnostic clues to FOU etiology

1. Age:
 - a. Under 3 years old: Kawasaki disease
 - b. Over 3 years old: Enteric fever, *Mycoplasma pneumoniae*
 - c. Over 6 years old: Collagen vascular diseases are equally prominent as infection; endocarditis
 - d. Adolescents: EBV mononucleosis, Kikuchi-Fujimoto disease
2. Length of fever:
 - a. Over 2 months: Collagen vascular diseases (JRA, SLE); malignancy (lymphoma, leukemia); TB; uncommon for bacterial causes
 - b. 10 days to <2 months: EBV mononucleosis
3. Previous or current antibiotic use, but non-improving:
 - a. With respiratory symptoms: *Mycoplasma pneumoniae*, TB, *Pneumocystis jirovecii*
 - b. No respiratory symptoms: Enteric fever
 - c. Broad spectrum intravenous: *Clostridium difficile* colitis
4. Toxicity:
 - a. Absence of, or little signs of toxicity: Paranasal sinusitis
5. Cervical lymphadenopathy:
 - a. With or without hepatosplenomegaly: EBV, lymphoma, TB
 - b. Without hepatosplenomegaly: Kawasaki disease, Kikuchi-Fujimoto disease
6. Rash:
 - a. Maculopapular, urticarial or erythema multiforme-like: Kawasaki disease
 - b. Maculopapular: EBV
 - c. Fleeting maculopapular: JIA
 - d. Malar maculopapular: SLE
 - e. Purpuric: Henoch-Schonlein purpura and leukemia
7. Transaminases (SGPT):
 - a. Elevated SGPT = 60-200: Kawasaki disease, enteric fever, EBV
8. WBC count:
 - a. Normal: Enteric fever, *Mycoplasma pneumoniae*
9. Platelet count:
 - a. Increased: Kawasaki disease, deep organ abscess

- b. Decreased: Enteric fever, after the 7th day of fever; EBV, SLE, leukemia, HLH, Kikuchi-Fujimoto disease

DISCUSSION

This report identifies etiologies of childhood FOU among 171 inpatients seen by one pediatric infectious disease specialist over 27 years in two private, urban, tertiary hospitals. Fever of unknown origin had an infectious disease cause in 68%, with EBV, TB, enteric fever, sinusitis, pneumonia and incomplete Kawasaki disease being most commonly seen; collagen-vascular disease in 13%, malignancy in 5%, with lymphoma being most common; HLH in 4%; and no diagnosis in 5%.

Mononucleosis due to EBV was the most common infectious cause of FOU in this study. This finding has not been previously reported in four local studies of childhood FOU from three Metro Manila tertiary hospitals.⁴⁻⁷ A recent local study of 23 childhood (mean age, 9 years) EBV cases from one of the hospitals in this study, showed a median fever length of nine days (range, 3-20 days); fever was seen in 100%, pharyngitis in 65%, cervical lymphadenopathy in 57%, a non-specific rash and exudates on tonsils.¹² Western studies and a Taiwanese study have reported EBV to be the most common infectious cause of FOU.^{3,16-17} Disease due to EBV should be suspected in adolescents and pre-adolescents who have fever, pharyngitis and/or tonsillitis, neck lymphadenopathy, splenomegaly, elevated serum transaminases and leukocytosis, especially if such patients continue to be febrile in spite of being given a beta-lactam or macrolide antibiotic that would normally treat *Streptococcus pyogenes*.

Tuberculosis was the second most common infectious cause of FOU with 22 cases (13%). In the four other local studies on FOU, TB was among the top three infectious causes of FOU.⁴⁻⁷ Among 174 inpatient cases of TB disease diagnosed in these two study hospitals between 1993-2020, illness was most commonly due to primary TB in 48%, TB cervical lymphadenitis in 16%, TB pneumonia in 14%, Pott's disease in 9% and TB meningitis in 6%; however, only 13% of the TB disease cases in this group presented as FOU (data not shown). Among the 22 that did cause FOU, 13 were due to either primary TB or TB pneumonia, while four had TB meningitis. Many cases with primary TB were admitted for fever, with no radiographic evidence of TB chest

infection initially, but because of non-defervescence, a repeat chest radiograph subsequently showed the findings of primary TB. Other cases presented with fever and clinico-radiographic evidence of a non-hypoxemic pneumonia, often, with a sub-acute course; after being treated with beta-lactam antimicrobials and/or macrolides, fever continued, and subsequent diagnostic procedures (5 TU PPD or serum TB quantiferon, repeat chest radiograph or chest CT, or sputum/gastric lavage for AFB smear, TB culture, and/or TB GeneXpert) showed that TB pneumonia was the cause of the prolonged fever, with defervescence occurring following the use of anti-tuberculous drugs. TB meningitis (TBM) caused four cases of FUO. In a report of 17 cases of TBM over 20 years from one of the hospitals in this study, fever (mean duration, 27 days) was seen in 100%.¹⁰ For the four TBM cases which were FUO cases in this study, an initial cranial CT or MRI did not show the characteristic findings of TBM, but a subsequent imaging study showed the sought-out findings. Cerebrospinal fluid (CSF) tests may not be readily indicative of TBM, as CSF pleocytosis may not be revealing. One boy in this series had FUO for three months, and was found to have disseminated TB (intra-peritoneal TB, ascites, hepatosplenomegaly, pleural and pericardial effusion and pulmonary nodules). On the other hand, although TB lymphadenitis is the second most common form of TB disease, it is usually an afebrile illness, and should not cause FUO.¹⁶⁻¹⁷ In a local report from one of the study hospitals, fever was only seen in 16% of cervical lymph node biopsy cases, for which TB lymphadenitis was the pathologic diagnosis.¹⁸

Enteric fever was the third most common infectious FUO cause in this study; in the other four local studies, it was the leading cause in three reports, and second most common in one.⁴⁻⁷ In Metro Manila, *Salmonella typhi* or *Salmonella paratyphi* used to be the top two causes of community-acquired bacteremia but in 2001, the Metro Manila Water Supply System was sold by the national government to two private companies, and the cases of enteric fever noticeably dropped steadily over the past two decades, so that most of the cases in this report were seen in the 1990s and early 2000s. In the two hospitals in this study, the author saw 242 cases of community-acquired bacteremia during the study period, 173 (72%) of which were due to *S. typhi* or *S. paratyphi* (data not shown). Enteric fever causes prolonged fever, often without respiratory signs,

accompanied by fatigue, anorexia and abdominal pain; a minority will have vomiting or diarrhea. Physical examination often only shows pallor and right upper quadrant tenderness. An epidemiologic history will often indicate a risk factor(s): eating street vendor food and/or shellfish, contact with chicken or turtles, and/or recent travel. Important clues in the laboratory results are a normal white blood cell count, unlike most other bacterial infections, in spite of a prolonged fever; a neutrophil predominance; and a mild to moderate elevation in the SGPT or SGOT levels. When the rapid test, Typhi IgM and IgG, became available in 1995, many cases of enteric fever were diagnosed earlier, and not labeled as FUO; previous to that, many such cases took some time to be diagnosed and treated, because blood cultures would yield no growth, often due to the previous outpatient use of antimicrobials like amoxicillin or cotrimoxazole before the hospital admission.

Sinusitis caused 11 FUOs. The usual findings in these children were prolonged low-grade fever with cough and prominent rhinorrhea, a history of allergic rhinitis, and absence of rales and/or wheezes, upon chest auscultation. Often, the child was admitted because of prolonged, intermittent fever, but not because the patient was ill-looking. The important hallmark noted in this study of children with prolonged fever and sinusitis was their non-toxic appearance.

Pneumonia was a cause of FUO in seven cases (4% of total). In two, mycoplasma was eventually diagnosed by serology; and in two cases, pneumonia occurred in children with congenital heart ailments. In one of the study hospitals, two previous studies found that 26% and 28% of children admitted for pneumonia tested positive for a serum mycoplasma IgM test; all such mycoplasma IgM-positive patients were febrile on admission, though fever, in general, was not prolonged. However, in the two studies, a frequent reason for the hospital admission was the child's continued fever in spite of receiving a beta-lactam antibacterial, which is not the suggested treatment for mycoplasma pneumonia.¹⁹⁻²⁰ This may explain why the two mycoplasma cases in this present study had prolonged fever, which resolved when a macrolide was given. One 18-year old, CD4-lymphocytopenic, HIV-negative, male, with pneumonia and fever for one month, was found to have *Pneumocystis jirovecii*.

There were five cases (3%) of incomplete KD as a cause of FUO. This number is 3% of the 160 KD cases seen by the author in the two study hospitals during the same time period (data not shown). Kawasaki disease may cause prolonged fever, especially when the physician is not familiar with the illness.¹⁷ In these two institutions, 22% of KD cases were incomplete Kawasaki cases, which may have led to a longer time to diagnose. Patients with KD also had pneumonia (4%), sinusitis (3%), cellulitis over the cervical node (3%), jaundice (3%), and toxic shock syndrome (1%), all of which, required evaluation and treatment, because part of the diagnosis of KD is to rule out all other reasonable causes for the illness; the process of evaluating and treating these co-morbid illnesses can extend the length of fever, before intravenous immunoglobulin is finally given (data not shown). In other countries, KD was the FUO cause in 6% of 185 childhood FUO cases in Serbia, and was the top miscellaneous cause of FUO in a Taiwanese study.^{3,14}

There was one case diagnosed to have a systemic viral infection. This occurred early during the study period, when many diagnostic tests (i.e., EBV, mycoplasma tests) were not yet available. The child eventually defervesced, without antimicrobial use.

Juvenile idiopathic arthritis (JIA) was the most common collagen-vascular disease cause of FUO, with 8% of the total. All cases were diagnosed using current criteria.⁸ Among the twelve JIA cases, all presented as systemic-onset disease with prolonged fever, and joint manifestations only appeared at two to three weeks, or longer, after the onset of fever. Serum ferritin levels were elevated in all. In American FUO reports, JRA was the most common collagen-vascular disease cause of FUO.^{2,13} In a classic childhood FUO article, Pizzo, et al, noted that when children are six years and older, connective tissue diseases are almost equal as infections, in frequency (32% vs. 38%), as the cause of FUO, as compared to children younger than six years, in whom infections are much more common causes, than collagen-vascular diseases (68% vs.8%).² Other than presenting as a systemic-onset illness, JIA cases become labeled as FUOs because, unlike infections and malignancies, there are no definitive diagnostic tests for JIA and a criterion for the diagnosis is that the illness has to have had a duration of six weeks, or more.

There were five cases (3%) of SLE as an FUO cause. Although an anti-nuclear antibody is frequently requested during an FUO work-up, the yield for a significant result has not been high (data not shown). In four local studies, including the present, JIA was a more common collagen-vascular disease to cause FUO, than SLE; only the PGH study found SLE to be more common. In foreign reports, SLE has also been found to be less common than JIA to cause childhood FUO.^{2,13}

Hemophagocytic lymphohistiocytosis (HLH), which is not classified as an infection, collagen-vascular disease, or malignancy, was diagnosed in seven cases (4%). Four cases were post-EBV infection, two were post-salmonella bacteremia, and one was post-COVID-19 infection in a 13-year old boy, who also had COVID-associated MIS-C. Earlier studies had used the term histiocytosis. In the two institutions in this study, HLH has been increasingly diagnosed between 2010 to 2020, with 16 cases seen, 13 of which were secondary to an identified infection (EBV in six; dengue or cytomegalovirus in two, each; and *Klebsiella pneumoniae* sepsis, *Salmonella spp.* sepsis, and COVID-19 infection in one, each) and one being secondary to JIA. The illness is an infrequent, life-threatening disease of severe hyperinflammation; cytokines are secreted in large amounts and macrophages phagocytose blood cells. The diagnosis is made in the presence of five of the HLH-2004 criteria.¹¹ This diagnosis should be kept in mind especially in EBV cases, in which prolonged fever and splenomegaly are commonly present; if such fevers continue, and cytopenias evolve, checking serum ferritin, triglyceride and fibrinogen levels should be considered, to determine if the EBV infection is being complicated by a secondary HLH, which will entail additional therapy.

Kikuchi-Fujimoto disease (KFD) was seen in three cases (2%). This illness has only been reported once, locally, in a 12-year old child, though not as an FUO cause; another local report was of three adults.¹⁹⁻²⁰ This report's three cases were of a 10, 15 and 16 year-olds who had fever of 14, 18 and 42 days, respectively; non-specific symptoms were rash, myalgia, malaise, and night sweats. Two had an ANA of 1:80. As the only other physical examination findings were enlarged cervical lymph nodes in two, and a supraclavicular and axillary lymph node in one, biopsies were performed, due to a concern for malignancy. The biopsy subsequently showed pathologic findings of KFD.⁹⁻¹⁰ This illness is a

cause of lymphadenitis, usually manifesting as painless, unilateral, cervical lymphadenopathy. Fever is seen in 33-40%, and the disease is a known cause of FUO.²¹ There may be a rash in 16-40%, with nonspecific skin lesions; less commonly, there may be weight loss, malaise, chills, night sweats, vomiting and diarrhea.²⁴ Rarely, lymphadenopathy may be generalized, to involve the mediastinum and peritoneum. Laboratory tests may show neutropenia, atypical lymphocytosis, thrombocytopenia, and elevated ESR, transaminases, lactate dehydrogenase and ferritin.²⁵ The diagnosis is made only by finding the characteristic lymph node biopsy features of KFD.²⁴ Not all pathologists are familiar with the disease, so that the clinician has to alert the former, beforehand, to look for KFD. There is no treatment necessary, and symptoms usually resolve in one to four months, but recurrence may occur, and illness may last as long as one year.²⁵

Inflammatory bowel disease (IBD) was seen in three cases (2%). All were suspected to have intestinal TB, but were eventually diagnosed with IBD, after colonoscopy and biopsies were performed.

Lymphoma was the most common malignancy, causing seven cases (4%). Due to the often, sub-acute growth of lymphomas in the neck, and the relative frequency of TB lymphadenitis locally, which similarly grows in a sub-acute manner, the diagnosis may be delayed because, as many Filipinos will have a positive PPD or TB Quantiferon test, many such cases of cervical lymph node enlargement will be treated for TB empirically, before it is realized that the mass is not diminishing in size, nor the fever breaking, if fever is prominent. An important clue against TB is that isolated TB of the lymph nodes is usually an afebrile illness;^{16,18,26} however, in a local study of biopsied enlarged lymph nodes, 80% of children with a pathologic diagnosis of lymphoma were afebrile.¹⁸ Lymphomas which are not found under cutaneous areas (intra-thoracic and intra-abdominal) may be even more difficult to diagnose because of the need for an invasive procedure, thereby causing prolonged fever.

Table 2 shows epidemiologic, clinical, and diagnostic clues to the etiology of FUO. The evaluation of childhood FUO should be individualized, based on a good history, epidemiology and physical examination. A complete blood count, cultures and serologic tests should be utilized, before more invasive tests are done.

A big aid in the earlier diagnosis of TB, which is likely the top cause of FUO locally, is the TB GeneXpert, a PCR test that can detect the presence of minute amounts of TB organisms in a body fluid sample, with a result available on the same day. Acute-phase reactants like ESR and C-reactive protein (CRP). are useful when the results are negative or low, which predict for a benign or viral illness. Radiologic tests that are most commonly done, in decreasing order, are: chest and paranasal sinus radiographs, abdominal ultrasound, and, as indicated, 2-D echocardiogram, and abdominal CT scan, and a cranial CT scan or MRI. Biopsies are usually saved for last, particularly if malignancy cannot be ruled out. Among the FUO cases seen in this report, an abdominal ultrasound aided in the diagnosis of mononucleosis, HLH and lymphoma, when splenomegaly, with or without, hepatomegaly was seen; and an occult retroperitoneal abscess that resulted from a femoral vein being punctured by a Broviac catheter. An abdominal CT scan revealed a diagnosis of a peri-renal abscess in a one-year old girl with a two-month FUO, which was not seen in an abdominal ultrasound; multiple hepatic, splenic and pelvic Klebsiella abscesses, in a 10-year old child; and a post-appendectomy abscess. A cranial CT scan showed the characteristic findings of TB meningitis, although the findings were not seen in an earlier scan upon admission; a subdural abscess was seen as a complication of *Escherichia coli* meningitis. In a third case, an occult craniopharyngioma in a 12-year old girl with a four-month FUO, was unexpectedly seen in a cranial CT, which was done because the child had a first-time seizure; the child did not have symptoms of increased intra-cranial pressure. Cranial MRI helped in the diagnosis of encephalitis cases. Biopsies yielded the diagnosis of Kikuchi-Fujimoto cases, and, more importantly, ruled out a malignancy. Biopsies also made the diagnosis for extra-pulmonary TB cases (spine, peritoneum, bone, disseminated), malignancies and inflammatory bowel disease (IBD), while ruling out intestinal TB disease among the IBD cases.



CONCLUSION

This 27-year study of 171 cases of childhood FUO found the etiology to be infectious in two-thirds of cases, followed by collagen-vascular disease and malignancy. There was no diagnosis identified in 5%. The most common infections were EBV mononucleosis, TB, enteric fever, sinusitis, pneumonia and incomplete Kawasaki disease. The most common collagen vascular diseases were JIA and SLE. Hemophagocytic lymphohistiocytosis was the most common miscellaneous cause. Lymphoma was the most common malignancy. EBV mononucleosis, sinusitis, pneumonia, incomplete Kawasaki disease, HLH, Kikuchi-Fujimoto disease and lymphoma are childhood FUO etiologies that have not been often reported in previous local reports.

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