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Case Presentation: Fever of Unknown Origin

Disclosure statement

- I have no disclosures.

Objectives

- Explore the differential diagnosis for fever of unknown origin (FUO)
- Discuss pertinent diagnostic testing
- Delineate the ultimate diagnosis

Chief Complaint

- 5 year, 7 month old female presents with fever for 3 weeks.
  - Definitions:
    - Fever of Unknown Origin: fever > 101°F (38.3°C) for more than 1-week duration, in which no diagnosis is apparent after initial outpatient or hospital evaluation that includes a careful history and physical examination and initial laboratory assessment.
    - Fever Without a Source: fever lasting for one week or less without adequate explanation after a careful history and thorough physical examination.

Cogulu O, Koturoglu G, Kurugol Z, et al. Evaluation of 80 children with prolonged fever. Pediatrics International. 2003; 45:564.

History of Present Illness

- Fevers present daily for 3 weeks
  - T max 105.8°F (axillary)
- At beginning of illness had ***enlarged right cervical lymph node*** which has resolved.
- Previous courses of: Cephalexin, Azithromycin and Amoxicillin-clavulanate

English, Robin. Cat-Scratch Disease. Pediatrics in Review. 2006;27;123-128.

Review of Systems

- ***General***: fevers
- ***Skin***: no rashes or lesions
- ***ENT***: no rhinorrhea, no sore throat
- ***Respiratory***: no cough or shortness of breath
- ***Cardiovascular***: no palpitations
- ***GI***: decreased appetite
- ***Neuro***: headaches
- ***Psychiatric***: no anxiety, no depression
- ***Hematology/Lymphatics***: significant right sided cervical LAD at initiation of illness, now resolved

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Past Medical History

- Full term infant
- Developmental milestones age appropriate
- Immunizations UTD
- Allergic to Penicillin: Hives

Social History

- Lives with mom and younger sister in Georgetown, KY
- Pets: dog (inside)
- Has played with cats at a friend's house, denies scratches or bites
- Attends kindergarten, appropriate performance at school
- Mom smokes in the house
- No recent travel history

Family History

- Positive for hypertension and diabetes
- Negative for rheumatologic diseases and cancer

Physical Exam

- Vital signs:
  - T- 39.2°C (102.6°F) HR- 113 RR-22 BP- 126/63
  - SpO2-100% RA
  - Weight: 21.1 kg (70th Percentile)
  - Height: 114 cm (75th Percentile)
  - BMI 16.2 (75th Percentile)

Physical Exam

- ***Gen***: well developed, no distress
- ***Skin***: warm and dry, no rash or lesions
- ***Eyes***: pupils equally round and reactive to light, extraocular movements intact
- ***ENT***: tympanic membranes normal bilaterally, no nasal discharge, throat non-erythematous, no exudate, mucous membranes moist
- ***Neck***: supple
- ***Respiratory***: clear to auscultation bilaterally

Physical Exam (continued)

- ***Cardiovascular***: regular rate and rhythm, II/VI systolic murmur, 2+ equal pulses
- ***GI***: soft, non-tender, positive bowel sounds, no masses or organomegaly
- ***MSK***: no joint swelling or erythema, full ROM
- ***Neuro***: alert, oriented, sensation intact, reflexes and strength normal
- ***Lymphatics***: right sided cervical node small but palpable, mobile and non-tender

Differential Diagnosis

- Infectious
  - EBV, Parvovirus, CMV, Bartonella, Toxoplasmosis, SBE, sinusitis, abscess, atypical mycobacteria, tularemia, brucellosis, tuberculosis
- Rheumatologic
  - Atypical Kawasaki, Sarcoidosis, JIA, Mediterranean fever, Lupus, PFAPA
- Oncologic
  - Neoplasm- leukemia or lymphoma

Work-up…

- CBC: WBC-11.3, Hgb-9.6, Hct-27.8, Plts-368
- Blood, Urine, Stool Cultures: negative
- Throat Culture: negative
- Viral Respiratory Culture: negative

- ESR: 57
- CRP: 11.5

- ANA: negative

- EBV IgG: positive, EBV IgM: negative
- Bartonella IgG: 1:640 (outside lab), Bartonella IgM: negative

Work-up…

- **ECHO**: normal function and structure, normal coronary arteries, no ectasia, aneurysm or stenosis. Trivial pericardial effusion, possible mild pericarditis.
- **Abdominal Ultrasound**: mild splenomegaly, perihepatic ***ascites***, and ***multiple hypoechoic hepatic lesions*** with no flow, consider malignancy vs. infectious.

Work-up…

- CT Neck: cervical LAD, mucosal thickening in sinuses
- CT Chest: unremarkable
- CT Abdomen/Pelvis: multiple nonspecific ***hypo-attenuating lesions*** in right and left hepatic lobes with central focused decreased attenuation. Enlarged para-aortic node and mild splenomegaly.

Consulting Specialists

- Infectious Disease
- Rheumatology
- Hematology/Oncology
- Ophthalmology

Work-up…

- Dilated eye exam: normal dilated eye exam
- Repeat Bartonella titers:
  - IgG: <1:64 (neg)
  - IgM: <1:16 (neg)

And the diagnosis is…

- Cat Scratch Disease

Cat Scratch Disease

- FUO without lymphadenopathy is the presenting symptom in 10-30% of cases of cat scratch disease (CSD).
  - 146 patients presenting with FUO→ 5% CSD.

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Cat Scratch Disease

- *Bartonella henselae*
  - Pleomorphic gram-negative bacilli

Cat Scratch Disease

- More common in autumn and winter months
- Seen more often in warm, humid climates

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Cat Scratch Disease

- Kittens have been shown to have a higher rate of:
  - *B. henselae* bacteremia
  - Antibody to *B. henselae.*

- Transmission between cats occurs via the cat flea.
  - Flea not believed to be responsible for the transmission from cats to humans.
  - Human-to-human transmission does not occur.

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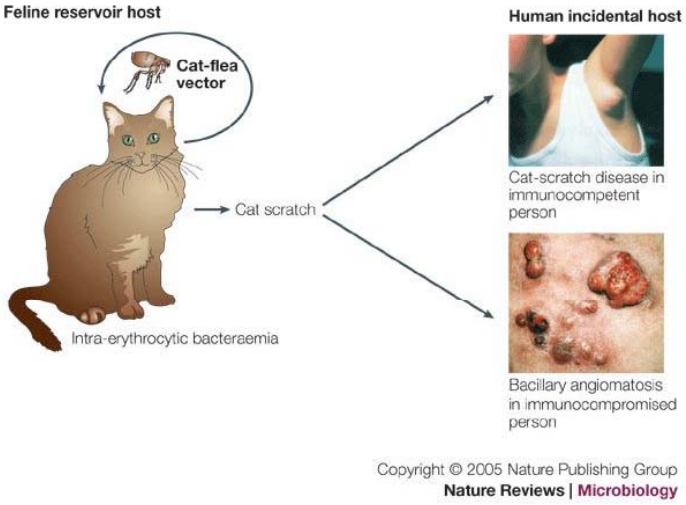
Cat Scratch Disease

- Cat scratches or bites= Transmission

- Patient recall not accurate

Cat Scratch Disease



Catch Scratch Disease

- Incubation period is 7 to 12 days.
- Regional lymphadenopathy occurs 1 to several weeks later.

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Cat Scratch Disease: lymphadenopathy

Cat Scratch Disease: lymphadenopathy

Cat Scratch Disease: lymphadenopathy

- Most common sites:
  - Cervical and Axillary
- Affected nodes vary in presentation:
  - Small, undetectable
  - Tender, warm, erythematous
    - 10-30% eventually suppurate
  - Enlarged nodes may persist for weeks to months

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Cat Scratch Disease: Rare Manifestations

- Parinaud oculoglandular syndrome
- Multifocal hepatosplenic microabscesses
- Osteolytic bone lesions
- Thrombocytopenic purpura
- Neurologic complications: headache→encephalopathy→seizures
- Neuroretinitis

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Cat Scratch Disease: Diagnosis

- Serologic testing-
  - Enzyme immunoassay (EIA)
    - IgM or IgG- sensitivity of 85% and specificity of 98-99%
  - Immunofluorescent antibody (IFA)
    - IgG- sensitivity of 88-100% and specificity of 92-98%

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Cat Scratch Disease: Diagnosis

- Recent study examined EIA results in 98 patients with CSD:
  - 53% were positive for IgM
  - 92% were positive for IgG

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Cat Scratch Disease: Management

- Generally self-limited
  - Warm compresses to affected nodes
  - Antipyretics
- Antibiotic treatments have shown little or no improvement
  - Macrolides, rifampin, doxycycline, ciprofloxacin and gentamicin.

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Cat Scratch Disease: Management

- Treatment of suppurative lymph nodes:
  - Needle aspiration
    - May decrease pain and provide material for diagnosis

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Cat Scratch Disease: Prevention

- Elimination of fleas
  - Decreased transmission among cats

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Cat Scratch Disease: Prognosis

- Excellent prognosis regardless of clinical presentation and antibiotic therapy.
- Most cases resolve within 2-4 months
  - Lymph nodes may remain enlarged for several months to years

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Review questions

- Which of the following statements is a true statement regarding cat-scratch disease?
  - A. *Afipia felis* is believed to be the causative organism.
  - B. Elimination of fleas is the best way to avoid cat-scratch disease.
  - C. Human-to-human transmission is the most common mode of transmission.
  - D. Pet cats have a higher incidence of bacteremia than stray cats.
  - E. Removal of the cat from the home is required for full recovery.

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Review questions

- You are evaluating a 5 year old girl who has had right anterior cervical lymphadenopathy for 3 weeks. She reports getting a new kitten 2 months ago. Findings on her physical examination are unremarkable except for a 3x3 cm mobile lymph node in the right anterior cervical triangle. You suspect cat-scratch disease. Which of the following is the most appropriate initial management of this patient?
  - A. Admit her to the hospital for intravenous gentamicin therapy.
  - B. Observe her on an outpatient basis without medications.
  - C. Perform a needle aspiration of the lymph node.
  - D. Prescribe a 5-day course of oral steroids.
  - E. Refer her to an otolaryngologist for surgical excision of the lymph node.

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Review questions

- An 8-year old girl who has a 3-week history of daily fevers to 102 presents to your office for evaluation. She denies other symptoms. She denies any cat scratches but reports that she occasionally plays with a cat behind her house. Overall, she appears well, and her physical examination findings are normal except for a 1x1 cm axillary node on the left. You suspect cat scratch disease but would like to confirm the diagnosis. Which of the following tests is most appropriate at this time?

- A. *Bartonella henselae* antigen skin testing.
- B. Blood culture for *Bartonella henselae*.
- C. Immunofluorescent antibody assay for *Bartonella henselae*.
- D. Lymph node biopsy.
- E. Magnetic resonance imaging of the liver and spleen.

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Sources

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Earhart K. and M. Power. Bartonella Neuroretinitis. Images in Clinical Medicine. 2000;343;20: 1459.

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Images: Google images