
بسم الله الرحمن الرحیم

Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)

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Recurrent fever :

- ✓ “A single illness in which fever and other signs and symptoms wane and wax and separated by periods of normal temperature with regular or irregular intervals”.

Periodic Fever:

- ✓“≥3 episodes of fever in a 6 month period with no defined medical illness to explain the fever and with an interval of at least 7 days in between febrile episodes”

Signs and symptoms suggestive of a specific diagnosis in the child with recurrent fever:

Uveitis: IBD, Behçet's disease
Painful conjunctivitis: TRAPS
Sensorineural deafness: Muckle-Wells syndrome
Pleuritis/pericarditis: FMF, Still's disease
Peritonitis/acute abdomen: FMF
Acute abdomen with preceding diarrhea: HIDS
Splenomegaly: Still's disease, HIDS, FMF
Genital ulcers: Behçet's disease
Localized myalgia: TRAPS
Erythema nodosum: IBD
Attack precipitated by immunization: HIDS
Attack precipitated by cold: familial cold urticaria

Approach

1- (**A.** Dairy fever pattern→ Pseudo-fever?!

B. Exam the pt at the time of fever)

2A.Hx:

- Age
- Onset
- Abx Usage
- Bad chance baby
- Duration
- Constant VS Recurrent

2B.P.Ex

- Establish fever
- Establish pattern of fever
- Associated Findings:

Dental caries , Sinusitis , Rash, Arthritis, Uveitis , LAP and HSMG

3. Fevers at Regular Intervals

- Fever occurring at regular intervals:
  - PFAPA syndrome
    - (high fever q21-28 days Leukocytosis, ↑ESR)
  - Cyclic neutropenia (Uncommon)
    - May be clinically indistinguishable from PFAPA
    - Usually no bacterial infection during neutropenia
    - Diagnosis
      - CBC X2-3/week for 6 weeks (ANC <500) and spontaneous recovery
      - Bone marrow

- **Relapsing fever** (*Borrelia* spp. other than *burgdorferri* - Fevers 1-6 days separated by 4-14 days
  - "Crisis" (↑BP,HR) followed by profuse diaphoresis, falling temperature, and ↓BP.

- Fever occasionally at regular intervals
  - *FMF*
  - *HIgD syndrome*
  - *EBV infection*

4.Fevers at Irregular Intervals

Fever occurring at irregular/unpredictable intervals
- Infectious
- Viral
  - Repeated viral infections*
  - Epstein-Barr virus
  - Parvovirus B19
  - ?Herpes simplex viruses 1 and 2
- Bacterial/mycobacterial
  - Repeated bacterial infections/occult bacterial infection* (must exclude urinary tract infection)
  - Relapsing fever (*Borrelia* spp. other than *B. burgdorferii*)
  - Chronic meningococcemia
  - Occult dental abscess
  - Brucellosis
  - *Yersinia enterocolitica*
  - Mycobacteria, nontuberculous (e.g. *Mycobacterium chelonae*)
- Parasitic
  - Relapsing malaria (*Plasmodium vivax*, *Plasmodium ovale*)
  - Reactivation of *Plasmodium malariae*
- Inflammatory/immunologic
  - Inflammatory bowel disease, usually Crohn's disease*
  - Still's disease (systemic onset juvenile rheumatoid arthritis)*
  - Behçet's disease
  - Hereditary periodic fevers
  - FMF
  - HIDS
  - TRAPS
  - Familial cold urticaria
  - Muckle-Wells syndrome
- Neoplasm
  - Lymphoma
- Other
  - Undiagnosed cause*
  - Drug fever
  - Factitious fevers
  - Central nervous system abnormalities (hypothalamic dysfunction, agenesis of corpus callosum)

5.What to order?

A. Early Work Up:

- CBC
- ESR/CRP
- Wright
- U/A
- Stool studies
- CXRay (if lymphadenopathy, hepatomegaly, splenomegaly, abdominal mass)
- PBS if Endemic areas

What to Order?

B. Late work up:

- Thin/Thick blood smear – travel to endemic area ≤1 year,
- Giemsa stain ,PCR for Rat bite fever(GN pleomorphic bacilli , spirillium minus)
- Dark Field Ex & Serology for Leptospirosis
- Hepatobiliary studies (ALT, GGT, ALP, …)
- Albumin (losses/decreased production)
- IgA &Urine Mevalonic Acid
- Rheumatologic Study (Behcet ,JIA,SLE, Crohn ,…)
- Auto inflammatory dx such as FMF
- Quantitative immunoglobulins

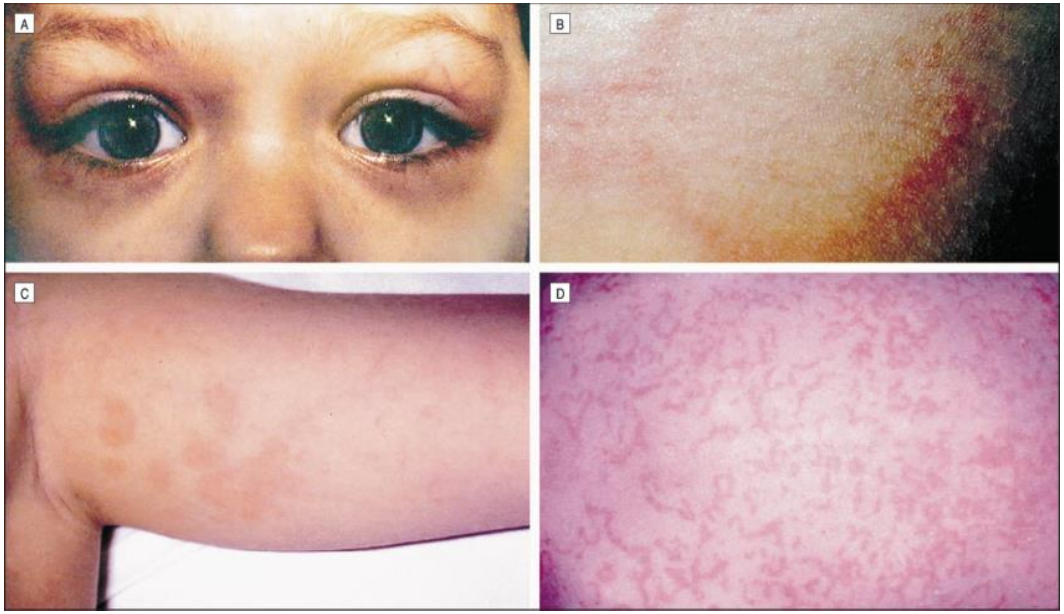
TRAPS

- TRAPS is also called familial Hibernian fever due to high frequency of incidence in people of Irish, Scottish, Austrian, or Northern European descent.

- It is characterized by febrile attacks that last for 1–3 weeks and occasionally up to 6 weeks.

TRAPS

- The clinical features include fever, arthralgia, myalgia, migratory rash, abdominal pain, pleuritis, conjunctivitis, periorbital edema, oral ulcers, and scrotal swelling.
- Skin manifestations include migratory macular erythematous rash or patches, ecchymoses, edematous dermal plaques, serpiginous or annular lesions, and periorbital edema.



TRAPS

- The disease develops due to mutation of the gene encoding P55 TNF receptor type 1.

- There are 46 missense mutations involving TNF receptor type 1 which are localized to distal chromosome 12 p.

- Etanercept is an effective treatment which reduces the frequency and severity of flares in TRAPS.

- A **10-year-old Japanese boy** was referred to our hospital because of a recurrent prolonged (about 2-week) fever, skin rash, abdominal pain, arthritis, and myalgia.
- He had a history of repetitive episodes of these attacks that had started at age 6 months and recurred at intervals of 1—2 months.
- At 3 years of age, pericarditis developed.

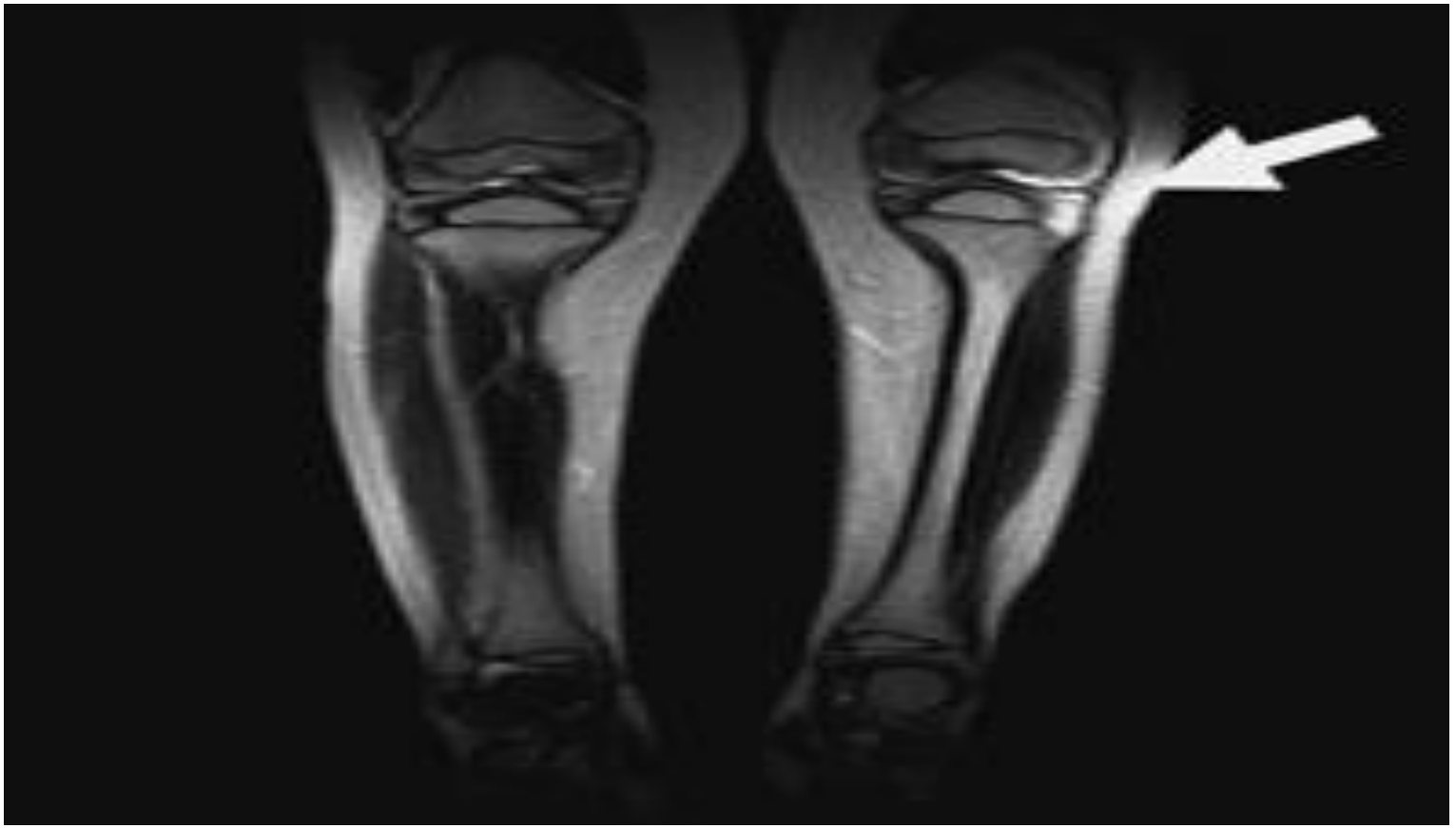
- Because of the irregularity of the recurrent attacks, his condition was misdiagnosed as systemic JIA based on the prolonged spike-fever, skin rash, arthritis, and pericarditis , which fulfilled the International League of Associations for Rheumatology (ILAR) criteria.
- Then he was started on oral predonisolone (about 0.9 mg/kg/day) and cyclosporine.

- The patient's 7-year-old sister had, at 3 years of age, also presented with similar symptoms, including prolonged fever (<2 weeks), neck pain, abdominal pain, and arthralgia .
- Although the clinical symptoms did not strictly fulfill the ILAR criteria, she had also been suspected of having systemic JIA and treated with oral prednisolone (1 mg/kg/day).

- Furthermore, although their 38-year-old mother had not had an obvious episode of periodic fever, she did have an episode of prolonged (<1 month) elevation of CRP accompanied only by fatigue.

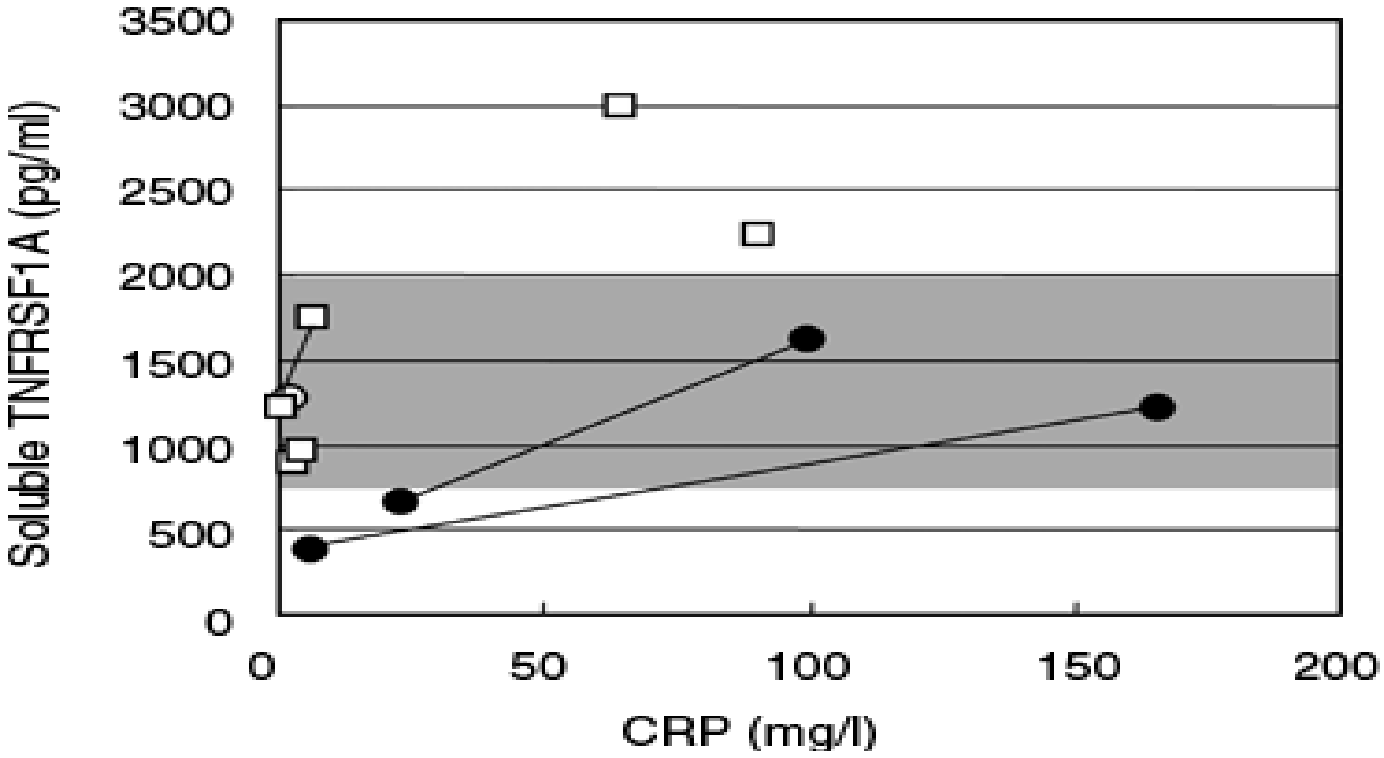
- Moreover, after the delivery of a daughter she had recurrent fever, arthralgia , and myalgia .

- At the time of referral to our hospital, the 10-year-old boy presented with a low-grade fever, fatigue, and mild arthralgia in the shoulder and knee.
- No skin rash, abdominal pain, or conjunctivitis was noted.
- At that time, the patient had a mild to moderate APR , as indicated by the WBC count (25400 /µl), CRP (48 mg/l) and ESR (70 mm/hour).
- However, at a later time when his symptoms were not present, the APR was not observed.
- Other initial laboratory investigations showed normal levels of ferritin (63.1 ng/ml), and immunoglobulin D (0.6 mg/dl).



Magnetic resonance imaging (T2 enhancement) of the 10-year-old boy shows synovial fluid collection in the knee joints.

- Since the patient's past history, family history, and the following laboratory findings strongly suggested the diagnosis of TRAPS, we tapered and stopped oral prednisolone treatment during a febrile periods, and added short-term NSAID during the febrile attacks.
- During a febrile attack, serum levels of APRs , cytokines, and cytokine receptors were as follows: CRP 166 mg/l; interleukin-6 (IL-6) 97.9 pg/ml; tumor necrosis factor-alpha (TNF-alpha) <5 pg/ml; soluble TNFRSF1A 1220 pg/ml.
- During the afebrile period, CRP was 6 mg/l; IL-6 was 0.9 pg/ml; TNF-alpha was <5 pg/ml; and soluble TNFRSF1A was 378 pg/ml.



Measurements of soluble TNFRSF1A and CRP in TRAPS (closed circle), systemic JIA (open square) and normal child (open circle).
Connected samples are from the same patients. The normal reference range of soluble TNFRSF1A is indicated by the shaded area.

- Serum soluble TNFRSF1A was measured by ELISA and its reference range was 750—1900 pg/ml.
- Since the patient's 7-year-old sister was also suspected of having TRAPS, her oral prednisolone was discontinued during afebrile periods.
- Attacks of fever, abdominal pain, and arthralgia were observed at intervals of 1 to 2 months, but disappeared after several days of short-term oral prednisolone treatment.

- During a febrile attack, the serum level of soluble TNFRSF1A was 1700 pg/ml (CRP: 73 mg/l), and while she was afebrile it was 700 pg/ml (CRP: 3 mg/l).
- Then, we investigated the serum levels of soluble TNFRSF1A in systemic JIA.
- In our patients with systemic JIA, soluble TNFRSF1A levels are within the normal range when serum CRP levels are low (<50 mg/l), and markedly increased (>2000 pg/ml) when serum CRP levels are high (>50 mg/l).

- After informed consent for the genetic analysis was obtained from their parents, DNA sequencing of exon 1—10 in the *TNFRSF1A* gene was performed.
- In both siblings, we found a single mutation, a heterozygous G to A transition in exon 2, which substitutes a tyrosine for a cysteine at position 30 (C30Y). As the same point mutation had been already reported, we confirmed the diagnosis of TRAPS. However, we could not obtain consent for serological nor genetic analysis of the parents themselves.

- ***Tumor Necrosis Factor Receptor-associated Periodic Syndrome Mimicking Systemic Juvenile Idiopathic Arthritis.***


Any Question Welcome!