Pediatric Rheumatology

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Pediatric Rheumatology

• Children suffer from many diseases that affect adults
  - Systemic lupus erythematosus
  - RF+ Rheumatoid Arthritis
  - ANCA associated vasculitis
  - ankylosing spondylitis
• I will focus on topics specific to Pediatrics
JIA-HISTORY

• 1897-G.F. Still publishes “On a Form of Chronic Joint Disease in Children”

• “Adult Onset Still’s Disease” remains term of preference
Juvenile Idiopathic Arthritis (JIA)

- Not a single entity
- Characterized by chronic arthritis
- Most common chronic rheumatic illness of childhood
- Clinical diagnosis
- One of 3 terms used to classify the chronic arthritides of childhood (JCA, JRA)
JIA: Etiology?

• Likely a Complex Genetic Trait
  – HLA associations
    • HLA-A2 associated with oligoarticular JIA
    • HLA-DRB1*08 and*11, HLA-DQA1*04 and*05, HLA-DQB1*04 associated with extended oligoarticular and persistent oligoarticular JIA
    • HLA-B1*04 associated with RF+ JIA
  – Non-MHC genes

• Immunology
  – Innate and Adaptive immune responses
  – Evidence for both cell-mediated and humoral immune responses

• Environmental

• Infections
JIA: Pathogenesis

• T cells
  – Those in synovial space are oligoclonal (c/w antigen-driven process)

• Monocytes, Macrophages, Synovial fibroblasts activated by T cells, which release:
  – IL-1, IL-6, TNF
  – Each subtype of JIA associated with different character of cytokine release in synovial fluid (validation of subtypes)

• B cells aggregate in synovium (like adult RA) and autoantibodies (e.g. ANA) are present in some

* Therefore there is evidence for both cell-mediated and humoral immune response contributing to the inflammatory process
JIA: Pathology
Arthritis: Definition and Physical Findings

- Objective signs of inflammation within the joint:
  1. Swelling or an effusion
     OR
  2. Presence of 2 or more:
     a. Limitation in range of motion
     b. Pain with motion or tenderness
     c. Warmth
JUVENILE IDIOPATHIC ARTHRITIS
Classification

• Oligoarticular (< 5 joints)(50%)
  – persistent
  – extended
• Polyarticular (> 4 joints)(30%)
  – RF positive (5%)
  – RF negative (25%)
• Systemic (10%)
• Psoriatic (2-15%)
• Enthesitis-Related Arthritis (1-7%)
  – Juvenile Ankylosing Spondylitis
  – Inflammatory Bowel Disease
  – Undifferentiated
Oligoarticular JIA

- ≤ 4 joints
- Most common form (50%)
- Average age 2 yrs
- Girls:Boys = 5:1
- Systemically well
- Knee (monoarthritis) > Ankle > Elbow
- ANA usually positive (60-90%)
- Not tender or very painful
- 15-20% develop uveitis
JIA: Uveitis

- May occur in all subtypes of JIA
- Most common in young, ANA +
- Requires slit lamp for early detection
- Synechiae and band keratopathy may develop later
- May potentially lead to visual impairment
### TABLE 1
Frequency of Ophthalmologic Examination in Patients With JRA

<table>
<thead>
<tr>
<th>Type</th>
<th>ANA</th>
<th>Age at Onset, y</th>
<th>Duration of Disease, y</th>
<th>Risk Category</th>
<th>Eye Examination Frequency, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoarthritis or polyarthritis</td>
<td>+</td>
<td>≤6</td>
<td>≤4</td>
<td>High</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>≤6</td>
<td>&gt;4</td>
<td>Moderate</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>≤6</td>
<td>&gt;7</td>
<td>Low</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>&gt;6</td>
<td>≤4</td>
<td>Moderate</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>&gt;6</td>
<td>&gt;4</td>
<td>Low</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>−</td>
<td>≤6</td>
<td>≤4</td>
<td>Moderate</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>−</td>
<td>≤6</td>
<td>&gt;4</td>
<td>Low</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>−</td>
<td>&gt;6</td>
<td>NA</td>
<td>Low</td>
<td>12</td>
</tr>
<tr>
<td>Systemic disease (fever, rash)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Low</td>
<td>12</td>
</tr>
</tbody>
</table>

ANA indicates antinuclear antibodies; NA, not applicable. Recommendations for follow-up continue through childhood and adolescence.
Polyarticular JIA

- > 5 joints
- 30% of all JIA
- Any age (RF+ usually teens)
- Average age 1-3
- Girls:Boys = 3:1
- Mild systemic symptoms (fatigue, poor PO)
- Large and small joints affected, hands and wrists most common
- ANA positive 40-50%
- RF + 10-20%
- Uveitis less common (5%)
JIA: Diagnosis

- History and Physical Examination
  - Detailed ROS, personal and social history
  - Examine every joint
- Radiographs
  - Exclude bone tumor, trauma, establish comparison baseline
  - MR usually unnecessary
- Laboratory testing (NO TESTS ARE SENSITIVE OR SPECIFIC FOR JIA)
  - CBC w/differential: exclude leukemia
  - ESR, CRP; particularly if examination difficult
  - Synovial fluid analysis only if infection/crystals suspected
  - Other testing individualized (ANA, RF, HLA-B27, ASO, chemistry profile)
Systemic JIA

- Arthralgias common early in disease
- Arthritis
  - Discomfort, swollen joints
  - Wrists, ankles, knees most common
  - Hands, hips, c-spine and TMJ
    - May begin in hips (unlike pauci or poly)
- Micrognathia
- Cervical spine fusion
Extra-articular symptoms

- Fatigue
- Fever
  - Quotidian fevers
  - Must occur ≥ 2 weeks
- Rash
  - 2-5mm macular salmon colored rash
  - Evanescent
  - Nonpruritic
  - Koebner phenomenon
- Hepatosplenomegaly
- Lymphadenopathy
- Serositis
Laboratory Findings

- Anemia
- Leukocytosis
- Thrombocytosis
- ↑ Liver Enzymes (AST, ALT)
- ↑ Acute Phase Reactants (ESR, CRP, Ferritin)
- Normal UA
- ANA and RF negative
Summarized Features of SOJIA

### Features of major subtypes of juvenile rheumatoid arthritis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Systemic onset JRA</th>
<th>Pauciarticular onset JRA</th>
<th>Polyarticular onset JRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of JRA patients</td>
<td>10-15</td>
<td>50</td>
<td>30-40</td>
</tr>
<tr>
<td>Sex</td>
<td>F = M</td>
<td>F &gt; M</td>
<td>F &gt; M</td>
</tr>
<tr>
<td>Age</td>
<td>any &lt;17 years</td>
<td>peak 2-3 years, rare &gt;10</td>
<td>peaks 2-5, 10-14 years</td>
</tr>
<tr>
<td>Joints</td>
<td>any</td>
<td>large joints, but rarely hips</td>
<td>any, rarely to start in hip</td>
</tr>
<tr>
<td>Fever, rash, lymphadenopathy, hepatosplenomegaly</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Uveitis</td>
<td>rare</td>
<td>20 percent, esp ANA +</td>
<td>less frequent</td>
</tr>
<tr>
<td>Laboratory abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>marked</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Anemia</td>
<td>marked</td>
<td>no</td>
<td>mild</td>
</tr>
<tr>
<td>Elevated ESR</td>
<td>marked</td>
<td>mild</td>
<td>mild</td>
</tr>
<tr>
<td>ANA</td>
<td>absent</td>
<td>low titer common</td>
<td>low titer common in younger</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>rare</td>
<td>absent</td>
<td>10-20 percent in those &gt;10 years</td>
</tr>
<tr>
<td>Destructive arthritis</td>
<td>&gt;50 percent</td>
<td>rare</td>
<td>&gt;50 percent</td>
</tr>
<tr>
<td>Disease modifying drugs</td>
<td>commonly used</td>
<td>rarely used</td>
<td>commonly used</td>
</tr>
</tbody>
</table>

UpToDate
JIA: Initial Treatment

• NSAID
  – Naproxen 15-20 mg/kg/d in two daily doses
  – Meloxicam 0.125 mg/kg/d single dose
    • Minimal toxicity: GI and pseudoporphyria

• Physical/Occupational Therapy

• Promote activity

• Consider intra-articular triamcinolone hexacetonide
JIA: Additional Treatment

• Methotrexate
  – 10 mg/M² to 1 mg/kg SQ or PO weekly
  – Adverse effects: nausea, malaise for 24 hrs, liver and bone marrow toxicity (follow CBC and ALT every 6-8 weeks), infection

• Glucocorticoids
  – Usually reserved for systemic JIA
  – Minimize dose and duration
  – Need to be certain that malignancy has been excluded prior to treatment

• Hydroxychloroquine, Sulfasalazine
• Leflunomide
JIA: Biologic Agents

• TNF inhibition
  – sTNF receptor: Etanercept SQ
  – Anti-TNF mab: Infliximab IV
  – Anti-TNF mab: Adalimumab SQ
• T-cell second signal blocker: Abatacept IV

• IL-1ra: Anakinra SQ
• IL-1 receptor fusion protein: Rilonacept SQ
• IL-6rab: Tocilizumab IV
Macrophage Activation Syndrome

- Severe complication of rheumatic diseases especially in systemic juvenile idiopathic arthritis\(^1\)
- Syndrome of excessive activation and expansion of T lymphocytes and macrophages leading to hemophagocytic activity and massive inflammatory response\(^2\)
- Categorized as a secondary or acquired form of HLH\(^3-4\)
Epidemiology

- MAS may occur spontaneously as a complication of active underlying disease or triggered by infection\(^5\)
- Lack of well-defined diagnostic criteria
- Reported to occur in \(~7\%\) of patients with sJIA\(^6\)
- May occur sub-clinically in another 30-40\% of cases\(^7\)

Clinical presentation of MAS

- Persistent high fever
- Hepatosplenomegaly
- Spontaneous bleeding, bruising
- Liver dysfunction
- Neurologic symptoms: Lethargy, seizures, coma, or shock
- Lymphadenopathy
Lab findings

• Pancytopenia
  – Falling WBC and Platelet count
  – Opposite of what we typically see in systemic JIA
• Coagulopathy
• Elevated hepatic enzyme levels
• High ferritin, high CRP, increasing D-dimers
• Drop in ESR (impending coagulopathy??)
• Hypertriglyceridemia
• Pathologic hallmark:
  – Bone marrow aspirate: benign macrophages engulfing hematopoietic cells
### Table 2 Distinguishing features of sJIA and MAS.

<table>
<thead>
<tr>
<th>Feature</th>
<th>sJIA</th>
<th>MAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Quotidian</td>
<td>Unremitting</td>
</tr>
<tr>
<td>Rash</td>
<td>Evanescent, maculopapular</td>
<td>Petechial or purpuric</td>
</tr>
<tr>
<td>Serositis</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>Very high</td>
<td>Low or rapidly lowered</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Very high</td>
<td>Low or rapidly lowered</td>
</tr>
<tr>
<td>ESR</td>
<td>Very high</td>
<td>Normal or recently lowered</td>
</tr>
<tr>
<td>ALT and/or AST</td>
<td>Normal or elevated</td>
<td>Substantially elevated</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>PTT</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Elevated</td>
<td>Lowered</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Normal or elevated</td>
<td>Substantially elevated</td>
</tr>
<tr>
<td>D-dimer</td>
<td>Elevated</td>
<td>Substantially elevated</td>
</tr>
<tr>
<td>sCD25</td>
<td>Normal or elevated</td>
<td>Substantially elevated</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; MAS, macrophage activation syndrome; PTT, partial thromboplastin time; sCD25, soluble CD25; sJIA, systemic juvenile idiopathic arthritis.

Pathophysiology-HLH

• In healthy people:
  – During viral infections, NK cells and cytotoxic T lymphocytes (CTLs) are activated to viral antigens
  – These immune cells secrete inflammatory cytokines and chemokines
  – Results in killing of infected cells, removal of antigen, and termination of immune response

• In HLH: inherited or acquired defect of NK and CTL cells – unable to cope effectively with infectious agent/antigen
  – NK cells and/or CTLs fail to virus → persistent activation of T-cells
  – “Cytokine storm” → tissue damage
  – IFN-γ, TNF-α, IL-1β, IL-6, IL-10, IL-12, soluble IL-2 receptor (CD25)
  – Toll-like receptor activation may be another cause (TLR9)
Cytolytic pathway proteins mutated

1. Perforin (*PFR1*)
   - 15-40% of FHLH

2. MUNC13-4 (*UNC13D*)
   - 10-30% of FHLH

3. Syntaxin 11 (*STX11*)

4. Syntaxin binding protein aka MUNC18-2 (*STXBP2*)
## Genes

<table>
<thead>
<tr>
<th>Genetic HLH</th>
<th>chromosome location</th>
</tr>
</thead>
<tbody>
<tr>
<td>familial HLH</td>
<td></td>
</tr>
<tr>
<td>known gene defects</td>
<td></td>
</tr>
<tr>
<td><em>PFR1</em></td>
<td>10q 21–22</td>
</tr>
<tr>
<td><em>UNC13D</em></td>
<td>17q25</td>
</tr>
<tr>
<td><em>STX11</em></td>
<td>6q24</td>
</tr>
<tr>
<td>unknown gene defects</td>
<td></td>
</tr>
<tr>
<td>immune deficiency syndromes</td>
<td></td>
</tr>
<tr>
<td>Chédiak-Higashi syndrome (<em>LYST</em>)</td>
<td>1q42.1–q42.2</td>
</tr>
<tr>
<td>Griscelli syndrome 2 (<em>RAB27A</em>)</td>
<td>15q21</td>
</tr>
<tr>
<td>X-linked lymphoproliferative syndrome 1 (<em>SH2D1A</em>)</td>
<td>xq25</td>
</tr>
<tr>
<td>2 (<em>XIAP</em>)</td>
<td>xq25</td>
</tr>
</tbody>
</table>

| Acquired HLH                      |                     |
| infectious agents                  |                     |
| autoimmune diseases (macrophage activation syndrome) |                     |
| malignant diseases                 |                     |
| immune suppression/organ transplantation |                 |

Preliminary studies suggest that children with sJIA and MAS frequently possess heterozygous mutations/polymorphisms in cytolytic pathway genes, which are disrupted in a homozygous fashion in infants with FHLH.

Henoch-Schoenlein Purpura
Henoch-Schoenlein Purpura (HSP)

- HSP is an autoimmune, self-limiting, immunoglobulin A (IgA) mediated small vessel vasculitis
- Most common pediatric vasculitis in the US
  - incidence of 9 to 20 cases per 100,000 in children aged 2 to 14
  - Much less common in adults with 3.4-14.3 cases per 1,000,000
- Male to female ratio of 2:1
- Immune-mediated vasculitis associated with immunoglobulin A (IgA) deposition.
- Although a variety of infectious and chemical triggers are recognized, the underlying cause of HSP remains unknown.
Presentation

• Classic Tetrad

  – Purpura - Classic dark-red and purple lesions on lower extremities and buttocks
  – Arthralgia/Arthritis
    – Ankles and knees
  – Abdominal Pain
    • Colicky, periumbilical pain
    • Intestinal wall thickening and abnormal peristalsis
    • GI bleeding in up to 75% of patients (Hematemesis, melena, bloody stools)
    • Intussusception
  – Renal Disease
    – Usually mild, rarely severe
    – Can occur months after
Treatment

• Self limited disease that lasts about 4 weeks on average.
• Up to 50% of patients will have recurrent symptoms, but generally subside after 4-6 months
• Supportive care (NSAIDs)
• Corticosteroids
• Immunosuppressant for severe renal involvement
Primary Immune deficiencies

- Innate Immune Deficiencies
- Adaptive Immune Deficiencies
- Autoinflammatory Disorders
- Autoimmunity/ immune dysregulation disorders

Balanced immunity
Autoinflammatory Disorders vs. Autoimmune Disorders

- **Autoinflammatory**
  - Typically early age of onset, sometimes at birth
  - No autoantibodies
  - No autoreactive T cells
  - Due to Innate immune system activation (PMNs, Macrophage, etc)
  - Characterized by recurrent bouts of inflammation of the same magnitude

- **Autoimmune**
  - Typically later age of onset
  - Characterized by autoantibodies and autoreactive T cells
  - Adaptive immune system activation due to failure of tolerance of T and B cell tolerance
  - Characterized by increasing severity of responses overtime

![Graph showing severity vs. age for Autoimmunity and Autoinflammatory conditions](image)
When to consider autoinflammatory disorders

• The VAST majority of children with recurrent fevers will resolve and are the result of childhood viruses

• Differential diagnosis of recurrent fevers
  – Malignancy (leukemia, lymphoma)
  – Autoimmune disease (Systemic JIA, Crohn’s)
  – Primary Immune deficiency
  – Healthy child with typical childhood viruses
  – Autoinflammatory disorders (should be last on your list)

• MOST autoinflammatory disorders do not cause short term harm..it’s OK to watch
My workup of a child with recurrent fevers

– CBC, uric acid, LDH
– ESR or C-reactive protein (when well!!!!)
– Imaging for any localizing findings on exam (ie masses)
– Immunoglobulin panel; tetanus, diptheria, pneumococcal titers
– Keep fever diary with ANY symptoms during these episodes (rash, conjunctivitis, mouth sores, abd. Pain)
– Watch and wait as long as return to baseline health in between episodes
Case #1

- 4 year old girl with “urticaria”
- Macular with central clearing, evanescent, non-pruritic
- Rash first seen hours after birth
- Also noted to have chronic fatigue, intermittent low grade fevers, intermittent neck and joint pains
- Treated with numerous anti-histamines without relief

- ESR 29 (nl < 20)
- CRP 2.0 (nl < 1.0)
- ANA negative
- IgE normal
Case #1 (con’t)

- Given the early onset of rash, chronic inflammation, lack of IgE or signs of autoimmunity, genetic testing of \textit{CIAS1} was performed.
- Heterozygous Arg262Try mutation discovered in Exon 3
- Dx: Muckle-Wells Syndrome
- Anakinra (IL-1R antagonist) started with resolution of all symptoms
Cryopyrin associated periodic syndromes (CAPS)

- Spectrum of disorders resulting from mutations in CIAS1 (cryopyrin)
  - Neonatal onset multisystem inflammatory disorder (NOMID)
  - Muckle-Wells syndrome
  - Familial cold urticaria syndrome

- Clinical phenotype: urticaria like rash (from birth), arthralgias, epiphyseal bone overgrowth, fever, chronic meningitis, sensorineural deafness, amyloidosis.

- Rash is universal and reflects neutrophil/lymphocyte infiltration (not true urticaria)

- Spectrum of symptoms (NOMID>MWS>FCUS)

Inflammasome activation

Kastner, Hematology, 2005
Neonatal Onset Multisystem Inflammatory Disease (NOMID)

- Rash from birth
- Frontal bossing, saddle nose
- Growth retardation
- Patellar and epiphysial/metaphysial abnormalities without synovial involvement
- Anemia, elevated ESR, leukocytosis, thrombocytosis common
Diseases implicated in inflammasome activation/regulation

• Familial mediterranean fever (mutations in pyrin, increased activation of the inflammasome)

• PAPA (pyogenic arthritis, pyoderma gangrenosum, acne: Defect in PSTPIP1 which binds pyrin)

• Hyper IgD syndrome (mutations in mevalonate kinase)
Familial Mediterranean fever (FMF)

• Clinical features:
  – Episodic presentation with fever (38.5-40°C), can be only manifestation particularly in young children
  – Episodic, not really periodic (episodes reported to occur weekly to months apart)
  – **Short duration** (last 1-3 days)
  – Pleuritis (15-35%), pericarditis (rare),
  – **Arthritis** (second most common manifestation), large joints, can lead to joint destruction
  – **Abdominal pain**, distention with peritoneal signs occur commonly (>90%) (vomiting and diarrhea possible)
  – Myalgias common (10%), erysipelas like rash common (28%)
Familial Mediterranean fever (FMF)

- Treatment
  - Prophylactic colchicine
    • Start at 0.6-1.2mg/day, increase up to 2mg/day until resolution of symptoms
    • Nausea and diarrhea can be limiting
    • Can lead to remission in significant percentage of patients (65% complete, 30% partial, 5% no effect)
  - Regardless of symptoms patients should remain on colchicine to prevent amyloidosis
  - Steroids DON’T WORK

autumn crocus, Colchicum autumnale, also known as "meadow saffron"
A new autoinflammatory disorder???

- 4 year old presents with knee swelling, poor growth, heme positive stools/non-specific GI inflammation vs celiac, seizures, development delay (mild), poor dentition
- No prominent fevers, no adenopathy
- High ESR, CRP, TTG, IgA, hypergam, hyperzincemia/hypercalprotecte mia
- Typical treatment for arthritis ineffective
• At 9yo develop swelling at the base of the left thumb and wrist. MRI showed metaphyseal lesion at base of thumb, multiple fluid collections around the wrist joint, aspiration demonstrate “frank pus”

• Unresponsive to iv antibiotics

• Because of persistent inflammation (ESR 30-70, CRP abnormal for 6 years) tried anakinra/IL-1RA

• Rapid response in symptoms and normalization of inflammatory markers

• Exome sequencing showed......
  – ARG40TRP, ILE268THR of mevalonate kinase

– **Dx: Hyper IgD syndrome**
Hyper IgD syndrome

- Early onset (median 0.5 years), can vary
- High spiking fever, preceded by chills in 76% of patients.
- **Lymphadenopathy** (94% of patients)
- Adominal pain (72%), vomiting (56%), diarrhea (82%)
- **Polyarthralgia** was noted in 80% of patients, and a **nondestructive arthritis in 68%**.
- Serositis is rare, and amyloidosis has not been reported.
- A minority of patients report painful, aphthous ulcers in the mouth or vagina.
- Erythematous macules are the most common cutaneous manifestation, followed by erythematous papules, urticarial lesions, and erythematous nodules.
Hyper IgD-laboratory findings

- Elevated acute phase reactants
- IgD persistently elevated (>100U/ml)
  - May be poor marker, elevated levels can be seen without diagnosis of Hyper-IgD
  - Patients with Hyper-IgD can have normal levels
- 85% have elevated IgA levels
- Urine mevalonic acid levels typically elevated during attack
- Reports of amyloidosis and renal failure have been reported
Case #3: Regulation of the Inflammasome

• Male infant born to consanguinous parents (half first-cousins) at 33 weeks
• At 10 days of life developed macular rash with central pustules
• Laboratory studies: ↑WBC, ↑monocytes/plts, anemia, ↑ESR/CRP
• Prominent osteopenia and lytic bone lesions
• Respiratory distress developed, and Bx showed alveoli filled with macrophage and PMNs (no organisms)
- Because of similarity to NOMID, anakinra (IL-1R antagonist was initiated)
- Rapid resolution of symptoms
- Since parents related ran deletion/duplication array (CNV)
Dx: IL1 receptor antagonist deficiency (DIRA)

175 KB deletion at 2q13 in patient and heterozygosity in patient’s parents
TRAPS-TNF receptor associated periodic syndrome

• Formerly known as familial Hibernian fever (Irish ancestry)
• Onset around 3 years of age, Episodes last up to 21 days and occur every 5-6 weeks.
• Clinical features
  
  – Myalgias common with migratory, erythematous rash typically occurs over the affected muscles.
  – Abdominal pain is very common (92%).
  – Conjunctivitis, periorbital edema, or periorbital pain can occur
Last case

- 4yo male, fevers, rash, high inflammatory markers
- Developed hemorrhagic stroke X2, presumed to be vasculitis
- Fever syndrome testing negative
- Whole genome sequencing performed...no causative mutation identified
- To NIH for second opinion
• The NIH detected the same variant in CECR1 (ADA2)

• Since they knew the gene, they performed high res SNP chip to detect a 28KB deletion in the promoter region of ADA2

• Deletions are often missed in WES

• Non coding regions are also missed

NEJM, 2014
Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

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Summary

• Autoinflammatory disorders are characterized by life-long inflammation without the generation of autoimmunity
• The inflammasome generating IL-1β is central to many autoinflammatory disorders
  – Intrinisic defects (CIAS1 mutations)
  – Extrinsic defects leading to inflammasome activation (FMF, PAPA)
• Numerous other disorders have been described (TRAPS, Blau, ADA2, interferonopathies)
• In all of these cases there are other physical findings...not just fevers
• A basic workup in a child with just fevers and watchful waiting is appropriate as long as child returns to baseline between episodes