Enteropathic Arthropathy

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Disclosures

• Advisory board Crescendo Bioscience
• Speaker for Horizon Pharma, Abbvie
Objectives

• Review link between gut and MSK diseases
Introduction

• Dysentery sometimes followed by arthritis
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- Now called Reactive Arthritis (ReA)
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• Dysentery sometimes followed by arthritis
• Now called Reactive Arthritis (ReA)
• Also associated with IBD, celiac, and less common conditions
Gut biology and microbiota

Key points

• Leaky barrier with “unstirred layer”
• 80% gut wall consists of immune cells
• Gut permeability is delicately regulated and disturbed by disease
Functions

• As a barrier
• Fluid and food absorption
• Excretion of waste

GI tract

- 300-400 m²
- 200 x surface area
- Defense/tolerance

Permeability

• Altered permeability in NAFLD
  – Zona occludens 1
• Factors affecting permeability
  – drugs
  – Nicotine
  – Microorganisms
  – cytokines

Hepatology 49(6):1877-1887, 2009
Microbiotia

- A mixture of native bacteria acquired at birth
- Stomach-duodenum $10^3$
- Jejunum $10^4$
- Ileum $10^7$
- Colon $10^{12}$
- Gram – aerobic small
- Anaerobic in colon
- Microbiotica cells 10x host

Digestion 73 (Suppl 1):5-12, 2006
Microbial diversity

• Bewildering number of phenotypes
• Genes in microbiome 100 x that of the host
• Most have no been cultured
• Functions remain unknown
• Great diversity between people
• Digest CHO into short-chain FA
• Facilitates absorption of Fe^{2+}, Ca^{2+}, Mg^{2+}
• Synthesize amino acids and vitamins
Physiologic roles of microflora

• 300-500 species
• Bifidobacteria may be inflammatory in AID
Bypass Arthritis-Dermatitis

• 1970’s patients with gastroiliial bypass
• Thought to be related to overgrowth in the blind loop
• Features
  – Intensely painful oligoarthritis
  – Inflammatory back pain
  – Papulopustular rash
• Neomycin or rifaximin or take down

Celiac Disease

- Common condition with global distribution
- Can occur in any age
- Intestinal symptoms may be minimal
- Found in 6-7% juvenile idiopathic arthritis
- Immune reaction to partly digested wheat gluten by T lymphocytes in the gut
- Tissue transglutaminase is a major autoantigen

Celiac Disease

- Microscopic colitis
- Collagenous enteritis/colitis
- Transaminitis
- Primary biliary cirrhosis
- Autoimmune hepatitis
- IgA deficiency

- Dermatitis herpetiformis
- Psoriasis
- Dermatomyositis
- Alopecia areata
- Vitiligo

- Autoimmune diabetes mellitus
- Addison’s disease
- Autoimmune thyroid disease

- Sjogren’s syndrome
- Inflammatory arthritis
- SLE
- Gluten ataxia
- Peripheral neuropathies
Celiac Disease

- Elimination of gluten is the rational therapy
- Assay of serum IgA antitissue transglutaminase antibodies and IgA antiendomysial antibodies is suggestive
- Small bowel biopsy gold standard
- Abstaining from wheat can give a false negative, but symptoms should subside too
- IgA deficiency 1:250

Whipple’s Disease

- Rare
- *Tropheryma whippelii* (Actinomycetes family)
- Articular symptoms 67% of cases
- May have recurrent fever; malaise; hematologic, pulmonary, cardiac disturbances; neurologic and ophthalmologic symptoms
- 83% develop diarrhea, abd pain, malnutrition
- Culture for research; PCR can detect
- Ceftriaxone x2wks then TMP/SMX 1-3 years

J Clin Microbiol 41:3916-3822, 2003
Microscopic Colitis

- Collagenous colitis; lymphocytic colitis; collagenous gastritis
- Diagnosis can only be made by biopsy
- Associated with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Sjogren’s syndrome.

Undifferentiated Spondyloarthropathy

- Inflammatory back pain
- Plus psoriasis, enthesitis, sacroiliitis

Table 76-4  Assessment of SpondyloArthritis international Society Classification Criteria for Axial Spondyloarthritis (SpA)

For patients with back pain for ≥3 mo and aged <45 yr:
- Sacroiliitis on imaging + ≥1 SpA feature
- or
- HLA-B27 + ≥2 other SpA features

Sacroiliitis on imaging defined as:
- Active acute inflammation on magnetic resonance imaging highly suggestive of sacroiliitis associated with SpA
- or
- Definitive radiographic sacroiliitis according to the modified New York criteria

SpA features comprising:
- Arthritis
- Enthesitis (heel)
- Inflammatory back pain
- Dactylitis
- Uveitis
- Psoriasis
- Inflammatory bowel disease
- Good response to nonsteroidal anti-inflammatoary drugs
- Family history of SpA
- HLA-B27
- Elevated C-reactive protein

Viral Arthritis

- Enterovirus; coxsackieviruses; echoviruses incidence unknown, but less than 1% cases
- Hepatitis B 10% joint symptoms
- Hepatitis C 25% joint symptoms
- Parvovirus B19 can cause arthritis in adults

Semin Arthritis Rheum 33:375, 2004
Reactive Arthritis (ReA)

• Any arthritis which comes on after infection
• Lyme, rheumatic fever, viral called “post-infectious” to minimize confusion
• ReA associated with spondyloarthropathies
  – Follows patterns of infectious arthropathies
• Enthesitis; arthritis; extra-articular signs
  – Eyes
  – Skin

Reiter’s syndrome
Reiter’s syndrome

- The dustbin of history
- Urethritis, conjunctivitis, arthritis
  - Hans Reiter
    - was not the first to describe
    - Attributed post-dystentary to spirochetes
    - Third Reich
    - Urethritis does not mean it was sexually transmitted
Proposed Definition

- Reactive Arthritis with one of these findings
- Classic clinical features
  - Asymmetric oligoarthritis (predominately lower limbs); enthesitis; extra-articular signs AND
  - Proven infection by *Salmonella, Campylobacter, Yersinia, Shigella*, or *Chlamydia* (symptomatic or not) OR
  - Proven infection with *Clostridium difficile, Mycobacterium bovis* bacillus Calmette-Guerin
- Any acute inflammatory arthritis, including monoarthritis and/or axial inflammation AND proven infection by ReA-associated bacteria
- Classical clinical features & diarrhea or urethritis/cervicitis within the previous 6 weeks infection not proven

Clinical Features

• Enthesitis
• Conjunctivitis often transient and may only be noted by others
• If small joints in the hands are involved less likely to be ReA
• Blood tests should show elevated ESR, CRP with neutrophilia
• Hyperuricemia may indicate an alternative
Keratoderma Blenorhagica
Synovial Fluid

- Differential includes sepsis so synovial fluid should be obtained whenever possible
- Cell count, crystals, gram stain, culture, sensitivity, and in the right person AFB
- *Campylobacter* has been identified in synovial cells from the knee in research setting
- HLA-B27 not required, but when present makes a case for DMARDs or biologics
O&P

• If you suspect *Salmonella* or *Yersinia* notify the lab
• *Salmonella* is contagious
• *Yersinia* has to be kept at 4 degrees C prior to culture
Treatment

• 80-90% self limiting disease
• NSAIDs and joint injections (once infection ruled out)
• PT can become important
• 6-12 months to remit at times
• Sulfasalazine
• Then methotrexate or leflunomide
• Rarely biologics have been used like TNF and IL-6
Antibiotics

• By definition the synovial fluid is sterile
• One controversial study showed improvement in chronic ReA, but findings have not been replicated
Outcome

• Full recovery is expected but it can 18 months or even longer

• If longer than that it may be ankylosing spondylitis

• The more severe the arthritis the longer it usually takes to recover
Summary

• Link between gut and skin/joints well known
• Antibiotics and probiotics have not been proven to have any efficacy in treatment
• Future there may be discoveries which open the path to new treatments for rheumatic diseases