Inflammatory Bowel Disease Related Arthritis and “gut problems” in JIA patients

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Parent Session
Goals

Part 1 (Dr Modica, Peds Rheum)
• Connection between gut and immune system
• General concepts behind autoimmunity
• Review IBD related arthritis
• Treatment Options

Part 2 (Dr Safder, Peds GI)
• “Gut issues” that occur in patients with arthritis
  – Inflammatory Bowel Disease (IBD)
    • Crohn’s
    • Ulcerative Colitis
  – Gastritis
  – Gastroparesis
  – Small bacterial intestinal overgrowth
  – Irritable Bowel Syndrome (IBS)
Gut and Autoimmunity Connection: Gut wall properties

- Lined by potential pathogenic microorganisms ("microbiome")
- Gut Wall = Leaky barrier
- 80% of gut wall consists of immune cells**

Gut: food, bacteria, toxins

Gut Wall

Blood supply & immune cells

**Note:** The text includes a diagram that illustrates the gut and autoimmunity connection, showing the interactions between gut wall properties, blood supply, immune cells, and various conditions such as autoimmunity, nutrient malabsorption, food intolerance, blood-brain barrier breach, and systemic inflammation.
To understand autoimmunity, need to look at:

“army” = white blood cells

“weapons” = Anti-bodies and inflammatory proteins
Autoimmune “inflammatory” diseases: Imbalanced immune response

Immune system gets “confused”
• Becomes “overactive”
• Attacks SELF
Thinks there is an infection

Antibodies & Inflammation Proteins (cytokines)
- TNF, IL1, IL6

Can lead to erosion
Inflammatory Bowel Disease

• Group of inflammatory conditions of the intestines

  – Autoimmune
    • Body’s immune system attacks
      – Small intestine (small bowel)
      – Colon (large bowel)

  – Main Types:
    • Crohn’s Disease (CD) and Ulcerative Colitis (UC)
      – Differentiated by
        » Location & nature of inflammatory change

25 % of IBD patients may develop arthritis
Arthritis: 2 main categories

**Juvenile Idiopathic Arthritis (JIA)**
- Pauci (oligo)
- Poly
- Systemic

**Enthesitis Related Arthritis (ERA)**
AKA: “Spondyloarthropathies”
- Juvenile Anklyosing Spondylitis
- IBD-related
- Psoriatic

Hallmark of this category is Sacroiliitis
Arthritis:
2 main categories

Juvenile Idiopathic Arthritis (JIA)
AKA: Juvenile Rheumatoid Arthritis

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Arthritis Categories: Main Differences

**JIA**  
*(Juvenile Idiopathic Arthritis)*
- ANA, RF, CCP Anti-bodies
- Female Predominant
- Young or adolescent
- Chronic iritis-damages
- Arthritis  
  - Large and small peripheral joints

**ERA**  
*(Enthesitis Related Arthritis)*
- HLA B27gene, (+) family history
- Male Predominant
- Adolescent
- Acute iritis-red eye
- Arthritis
  - Spine  
    - Sacroiliitis
  - Primarily lower extremity
  - Enthesitis
Sacroiliitis & IBD

Features of Sacroiliitis

• Occurs in 10-20%
• May be “silent” or have:
  – Back pain/Leg pain
  – Butt pain
  – Lower back stiffness
• Can start before or after IBD starts
• Sacroiliitis
  – often does NOT correlate with intestinal symptoms

**Target of Sacroiliitis:**
"Peripheral arthritis" & IBD

**Peripheral arthritis (not spine)**
- *Mostly* lower extremities
  - Hips, knees, ankles, feet, toes
- Non-deforming
- Erosions may occur
- Flares may correlate with gut activity

**Enthesitis**
- Enthesis = site of insertion of a tendon, ligament, or joint capsule into bone
- Enthesitis = inflammation of enthesis
- Hallmark of spondyloarthropathies

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Enthesis

[Image: Illustration of enthesitis at the site of insertion into bone, alongside an image showing inflamed entheses in the legs.]
Labs:

- No defining lab test
- HLA-B27 gene
  - Helps establish diagnosis
- Antibodies negative
  - ANA, RF, CCP
- ↑ inflammatory markers
  - ESR ("sed" rate) & CRP
  - Anemia
- Fecal (stool) calprotectin
  - Protein found in inflammatory cells
  - ↑ with IBD

- IBD serology panel
  - ANCA and ASCA
  - Differentiate CD & UC if non-diagnostic biopsy
  - Differentiate IBD from other bowel disorders
  - Predict disease course and severity
Family History

HLA-B27 gene

• HLA-B27 is a gene
  – When present may produce arthritis causing proteins

• HLA-B27 is present in
  – < 10% of the general population
  – > 90% of patients with ERA
    • = Genetic predisposition for
      – ERA and sacroillitis
      – Acute iritis (red painful eye)
IBD Arthritis Course

2 “general” patterns seen based on HLA-B27

- **HLA-B27 (-)**
  - Lower extremity arthritis
  - Arthritis flares w/ IBD flares
    - Arthritis treated with IBD flare
  - Female = Male

- **HLA-B27 (+)**
  - Sacroiliitis
  - Arthritis flares are **INdependent** of IBD flares
    - Arthritis treated separate from IBD flare
  - Male >> Female
Treatment Options for JIA/ERA: possible immune targets

“The General”
Gives orders to B cells & other inflammatory cells

“The Troops”
White blood cells

“Macrophages"
Inflammatory proteins

Antibodies

***Multiple targets for treatments by blocking specific areas of the immune system***
**Immune cells**

End result......

“showering of inflammatory proteins”
key inflammatory proteins

The Weapons:

• 1L-1, IL-6, and

• TNF = Tumor Necrosis Factor =
• Main target for IBD

In the body TNF helps “destroy” tumors and fight infections

» In JIA & IBD they destroy the joints & the gut

» Currently, they are a target for treatments
Biologics used in IBD:
“Soak up” or “block”
Inflammatory proteins:

-TNF Blockers*
--->Remicade, Humira, Simponi

*Note: enbrel is often not used in IBD because may cause IBD flare

Targets of Immunosuppression

Immunosuppression
“Cell blocking” drugs:
-Methotrexate, Immuran, 6-MP
-Steroids
“blanket of immunosuppression”
“Biologic agents”

• Drugs which mimic substances already present in the body
  – Antibody-like molecules

  • Anti-Body:
    – Immune protein
    – Recognizes foreign substances
    – Binds to and removes
Main **Anti-TNF** biologics used in pediatric IBD
(Antibody medicines that block TNF)

**Remicade**
- IV infusion
- Monthly
- Half human/half mouse

**Humira**
- SQ injection
- Weekly or every other week
- Humanized
Treatment Pyramids for IBD: 2 approaches—depend on severity and course “step up” or “top down”

- **Biologics**: Anti-TNFs (Remicade, Humira, Simponi)
  - Bind soluble TNF
  - Blocks prostaglandins and leukotrienes
  - Suppresses White Blood Cells
  - Controls acute inflammation rapidly
  - Oral, IV, enemas

- **Immunomodulators**: 6-MP, Imuran, Methotrexate, Cyclosporine, Tacrolimus
  - Suppresses White Blood Cells
  - Blocks prostaglandins and leukotrienes
  - Inflammatory mediators

- **Corticosteroids**: Controls acute inflammation rapidly
  - Oral, IV, enemas

- **Aminosalicylates**: Blocks prostaglandins and leukotrienes
  - Inflammatory mediators
Treatment Goals

• Improve Quality of life

• Prevent or cure complications

• Clinical Remission (restore and maintain)
  – Defined by:
    • No evidence of active disease by:
      – Clinical symptoms, MD exams, labs, radiology
      – For IBD: scope (heal mucosal lining)
  – 2 scenarios:
    • On meds
    • Off meds
  – Difficult to predict
  – Research underway
Side Effects of Meds

**Infection**
- Remember to tell other providers that you are on immunosuppression
- If fever, see PMD

**Malignancy**
- Anti-TNFi higher risk
- Greater issue in adults and in combination with other meds
- Duration of treatment
- Med watch reporting

**Infusion reaction**
- Premedicate
  - Tylenol, benadryl, steroids
- Epi at bedside

**Autoimmune response**
- Especially for remicade
  - Lupus antibodies
  - Remicade antibodies
  - Can affect efficacy of medication
Gastrointestinal issues seen in JA

Shaista Safder MD
Pediatric Gastroenterologist
Arnold Palmer Hospital
Common Symptoms that warrant referral to a GI doctor

- Abdominal pain
- Change in bowel pattern
- Bloating
- Feeding difficulty
- Chronic nausea
- Weight loss
- Blood in stool
- Ulcer
GI Comorbidities

- IBD
- Gastro paresis
- Anorexia
- Motility disorders
- Small bowel bacterial overgrowth
- Ulcer disease
- NSAID related GI side effects
Inflammatory Bowel Disease (IBD)

• Arthritis may occur as an extraintestinal manifestation of several conditions, including inflammatory bowel disease (IBD)

• Arthritis occurs in a significant minority of patients with IBD, including both ulcerative colitis and regional enteritis (Crohn’s disease); it is more likely in patients with large-bowel disease

• Other conditions with both intestinal involvement and arthritis as prominent clinical features include reactive arthritis (Reiter syndrome), Whipple's disease, Behçet’s syndrome, celiac disease, parasitic infestation, and pseudomembranous colitis.
Exposome: sum of all environmental factors a human is exposed to during lifetime that influence the onset and course of IBD
ULCERATIVE COLITIS

- Ulcerative colitis typically begins in the rectum and may extend continuously to involve the entire colon.

CROHN’S

- Crohn disease most commonly involves the end of the small intestine and beginning of the colon and may affect any part of the GI tract in a patchy pattern.

Histology is key to diagnosis
Upper endoscopy and
Lower colonoscopy
CROHN’S

**CROHN DISEASE**
- Transmural inflammation
- Skip lesions
- Strictures
- Linear ulceration
- Fissures

**Small intestine**

ULCERATIVE COLITIS

**ULCERATIVE COLITIS**
- Pseudopolyp
- Continuous colonic involvement, beginning in rectum
- Active disease: superficial ulceration
- AND/ OR
- Inactive disease: atrophy

**Large intestine**

**Crohn’s**

**Ulcerative Colitis**
Video Capsule Endoscopy

- Evaluate small bowel
  - Inflammation
  - Eosion
  - Ulcer
  - Bleeding
  - Polyps
  - Tumors
Imaging

- UGI with SBFT
  - Barium Contrast Study
  - Stricture
  - Assess terminal ileum

- CT scan
  - Stricture, fistulae, abscess, obstruction, perforation

- MRI
  - Active inflammation vs fibrosis
  - Fistulae
Extra-intestinal manifestations IBD

- Eyes: Episcleritis, Uveitis
- Liver: Steatosis
- Biliary tract: Gallstones, Sclerosing cholangitis
- Joints: Spondylitis, Sacroiliitis, Peripheral arthritis
- Skin: Erythema nodosum, Pyoderma gangrenosum
- Circulation: Phlebitis
- Mouth: Stomatitis, Aphthous ulcers
Location of Pain and Related Organic Origin
Model of Functional Bowel Conditions

?Motility Disorder
NSAID related side effects

• NSAIDs, corticosteroids and most disease-modifying antirheumatic drugs (DMARDs) – list GI problems as a common side effect.

• Upper-GI events include bleeding, GI perforation, ulcers, obstruction and esophagitis.

• An increased awareness of the side effects of NSAIDs, their wiser use and the addition of proton pump inhibitors to control upper-GI symptoms have helped to reduce the incidence of upper-GI problems associated
Peptic ulcer and Helicobacter pylori
Gastroparesis

• Gastroparesis is a syndrome of objectively delayed gastric emptying in the absence of a mechanical obstruction and cardinal symptoms of nausea, vomiting, early satiety, bloating, and/or upper abdominal pain.

• Patients with gastric stasis present with nausea, vomiting, abdominal pain, early satiety, postprandial fullness, bloating, and, in severe cases, weight loss.

• Gastroparesis should be suspected in patients with nausea, vomiting, early satiety, abdominal pain or bloating. Delayed gastric emptying on scintigraphy is required to establish the diagnosis of gastroparesis.

• On scintigraphy, delayed gastric emptying is defined as gastric retention of >10 percent at four hours and/or >60 percent at two hours.
Gastroparesis
Delayed gastric emptying

Stomach
Duodenum
Stomach contents
Small intestinal bacterial overgrowth (SIBO)

- Small intestinal bacterial overgrowth (SIBO) is characterized by nutrient malabsorption associated with an excessive number of bacteria in the proximal small intestine.

- Intraluminal bacterial catabolism of nutrients, leads to production of toxic metabolites and injury to the enterocytes.

- SIBO is characterized by diarrhea, bloating, flatulence, nausea, abdominal pain and weight loss.

- Subjects with SIBO may have protein, carbohydrates and fat malabsorption.

- The most common underlying factors are dysmotility and acid suppression.

- Inflammation and toxin production may result from an inappropriate or overaggressive reaction to absorbed bacterial antigens. This immune dysregulation may result in large joint arthritis resembling that seen with inflammatory bowel disease.
SIBO causes

DECREASED:
- digestive Enzymes
- stomach acid
- migrating motor complex

Taking reflux medication, antibiotics and birth control
- Acute gastroenteritis

Nutritional deficiencies/hormonal imbalances

Diet high in carbohydrates such as:
- starches
- complex sugars
- FODMAPs
What can cause IBS?

Fruits contain lots of important nutrients which our body needs, making it important to include them in our diets. However, some individual’s digestive systems struggle to breakdown natural sugars in fruit, and this can lead to a bloating feeling shortly after consumption.

Legumes, nuts and many varieties of seeds are known as ‘in soluble’ fibres. This type of fibre can create a challenge for our digestive system, and as a result, can cause discomfort and symptoms of IBS when consumed.

Similarly to fruits, vegetables are a very important part of any balanced diet. Nonetheless, they are recognised as a cause of bloating as they can create trapped air. Particular vegetables to keep an eye on include broccoli and cauliflower as they produce natural gas.

Milk and dairy products are further types of foods to be cautious of. Individuals with symptoms of IBS often find that dairy is a root of their problem because they are lactose intolerant. Lactose is found in dairy products such as milk and ice cream in many puddles and sugars however it is worth noting lactose is often a hidden ingredient in prepared meals, so make sure you read labels.

Reduce IBS with a low FODMAP diet

FODMAP’s are certain types of carbohydrates that are poorly absorbed in the gut. Once FODMAP foods reach the lower intestines they start to ferment, producing gas, and act like a sponge changing the water balance within the gut. This leads to bloating, excessive gas, diarrhoea, constipation and abdominal pain.

Source: http://www.ansleyan.org.uk/about-ansley/irritable-bowel-syndrome-ibs/
IRRITABLE BOWEL SYNDROME
13 THINGS YOU PROBABLY DIDN'T KNOW ABOUT ITS CAUSES, SYMPTOMS & TREATMENT

IBS
A CHRONIC FUNCTIONAL GASTROINTESTINAL DISORDER IS CHARACTERISED BY ABDOMINAL PAIN, DISCOMFORT AND VARIABILITY IN BOWEL MOVEMENTS WHICH SIGNIFICANTLY AFFECT QUALITY OF LIFE FOR THE PATIENT. IT IS ONE OF THE TOP 10 REASONS FOR SEEKING PRIMARY CARE AND FEW EFFECTIVE THERAPIES HAVE BEEN IDENTIFIED.

17% OF PATIENTS TESTED POSITIVE FOR BACTERIAL INFECTION
62% OF PATIENTS HAVE INSUFFICIENT BIFIDOBACTERIUM COMMENSAL BACTERIA

CLASSIFICATION
IBS-D: DIARRHEA PREDOMINANT
IBS-C: CONSTIPATION PREDOMINANT
IBS-M: MIXED FORM

60% OF PATIENTS TESTED POSITIVE FOR YEAST OVERGROWTH
36% OF PATIENTS TESTED POSITIVE FOR PARASITE INFECTION

87% OF PATIENTS HAVE INSUFFICIENT LACTOBACILLUS COMMENSAL BACTERIA

STRESS
PSYCHOLOGICAL STRESS HAS THE PROPENSITY TO EXACERBATE IBS SYMPTOMS PARTICULARLY BOWEL FUNCTION, DEPRESSION AND ANXIETY FURTHERMORE AGGRAVATE SYMPTOMS OF IBS

EXERCISE
THE BEST MODE OF EXERCISE IS SAID TO BE YOGA, WHICH DEMONSTRATED IMPROVEMENTS OF IBS SYMPTOMS EQUIVALENT TO CONVENTIONAL TREATMENT.

FOOD PRODUCTS
SOFT DRINKS, CEREALS, PACKAGED OR BAKED GOODS, SORBET, AND OTHER SUGAR-FREE PRODUCTS MAY CAUSE INCREASED FLATULENCE, ABDOMINAL DISCOMFORT AND DIARRHEA

DIEt
FOOD INTOLERANCES AND ALLERGIES ARE STRONGLY ASSOCIATED WITH IBS. FOODS ASSOCIATED WITH IBS SYMPTOMS: WHEAT, DAIRY, EGGS, COFFEE, YEAST, POTATOES, AND CITRUS FRUITS

75% OF PATIENTS SUFFERING WITH IBS IN THE USA GO UNDIAGNOSED

GENDER
WOMEN ARE STATISTICALLY 3-7 TIMES MORE LIKELY TO DEVELOP IBS COMPARED TO MEN

SOURCES
Common Symptoms that warrant referral to a GI doctor

- Abdominal pain
- Change in bowel pattern
- Bloating
- Feeding difficulty
- Chronic nausea
- Weight loss
- Blood in stool
- Ulcer