EDS ECHO SUMMIT SERIES

PRESENTATION

Allergy and Immunology- Gastrointestinal Manifestations of Mast Cell Disorders

SPEAKER

Matthew J. Hamilton MD

Lead Gastroenterologist, Mastocytosis Center

Brigham and Women's Hospital

Assistant Professor of Medicine

Harvard Medical School

Disclosures

Consulting/Advisor

Allakos

GSK

Inveniai

Blueprint Medicine

GI Symptoms are Common in Mast Cell Disorders

MCAS- published BWH Cohort 20 pts

- 19/20 with abdominal pain/cramping
- 16/20 with diarrhea

MCAS- unpublished BWH Cohort 334 pts

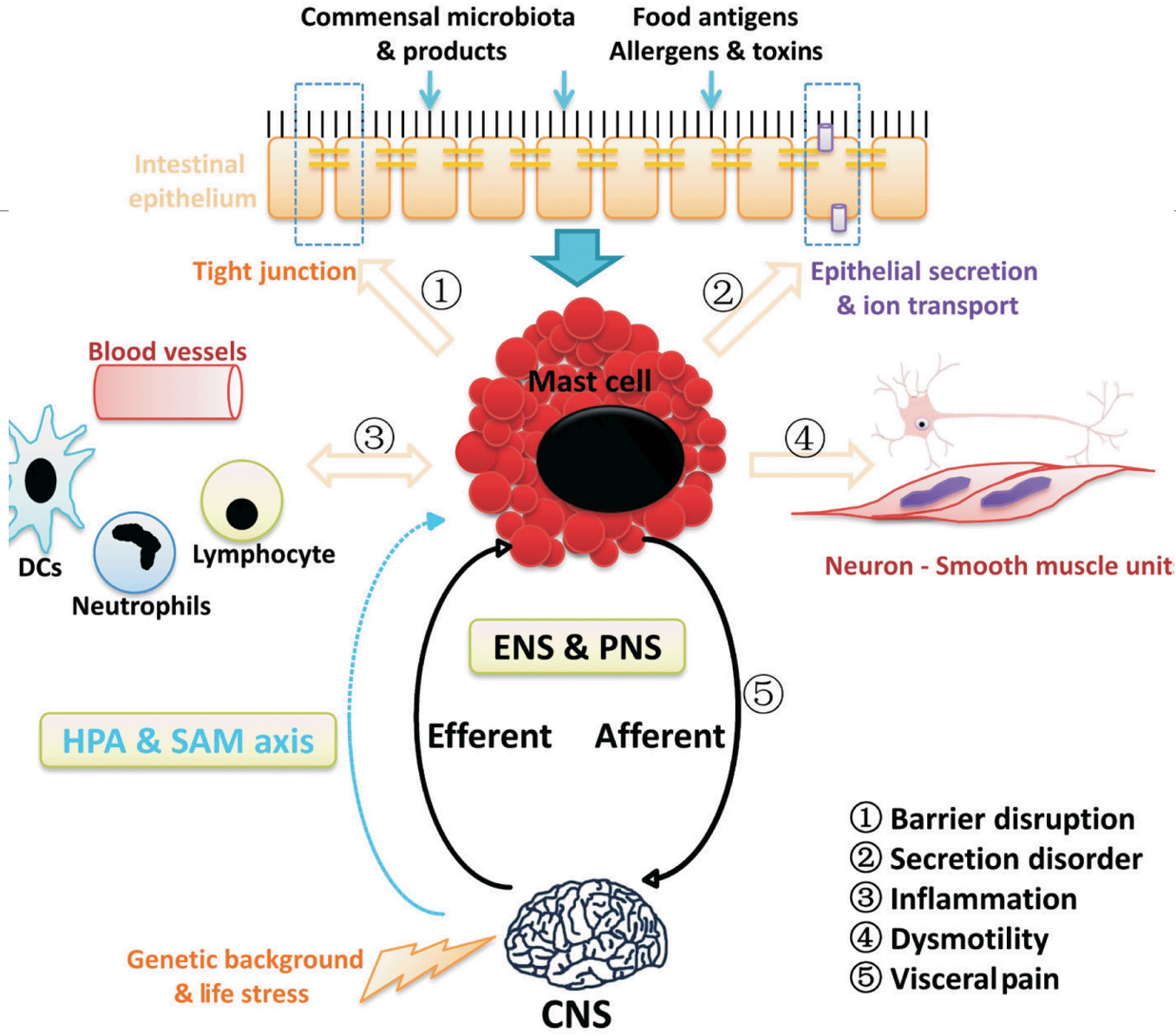
- 87% with GI symptoms

Mastocytosis- French Cohort 83 pts

- 59% had GI symptoms (similar number to itching)
- Diarrhea>bloating>abdominal pain>nausea
- No association between GI symptoms and objective markers (Kit mutation, tryptase level, histologic lesion)

Hamilton et al, JACI 2011 Sokol, JACI 2013

Mast cell function in the intestine



Zhang L et al, J Neurogastrol Motility, 2016

What are the GI symptoms of mast cell disorders?

Symptoms related to mast cell activation (MCAS/SM)

- Crampy abdominal pains and abdominal bloat
- Intermittent loose stools
- Heartburn/reflux/nausea

Symptoms related to tissue infiltration (SM)

- More persistent loose stools

Symptoms indirectly or not related to the mast cell disorder

Sokol et al, JACI, 2013 Libel R, Dig Dis Sci, 1993 Castells, Int Arch Allergy, 2002

GI symptoms due to mast cell activation

Episodic with predictable triggers

Associated with other organ system symptoms

Severity may wax and wane depending on the state of activation

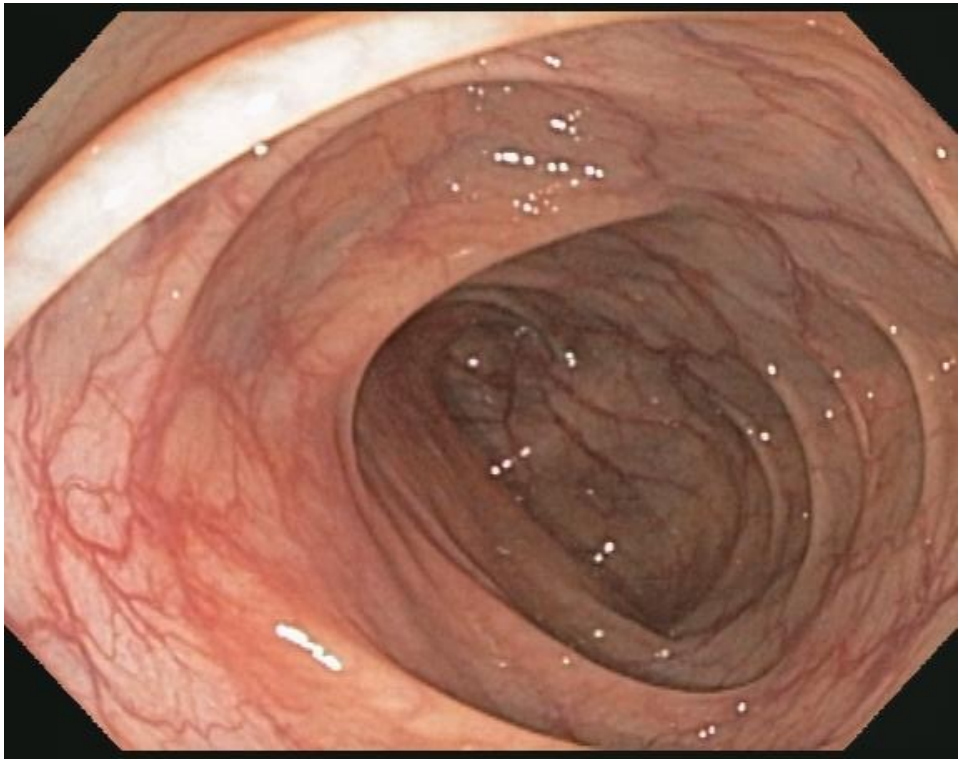
Treatable with standard MC therapies

GI manifestations related to mast cell activation syndrome

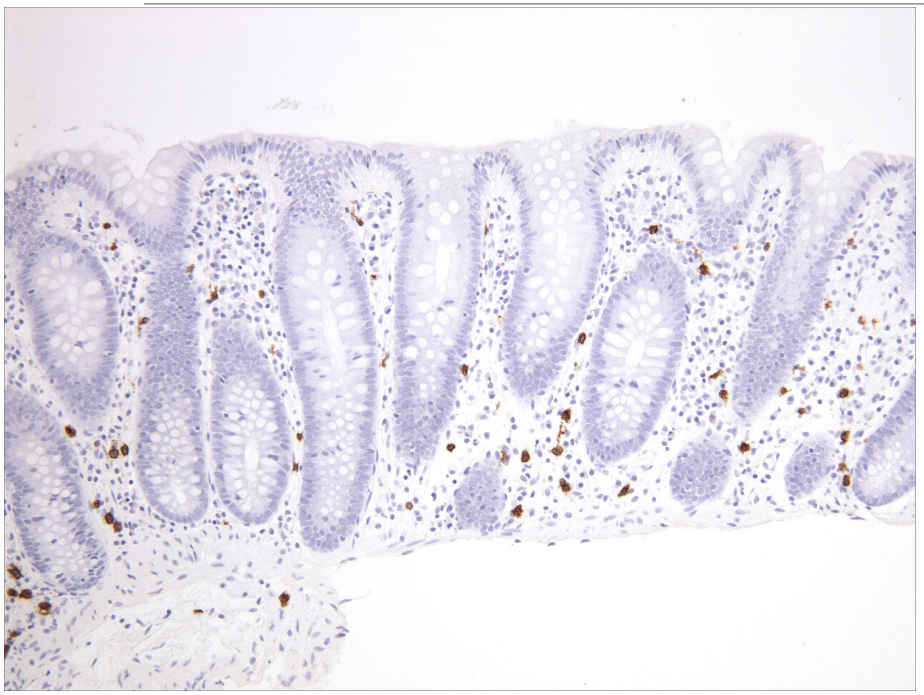
Endoscopic Features in MCAS

MCAS- usually normal

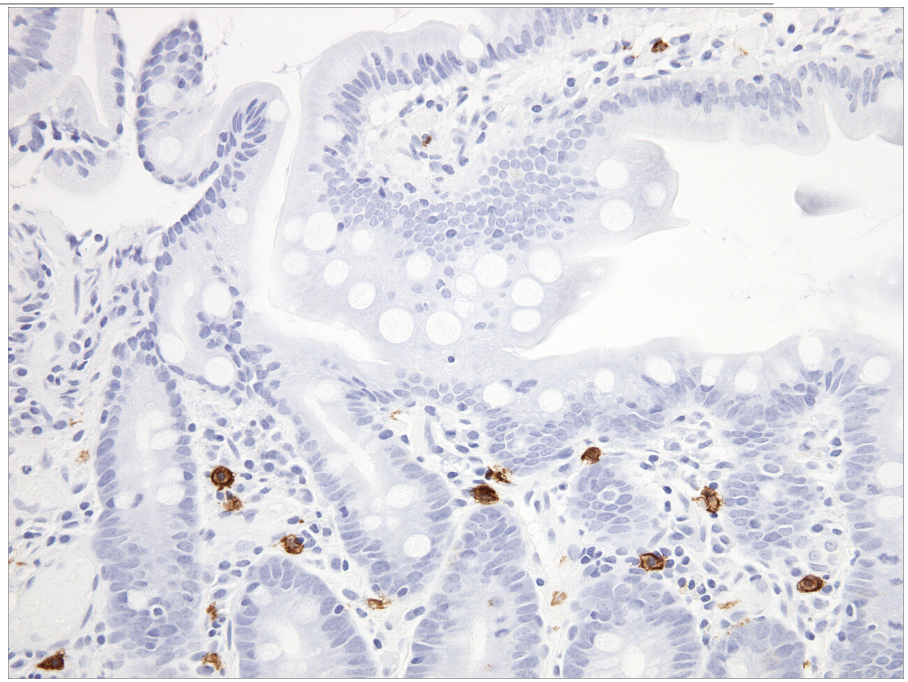
Normal Colon



Intestinal pathology features in MCAS



Normal mast cells- duodenum



Normal mast cells- colon

Mast cell numbers in colon biopsies- What is normal?

	Mean highest mast cell count in a single high power field	Mean mast cell count across five high power fields
Control (n=100) Mean (range) SD	**26** (11-55) 8.5	**19** (7-39) 6.1
Diarrhea-Predominant IBS (n=100) Mean (range) SD	**30** (13-59) 9.0	**23** (9-45) 6.7
MCAS (n=10) Mean (range) SD	**28** (14-48) 9.0	**20** (12-31) 5.4

Adapted from Doyle et al, Am J Surg Pathol, 2014

Conclusion- Excluding SM and possibly HαT, the yield of staining for MCs and quantifying is low

Are there other MC-specific features in the intestine that we can look at to help better characterize patients with MCAS?

- Morphology, cell surface marker expression, protease content

What other GI disorders do we look for? (chronic, persistent symptoms)

Endoscopy
- Inflammatory- eosinophilic disorders, celiac, IBD, peptic ulcer disease, autoimmune gastritis
- Infection- H. Pylori
- malignancy

Colonoscopy
- Inflammatory- IBD, microscopic colitis
- infection (c diff)
- diverticular disease, malignancy

Radiology
- Cross-sectional (CT/MRI)- IBD, malignancy, anatomic (stricture)
- Motility- gastric emptying, smart capsule, MR defecography

Breath tests- lactose/fructose intolerance, small intestinal bacterial overgrowth

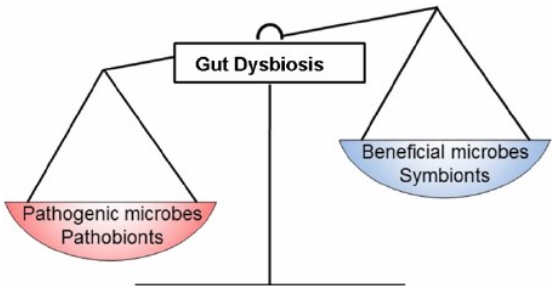
What we can not easily test

Mast cell activation syndrome

Functional GI disorders

- Esophageal hypersensitivity- non-acid reflux symptoms
- Dyspepsia- upper GI pain, bloat, nausea
- Irritable bowel- diarrhea, constipation, or mixed

Dysbiosis



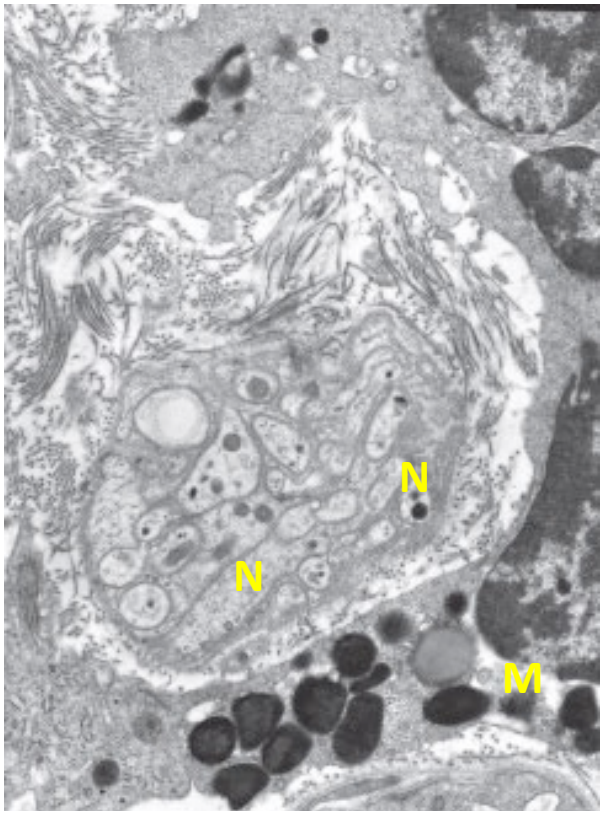
Functional GI Syndromes and Mast Cells

>40 studies describing MC numbers, MC function, correlation w/ symptoms

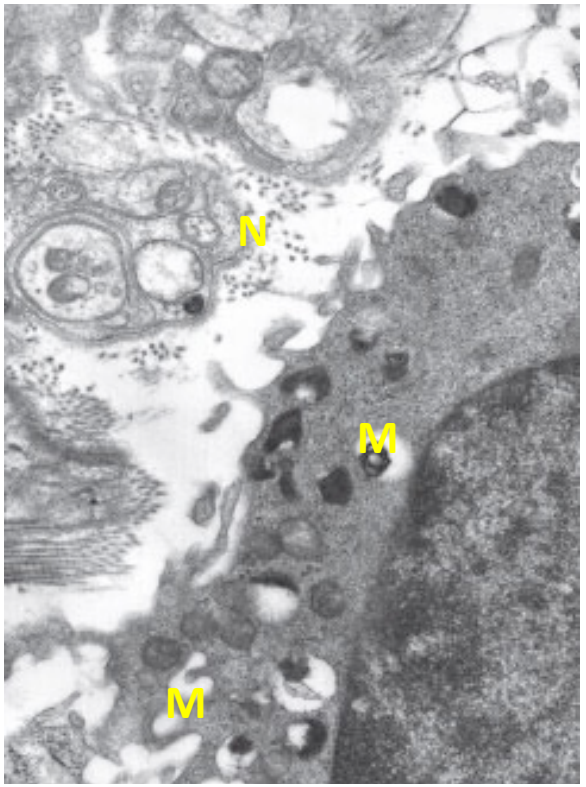
IBS pathophysiology mirrors MC intestinal pathologic functions

Numerous studies linking IBS with MCs and stress and nerves

Reviewed by Wouters M, *Gut* 2016 and Zhang L, *Neurogastroenterol Motil* 2016
Martinez C, *Am J of Gastro*, May 2012, Van Heel H, *Sci Report*, March 2018



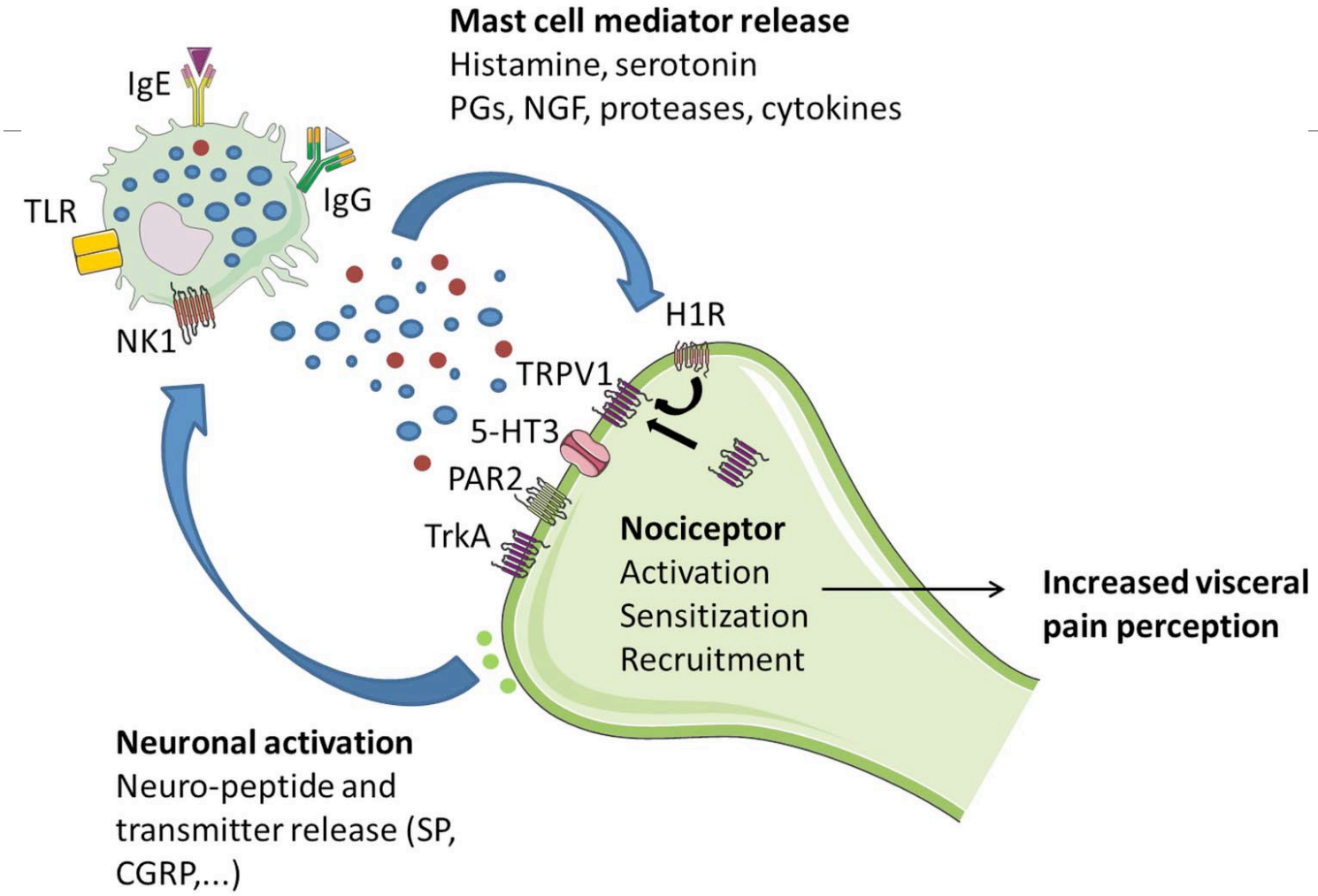
Mast cell near nerve ending



Degranulating mast cell near nerve

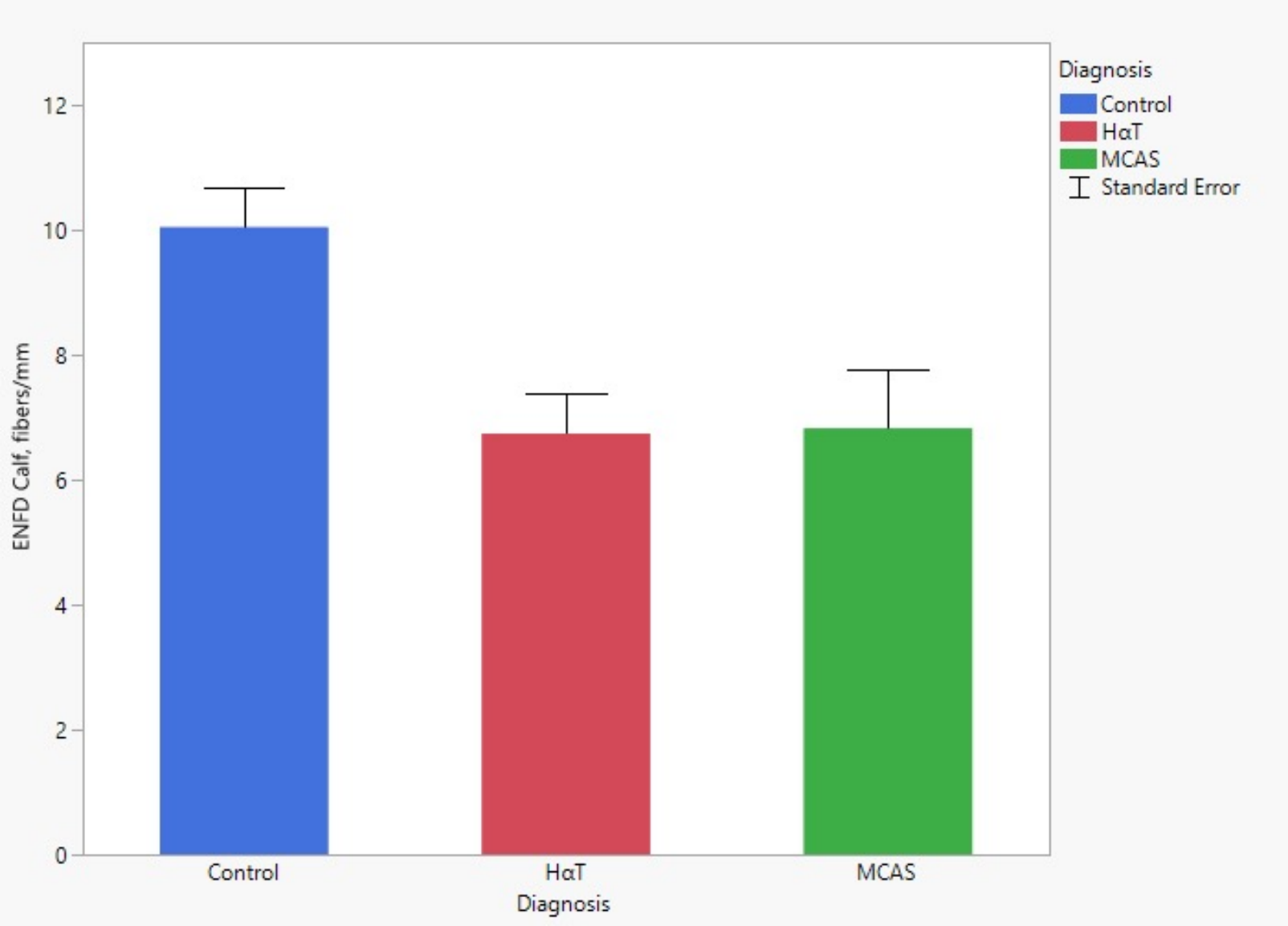
Barbara G et al, *Neurogastroenterol Motil* 2006

MC-nerve interactions



Wouters M, *Gut* 2016

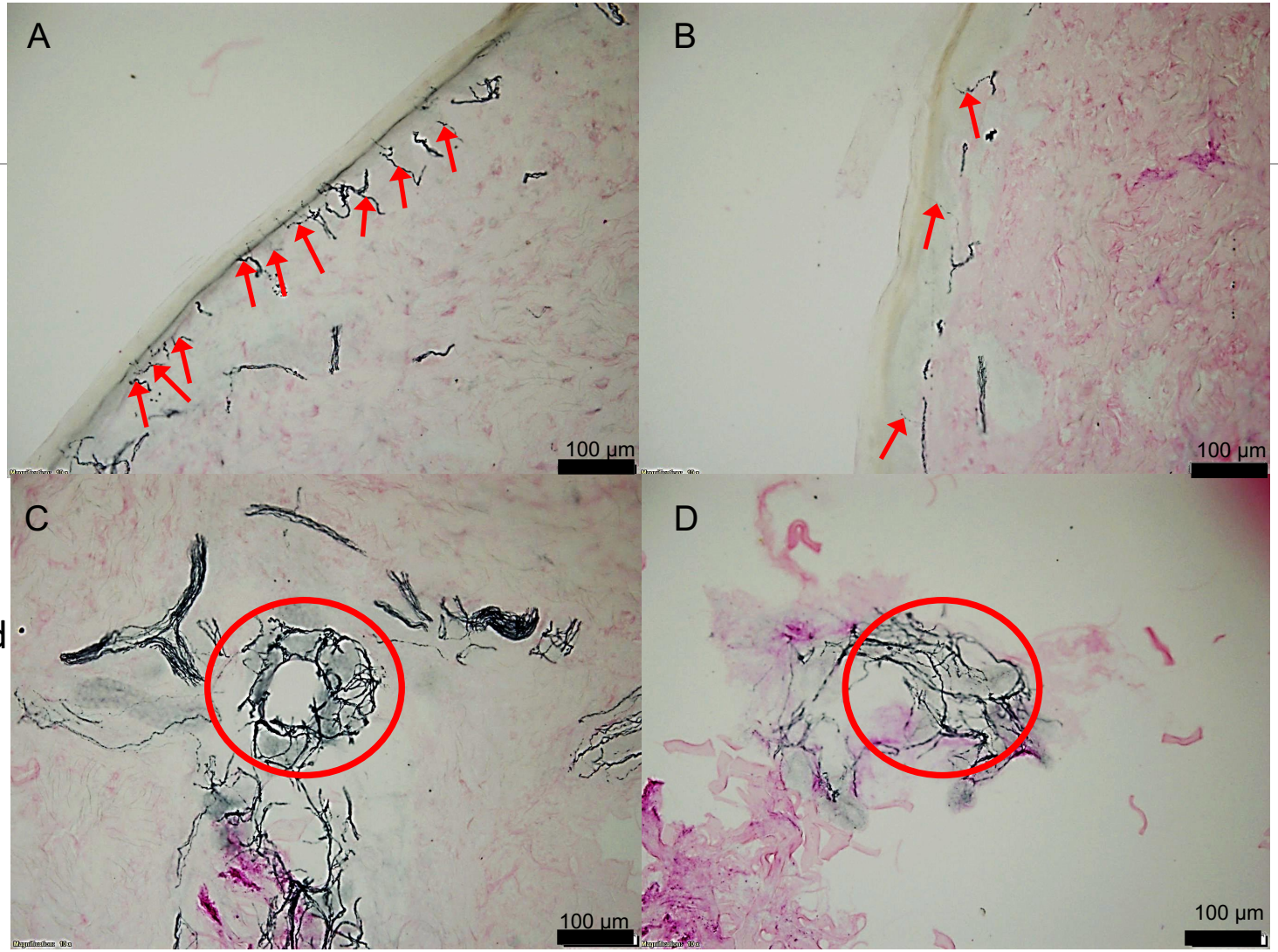
SFN observed in MCAS and HαT



Control **MCAS**

Epidermal

Sweat gland



Small Fiber Neuropathy

Structural abnormality of small fiber nerves with degeneration of the distal terminals of nerve endings

Diagnosed with skin biopsy- Assessment of epidermal nerve fiber density, lower than 5 percentiles

Associated with various medical conditions DM, B12 def, alcohol abuse, MGUS, chemotherapy, fibromyalgia, EDS

Affects mostly unmyelinated nerves of the peripheral system (somatic and autonomic)

SFN may lead to enhanced nociceptive pain response and central sensitization (hypersensitivity)

Treatment of GI symptoms in patients with MC disorders

The best mast cell disorder treatment is multi-pronged

Medications to target mast cells

Medications to treat symptoms

Dietary Interventions

Mind/Body Support

Social support

Management of Mast Cell Disorders

Patients with Symptoms Due to MCA

1) Antihistamines (type 1 and type 2)
2) Mast cell stabilizers (cromolyn, ketotifen)
3) Leukotriene Antagonists (montileukast)
4) Omalizumab, ?newer biologics

Include disease Specific treatments

Other therapies

Anticholinergics/ SSRIs
Anti-nausea/ anti-diarrheal meds
Pro-intestinal motility agents
Probiotics, antibiotics (SIBO)
Exercise, relaxation techniques
Diet

What About Diet?

"……so, what should I eat??"

"that goes right through me"

"I can only eat 8 different foods"

"I don't know what my "safe foods" are anymore"

The Mastocytosis Society Survey on mast cell disorders

- Web-based survey, 420 total respondents
- 50% reported “allergy” to a food or beverage

Different Mechanisms of Food-Induced Symptoms

Food Allergy
- IgE-mediated- tests are actually positive
- Predictable reaction
- No symptoms without that food

Food intolerance
- Lactose, fructose, gluten/wheat
- May wax and wane depending on health/age/other diseases

Mast Cell Activation
- Multi symptoms, symptoms in between foods
- Not predictable

Histamine intolerance
- Symptoms only with high-histamine foods
- DAO deficiency

So how to approach diet in mast cell disorders?

Food diaries can be helpful

Elimination of food sensitivities, triggers, and allergies

Prepare own meals and eat “whole foods”

Avoid- sugars, chemicals, processed foods, preservatives, alcohol, ?high-histamine foods

Eat a balanced, nutritious diet- a nutritionist can be helpful

Summary Statements

GI symptoms are prominent in mast cell disorders and may have different causes beyond mast cell activation

GI symptoms of mast cell activation are treatable

Much of the diagnostic work up centers on ruling out other conditions

Dietary factors often cause symptoms

The BWH Mastocytosis Center (Boston, MA)
Mariana Castells MD, PhD
Matthew Giannetti MD
Raied Hufdhi MD
Peter Novak MD
Jason Hornick MD, PhD
Olga Pozdnyakova MD, PhD

Other Mentors
Cem Akin MD
Richard Stevens PhD
Norton Greenberger MD
The Mastocytosis Society

Other collaborators
Sarah Glover (U Miss)
Jonathan Lyons (NIH)
Liza Konnikova (U Penn)
Vanessa Mitsialis (BWH)