Active herpes simplex virus type 1 infection of the gastric mucosa is associated with functional gastrointestinal disorders: A pilot case-control study

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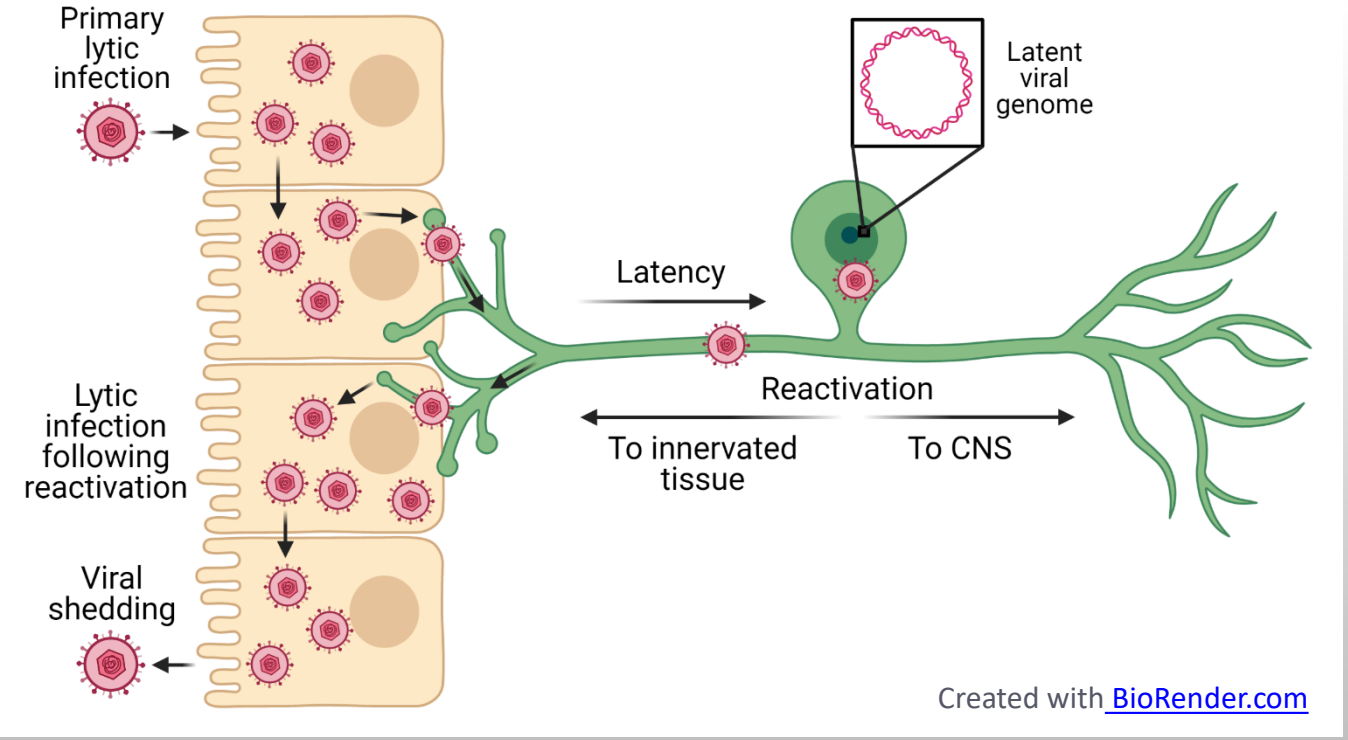
Disclosure: Research funded by Virios Therapeutics, Inc. via a sponsored research agreement with the University of Alabama

Neurotropic herpesvirus infections

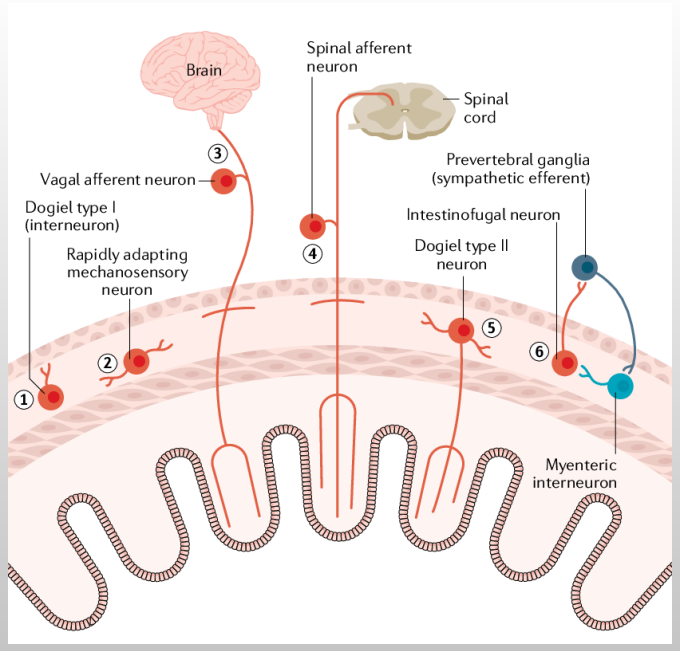
Neurotropic human herpesviruses:

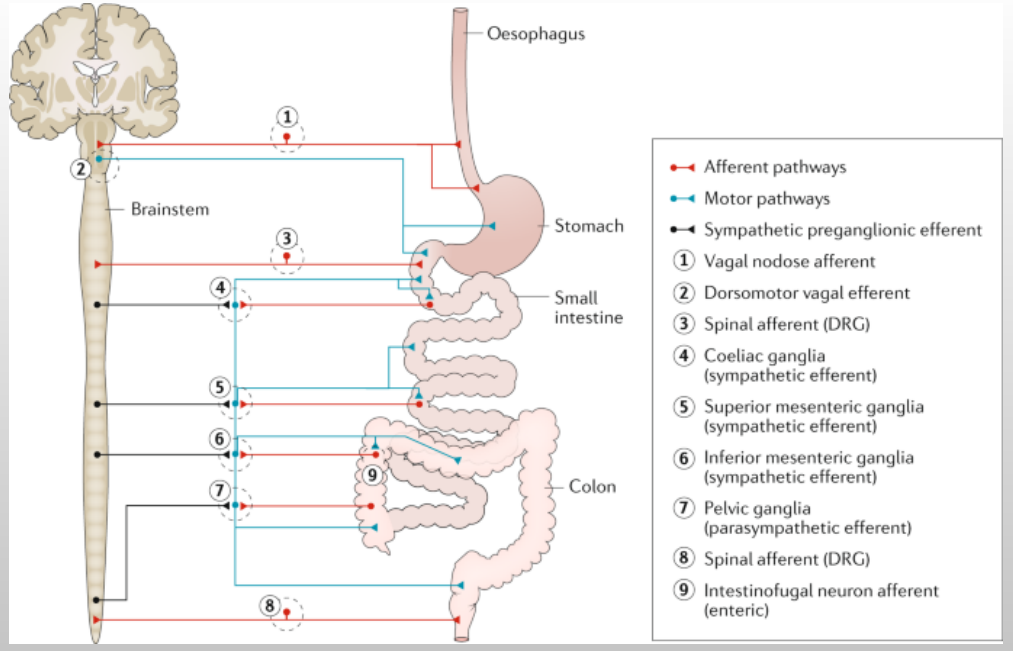
- Herpes simplex virus type 1 (HSV-1)
- Herpes simplex virus type 2 (HSV-2)
- Varicella zoster virus (VZV)



Neurotropic herpesviruses invade the GI tract

- Proper gut function depends on both extrinsic and intrinsic neural pathways
- Neurotropic herpesviruses infect intrinsic ganglionic neurons and extrinsic ganglionic neurons that project to the GI tract





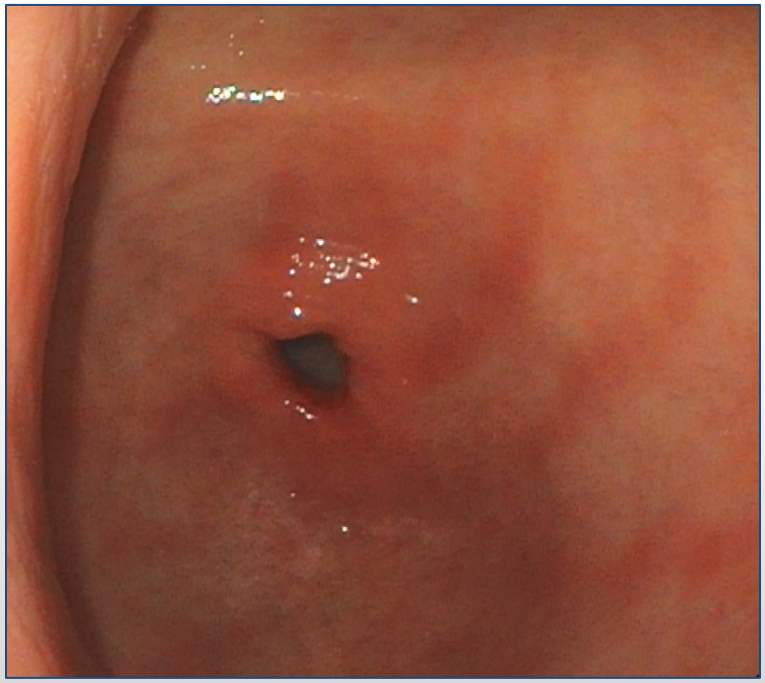
Figures: N.J. Spencer and H. Hu, 2020, *Nat Rev Gastroenterol Hepatol*, 17(6): 338-351.

Herpesviruses, fibromyalgia, and functional gastrointestinal disorders

- Neurotropic herpesviruses have been theorized to contribute to fibromyalgia (FM)
  - W.L. Pridgen et al., 2017, *J. Pain Res.*, *10*, 451-460
- FM is a functional somatic syndrome characterized by chronic widespread pain, allodynia, and hyperalgesia
- Other symptoms include debilitating fatigue, sleep disturbances, and cognitive dysfunction
- Irritable bowel syndrome (IBS) and other functional gastrointestinal disorders (FGIDs) are often comorbid with FM

Herpesviruses, fibromyalgia, and functional gastrointestinal disorders

- Patients with FGIDs exhibit radial streaking near the antrum of the stomach
- Overlapping upper and lower GI symptoms are common in patients with FGIDs
- Hypothesis: Gastric herpesvirus infections contribute to the symptoms of IBS and other FGIDs



Gastric biopsy study design

- Pilot case-control study
- Gastric mucosa biopsies were collected with informed consent under IRB approval
- Study groups:
  - Case group 1: 15 patients who met the Rome IV criteria for one or more FGIDs
  - Case group 2: 30 patients who presented with both FM (2010 ACR criteria) and one or more FGIDs (Rome IV criteria)
  - Control group: 15 patients who presented with neither FGIDs nor FM, but who required an upper endoscopy for screening/diagnostic purposes

Study design: Participants

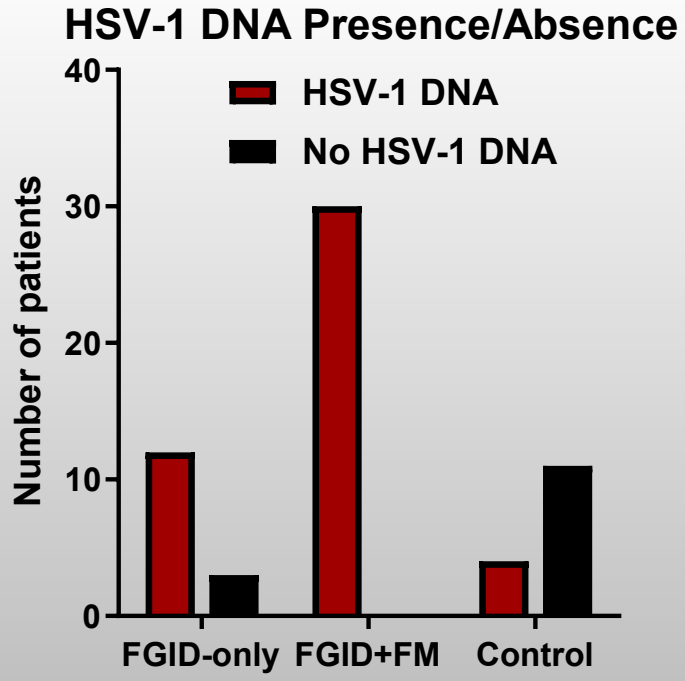
Group	Case 1 (FGID only)	Case 2 (FGID+FM)	Control
Sex	Male: 9/15 (60%) Female: 6/15 (40%)	Male: 3/30 (10%) Female: 27/30 (90%)	Male: 9/15 (60%) Female: 6/15 (40%)
Mean age	61	45	57
Race	White: 8/15 (53.3%) Black: 7/15 (46.7%)	White: 23/30 (76.7%) Black: 7/30 (23.3%)	White: 6/15 (40%) Black: 9/15 (60%)
FGIDs	EPS: 53.3% IBS: 40% Funct. dysphagia: 13.3% Functional heartburn, chronic idiopathic nausea, functional bloating, centrally mediated abdominal pain syndrome, unspecified functional bowel disorder, each 6.7%	IBS: 96.7% Funct. dysphagia: 33.3% Funct. gallbladder disorder: 33% Funct. dyspepsia: 16.7% Chronic idiopathic nausea: 6.7%	None

Study design: Experimental methods

- Gastric biopsies from each subject were divided
  - Part was examined histologically for gastritis and *Helicobacter pylori*
  - Part was used for DNA purification →
    - PCR using herpesvirus consensus primers to identify biopsies that contained herpesvirus DNA
    - PCR was followed by DNA sequencing to identify the herpesvirus present in the biopsy
  - Part was examined via immunoblotting using an antibody specific to a viral non-structural protein (ICP8) to identify active gastric herpesvirus infection

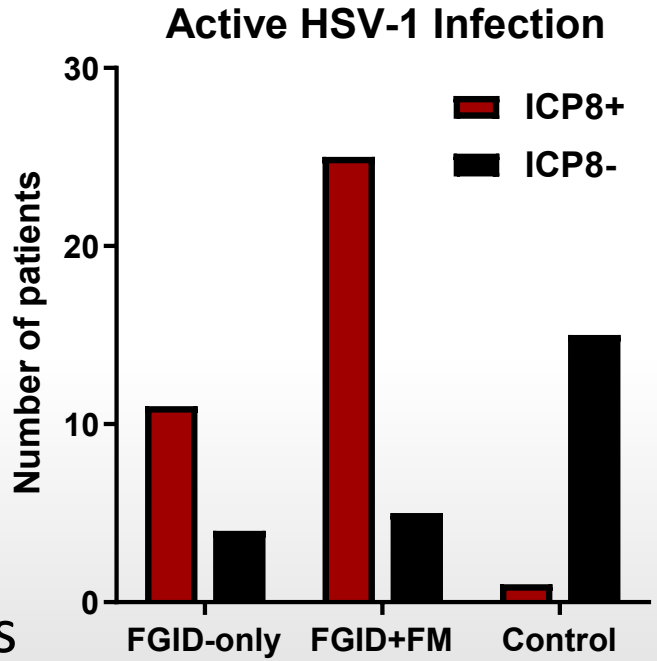
Study results: Herpesvirus DNA presence and virus identification

- Herpesvirus DNA was detected in the biopsies of:
  - 12/15 (80%) case group 1 subjects (FGID-only)
  - 30/30 (100%) case group 2 subjects (FGID+FM)
  - 4/15 (26.7%) control group subjects
- DNA sequencing revealed HSV-1 was the only herpesvirus present in any of the PCR+ biopsies



Study results: Active HSV-1 infection

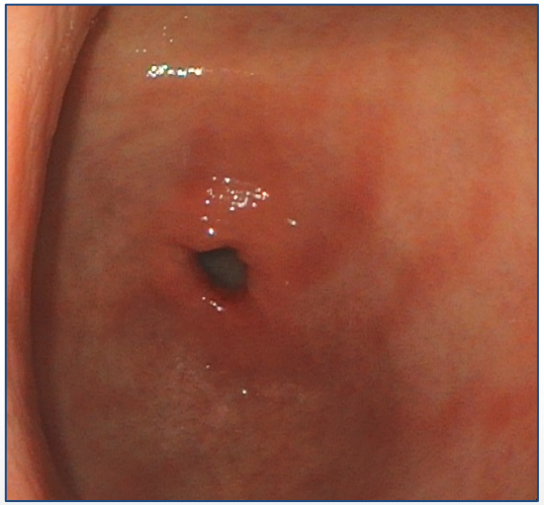
- Active gastric HSV-1 infection (ICP8+) was detected in the biopsies of:
  - 11/15 (73.3%) group 1 subjects
  - 25/30 (83.3%) group 2 subjects
  - 1/15 (6.7%) control subjects



- Active gastric HSV-1 infection was significantly associated with FGIDs in the presence and absence of comorbid FM
  - FGID-only: Odds ratio 38.5, 95% CI:3.75-395.42, *P*=0.0021
  - FGID+FM: Odds ratio 70.0, 95% CI:7.42-660.53, *P*=0.0002
- Active gastric HSV-1 infection was significantly positively associated with IBS (Odds ratio 5.4, 95% CI:1.73-17.17, *P*=0.0038)

Study results: Endoscopic findings

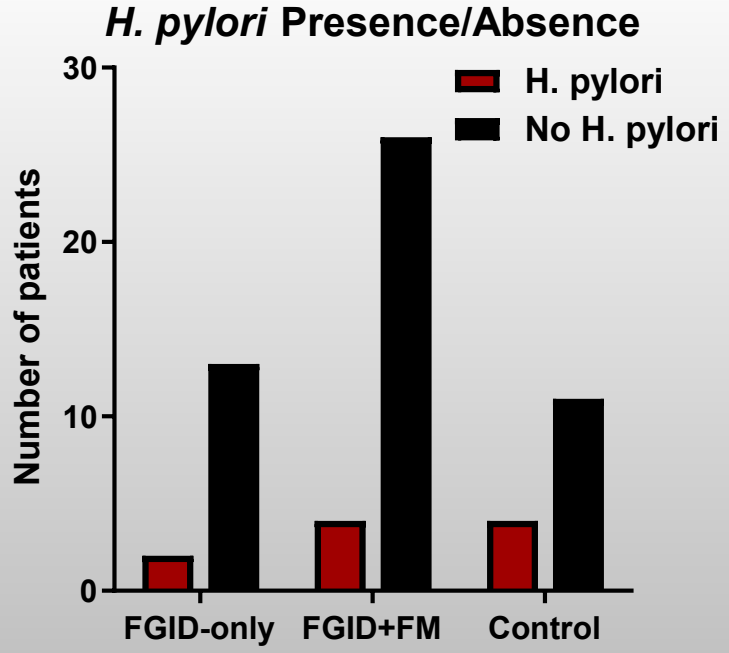
- Endoscopic examination revealed radial streaking near the antrum of the stomach in:
  - 11/15 (73.3%) case group 1 subjects
  - 22/30 (73.3%) case group 2 subjects
  - 0/15 (0%) control group subjects



- Radial streaking near the antrum of the stomach was significantly positively associated with:
  - Active HSV-1 infection (OR 3.9, 95% CI:1.30-11.74, *P*=0.0152)
  - FGIDs in general (OR 83.1, 95% CI: 4.62-1495.13, *P*=0.0027)
  - IBS in particular (OR 6.31, 95% CI: 2.01-19.80, *P*=0.0016)

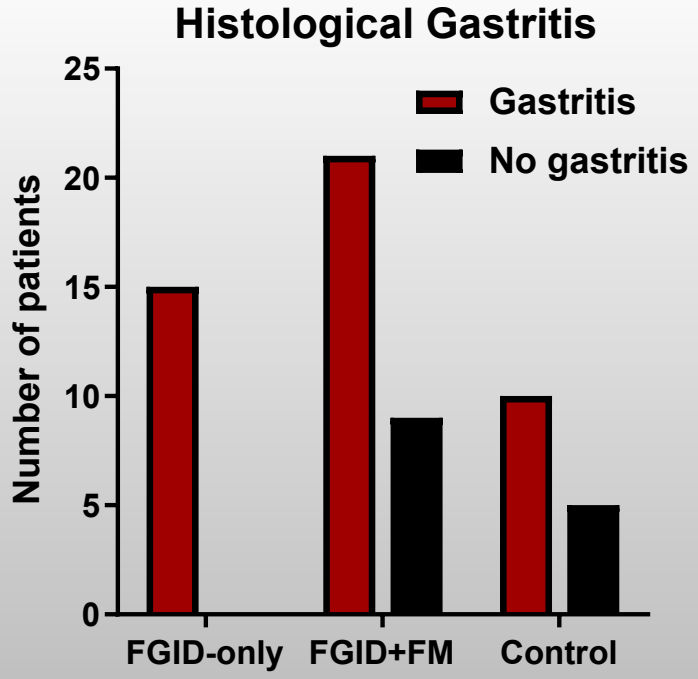
Study results: Histological examination

- Histological examination identified *H. pylori* in the biopsies of:
  - 2/15 (13.3%) case group 1 subjects (FGID-only)
  - 4/30 (13.3%) case group 2 subjects (FGID+FM)
  - 4/15 (26.7%) control group subjects
- *H. pylori* infection was not significantly positively associated with FGIDs in the presence or absence of comorbid FM



Study results: Histological examination

- Histological examination identified gastritis in the biopsies of:
  - 15/15 (100%) case group 1 subjects (FGID-only)
  - 21/30 (70.0%) case group 2 subjects (FGID+FM)
  - 10/15 (66.7%) control group subjects
- Histological gastritis was not significantly associated with FGIDs in the presence or absence of comorbid FM
- Histological gastritis was not significantly associated with active HSV-1 infection



Gastric biopsy study summary

- Active gastric HSV-1 infection was significantly positively associated with FGIDs both in the presence and absence of comorbid FM
- Active gastric HSV-1 infection was significantly positively associated with IBS
- Radial streaking near the antrum of the stomach was significantly positively associated with active gastric HSV-1 infection, FGIDs in general, and IBS in particular
- *Helicobacter pylori* was much less prevalent than HSV-1 and was less prevalent in case group subjects than in control subjects. *H. pylori* was not associated with FGIDs.
- Histological gastritis was not significantly associated with IBS, other FGIDs, or active HSV-1 infection

Acknowledgements:

Collaborator:

- Dr. William Pridgen

Institutional Review Boards:

- University of Alabama, Tuscaloosa, AL
- Druid City Hospital, Tuscaloosa, AL

Surgical sites:

- Druid City Hospital, Tuscaloosa, AL
- Northport Surgical Center, Northport, AL

Histopathology:

- Druid City Hospital, Tuscaloosa, AL

Funding:

- Virios Therapeutics, Inc.

Thank you to all the patients who generously agreed to participate in this study!

VIRIOS Therapeutics

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