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SARS-CoV-2 and Helicobacter Pylori: Can they Become Co-Pathogens?

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Abstract

Objective: SARS-CoV-2 binds to ACE (Angiotensin Converting Enzyme)-2 receptors that are expressed not only in the respiratory tract but also in the gastrointestinal tract. During Pandemia we treated more outpatients for Helicobacter pylori infection with high bacterial load. Helicobacter Pylori (HP) is known to increase the expression of ACE-2 receptors in the gastrointestinal tract.

Aim of the study to investigate: the prevalence of HP infection in pre-Pandemic (2017-2019) *vs* pandemic period (2020-2022); the relationship between SARS-CoV-2 and Helicobacter pylori: are they co-pathogens?

Methods: This is a preliminary retrospective study of consecutive outpatients. HP had been investigated by 13C Urea Breath test and the DOB (Delta Over Baseline). Pre-Pandemic: 179 patients. Pandemic: 137 patients. In the 137 Pandemic patients we searched for anamnestic COVID-19.

Results: The number of HP positive patients, 74 out of 137 in Pandemic, was significantly higher than that of pre-Pandemic: 36 out of 179 (p=0.000016). The DOB of pandemic was 40.4 ± 17.5, significantly higher than that of pre-pandemic: 17.4 ± 16.5 p<0.0001. Both SARS-CoV-2 and Helicobacter pylori infections were found in 5 out of 9 COVID-19 patients (55.5%). All COVID-19 affected patients, that were 12 out of 137 in Pandemic, suffered for SIBO/ Dysbiosis and Lactose intolerance/malabsorption.

Conclusion: SARS-CoV-2 enters and disrupts the GI epithelial cells through ACE-2 receptors and its Spike glycoproteins. This correlates with gastrointestinal symptoms. It also favours the entry and replication of HP into the broken cells enhancing the bacterial load. HP favours SARS-CoV-2 by increasing ACE-2 receptors. Suggestions for practitioner- To search HP also in COVID-19 current Pandemic, remembering its oncogenic properties (gastric cancer and MALT lymphoma). To put also COVID-19 in the differential diagnosis of GI diseases: COVID-19 is currently underdiagnosed.

Keywords: Helicobacter Pylori (HP); COVID-19; SARS-CoV-2; Pandemic; Co-Pathogenicity; Secondary Infections; ACE-2 receptor.

Introduction

It is well known that viral respiratory diseases are often complicated by co-infections due to bacteria, viruses, fungi; the term co-infection means that the infection is concurrent with the initial one; if a new infection follows, this one is named secondary or super-infection [1]. There is a lot of evidence that proves to be co-infections or secondary or super -infections worsening the course and the outcome of the viral disease, instead of the virulence of the primary agent [1]. To date, Living Reviews report in COVID-19 bacterial co- infections worsening viral pneumonia, most of them in critically ill patients.

The interaction between SARS-CoV2 and non-respiratory bacteria has been almost neglected; bacterial co-infections or secondary or super infections worsening COVID-19 viral pneumonia have only rarely reported in literature. However super-infections were reported in the late stage of the disease [1].

It has been already proven that COVID-19 Pandemic has overshadowed the diagnosis and the therapy of numerous other diseases. In particular, the medical attention for chronic diseases, some of whom also life-threatening, has been diverted or neglected. Diagnosis, therapy, follow-up of many severe diseases was adversely affected by the restrictive organisational directives, concerning public hospitals and clinics that have been issued by the government in order to contain the spread of the virus.

As concerns Gastrointestinal Diseases (GI), the accessibility to endoscopy and Breath tests was poor and difficult. In this case alterations of Microbiota including Helicobacter Pylori (HP) were underdiagnosed.

Throughout the Pandemic period, we set out to give a clinical significance to the prevailing clinical presentation of patients

referred to our private Internal Medicine setting of Rome (Lazio) where patients also converged from other Italian regions, in particular Emilia-Romagna and Abruzzo.

Digestive symptoms that have been noted were epigastralgia, hearth burn, belching, nausea, dyspepsia, loss of appetite, gastroesophageal reflux, abdominal pain, bloating, and changes in the bowel habits such as diarrhea or constipation. Other bowel disorders as Lactose intolerance, Small Bowel Bacterial Overgrowth or Dysbiosis were taken into account. Many of these symptoms are suggestive for alteration of gastrointestinal Microbiota, including Helicobacter Pylori (HP) that is known to represent the strongest risk factor for gastric carcinoma [2]. We have had the opportunity to test patients in a private setting using maximum safety criteria of non-contagion; for example a single patient daily was submitted to H2 or 13C-Urea Breath test in large sanitized room. This allowed us to make more precise diagnoses.

Another point caught our attention: SARS-CoV-2 is a pathogenetic agent of a systemic disease. The virus binds to ACE (Angiotensin Converting Enzyme)-2 receptors through the Spike glycoproteins; and enters the cells. They are located not only on lung alveolar epithelial cells, but are also widely expressed in the gastrointestinal tract. In addition, Helicobacter pylori is known to increase the expression of ACE-2 receptors [3].

Aim of the study

To investigate

- The prevalence of HP infection in subjects of pre-Pandemic VS Pandemic period;
- The possible relationship between SARS-CoV-2 and Helicobacter pylori in COVID-19: are they co-pathogens or their association is for chance?;
- If we recognize that Helicobacter pylori represents a bacterial non-respiratory co-infection in COVID-19 or rather a secondary infection;
- If SARS-CoV-2 facilitates HP infection;
- How much one pathogen influences the other?;
- How much HP infection affects or worsens the outcome of primary disease;
- Despite the study is preliminary, can suggestions be obtained for clinical practice?

Methods

This is a preliminary retrospective study of 1532 out patients consecutively referred to Internal Medicine (Gastroenterology) private setting. They presented the aforementioned digestive symptoms. The patients referring to pre-pandemic period (years 2017, from September, 2018, 2019) were 825; patients of Pandemic (years 2020, 2021, 2022-up to April) were 707. Helicobacter pylori infection had been investigated on the basis of 13C-Urea Breath test and the DOB (Delta Over Baseline) as a reliable indication of bacterial load. Patients that had been studied with 13C-Urea Breath test for HP infection were enrolled. Chi squared statistic was applied.

Pre-Pandemic period: 179 patients; Pandemic period: 137 patients.

In the Pandemic patients (137) we searched in clinical history for anamnestic COVID-19 and concurrent or secondary HP infection. In all COVID-19 patients we looked for GI symptoms compatible with Microbiota alteration by means of clinical observation and H2-Breath tests (4).

Results

Patients who underwent 13C-Urea BT for the diagnosis of HP gastric infection were 316: 36 out of 179, and 74 out of 137, in pre-Pandemic, and in Pandemic period respectively, were found positive for HP infection. The 36 pre-Pandemic HP-positive patients were 13 males aged 32-73, Mean 52.15; SD ± 13.00, and 23 females aged 21-87, Mean 51.21 ± 17.68.

The 74 Pandemic HP- positive patients were: 34 males aged 16-69, Mean 45.46 ± 13.04, 40 females aged 16-86, Mean 48.1 ± 17.89; of particular note is that the number of HP positive patients of Pandemic period was significantly higher than that of pre-Pandemic ($p=0.000016$).The DOB of Pandemic patients was 40.4 ± 17.5, significantly higher when compared to the mean value found in pre-Pandemic period: 17.4 ± 16.5 (the cut off for positivity is >5), $p<0.0001$.

We then carried out a subgroup analysis of the 137 patients evaluated in the Pandemic period: 12 reported in the clinical history a previous infection with SARS- CoV-2 (8%,7%). Only 9 patients had been tested for HP. Among the 74 HP positive patients diagnosed in the Pandemic period, 5 reported a previous SARS-Cov2 infection at the time of the 13C- UBT execution. In conclusion SARS-CoV-2 and Helicobacter pylori infection were found in 5 out of 9 COVID-19 patients (55.5%). Due to the low number of cases, we reported clinical data on COVID-19, infected or not by HP, in Table 1 and in Table 2 respectively. In these Tables the 3 patients that had not been tested for HP are not reported. We counted them when they were taken into consideration as concerns the clinical findings of COVID-19 infection.

OUTPATIENT GENDER AND AGE YEARS CLINICAL EXAMINATION DATE post – COVID-19	COVID-19 ONSET DATE SYMPTOMS	13C UREA BT DATE HP infection	GASTRIC SYMPTOMS	INTESTINAL SYMPTOMS	DIGESTIVE DISEASES	COMORBIDITIES
AA F 36 June 2021	COVID-19 March 2020 HP+ Ageusia Aphthous stomatitis Diarrhoea/ Constipation Abdominal pain	HP + tested on biopsy during COVID-19 HP + 13C UREA BT July 2021	Acid and basic gastric hypersecretion.	Dysbiosis		
AM M 56 October 2021	COVID-19 March 2020 Respiratory failure	HP + January 2022	Gastric acid hypersecretion and oesophageal reflux	Dysbosis	Colon diverticulosis	Metabolic syndrome
SG F 28 January 2022	COVID-19 January 2020 HP+ Gastric acid hypersecretion	HP+ August 2022		H2 Breath tests: -SIBO -Lactose malabsorption		Allergic Asthma
GF F 62 February 2022	COVID-19 January 2021 Oligo-symptomatic	HP ++++ February 2022		H2 Breath test: -SIBO Abdominal pain	Colon diverticulosis Cholelithiasis Kidney stones	Metabolic syndrome
SG M 32 December 2021	COVID-19 February 2020 Arthritis Fever	HP ++++ December 2021		H2 Breath test: -SIBO Abdominal pain Constipation		Allergy to inhalants

Table 1: Patients with COVID-19 and Helicobacter pylori infection.

HP was found in 2 out of 5 patients, in the course of COVID-19 (Co-infection). HP infection was searched for and diagnosed in the other 3 patients at the time of medical examination that was performed from a few months to 1-2 years after COVID-19. Bacterial load range: + to ++++. H2 Breath test was performed on 3 out of 5 patients that tested positive for SIBO (Small Intestine Bacterial Overgrowth); another patient had a clinical diagnosis of Dysbiosis. One patient tested positive to H2 Breath test for Lactose malabsorption. The 2 high grade HP bacterial load patients complained for abdominal pain. No major digestive diseases were found.

OUTPATIENT GENDER AGE YEARS CLINICAL EXAMINATION DATE post – COVID-19	COVID-19 ONSET DATE SYMPTOMS	C13 UREA BT DATE HP infection	GASTRIC SYMPTOMS	INTESTINAL SYMPTOMS	DIGESTIVE DISEASES	COMORBIDITIES
ST F 43 February 2022	COVID February 2020 Arthromialgia, Dizziness	HP – February 2022		H2 Breath tests: -SIBO -Lactose malabsorption		Herpes stomatitis
DP F 55 March 2022	COVID March 2022 Abdominal pain, diarrhoea, bloating poliartromyalgia	HP – March 2022	Gastric acid hypersecretion	Dysbiosis Lactose intolerance	Cholecystectomy Ulcer juxta duodenal bulb HP- by Histology	Relapsing herpetic cheilitis
AV F 25 November 2021	COVID July 2021	HP – November 2021	Gastro-oesophageal reflux	Breath tests: -Dysbiosis -Lactose malabsorption	Gluten-free diet (uncertain diagnosis of celiac disease)	
LS F 48 December 2021	COVID November 2020 Asthenia Diarrhoea	HP – December 2021	Gastro-oesophageal reflux	Breath test: -Dysbiosis		

Table 2: Patients with COVID 19, without evidence of Helicobacter pylori infection.

There was no evidence of HP infection in these 4 out of 9 patients, both during COVID-19 and subsequent clinical examination that was performed 1-2 years later in 2 patients and earlier in the other 2. SIBO and Dysbiosis affected all patients. Lactose malabsorption/intolerance affected 3 out of these 4 patients. A juxta duodenal bulb ulcer was found in one patient.

In summary all COVID-19 affected patients were suffering from SIBO/Dysbiosis and also Lactose intolerance/malabsorption (50%) .

Discussion

Our data, even preliminary, are in agreement with our clinical insights. In COVID-19 Pandemic, the patients undergoing 13C Urea Breath test for HP were less than those of pre-Pandemic period, probably in order to avoid the diffusion of SARS-Cov-2 through breath droplets; nevertheless those positive for HP infection were significantly more numerous than pre-Pandemic ones. Moreover the bacterial load was strikingly higher in Pandemic patients. This suggests an association between the viral and the bacterial pathogen.

Our data show that HP infection was searched and found when outpatients referred to medical examination after COVID-19 that is from few months to 2 years later. We hypothesize that HP was a secondary infection, but only few patients underwent HP diagnostic tests during the viral disease.

We have to take into consideration the pathogenetic role of these microorganisms and how they can be considered as agonist.

It has been demonstrated that SARS-CoV-2 has also a tropism towards the digestive tract (3) with the onset of early and mild gastrointestinal symptoms during COVID-19. Specific ACE-2 receptors are distributed not only in the respiratory tract but also overall gastrointestinal tract from oesophageal mucosa to enterocytes, and also hepatocytes and cholangiocytes; pathogenicity and transmissibility depend on the interaction virus-host cell, transmembrane Spike glycoprotein (S-protein), specific cell receptor ACE-2 and host cellular transmembrane serine protease [3]. Virus detected in mucosal biopsies and in stools favours transmission and recurrence of the disease. SARS-CoV-2 damages the lining epithelium, alters the mucosal barrier, increases intestinal permeability.

It is recalled that there are a few data in literature regarding the immune-histo-morphological and ultra-structural changes of GI epithelial cells, in COVID-19. Alterations in small intestine lining epithelium were described in a patient with COVID-19 suffering from ileal bleeding ulcers [5]. SARS-CoV-2-nucleocapsid proteins were found in ulcerated mucosa. Transmission electron microscopy revealed microvilli that were shorter, with deranged fuzzy coat (glycocalix), or even absent. Lamers et al. [6] demonstrated in mini- gut, that is a human intestine organoid constituted of human intestine organelles in culture, SARS-CoV-2 replicates in gut lining enterocytes producing infective virus particles. The higher expression of ACE-2-receptors is found in the so-called brush border. Rhonda et al. [7] argue that the information comes for the most part from the study of surgical and autopsy specimens, rather than endoscopic biopsies, due to Pandemic. SARS-CoV-2 induces a direct cytopathic effect in epithelial cells; in fact, transmission electron microscopy revealed the presence of virus into the cells which form blebs and appear tufted, without inflammation. All this in the absence of symptoms. SARS-CoV-2, even after the virus is no longer detected, can cause symptoms by inflammatory activation of cytokines and complement cascades.

Helicobacter pylori adhesion and subsequent cell damage mechanism is well known: adhesion takes place exclusively on gastric mucous cells; no HP is found on intestinal mucosa, even if close to the gastric one (duodenal bulb, intestinal metaplasia). Specific receptors have been hypothesized. In our previous study [8] we demonstrated morphological ultra-structural aspects of this exclusive adhesion in human gastric mucosa: the outer membrane of HP can project needle-like structures (pili formed by the Type IV Secretion System of virulent strains) and other structures like appendages and humps that contribute to adhere to host gastric cell. Mucous gastric cell microvilli become taller, with a kind of pedestal on microvillus tip in which pili insert.

Furthermore a recent study [9] demonstrates the role of glycans in the mechanism of adhesion of HP to human gastric mucosa. Adhesins involved in host colonization and infection is the Blood Group Antigen-Binding Adhesin (BabA) and the Sialic Acid-Binding Adhesin (SabA).

Sars-CoV-2 facilitates the entry of HP in gastrointestinal epithelial cells.

We searched for SARS-CoV-2 and HP co-infection in the same patient.

The problem was that we could not verify the real prevalence of SARS-CoV-2 infection. It should be noted that this is a retrospective study and that information about a previous COVID-19 was often absent from the patients' medical records, due to missed diagnosis for poorly symptomatic disease or lack of reliable diagnostic tests. For example, COVID-19 onset with mild digestive symptoms could have been missed. In the 9 COVID-19 patients, 5 had also HP infection and in 2 of them it was a real co-infection. This type of both viral and bacterial infection did not worsen seriously the clinical conditions of patients under investigation. In a recent paper [10] abdominal pain and diarrhea are reported as strongly associated with HP infection in COVID-19 of hospitalized patients.

A very interesting multicentre study [11] on 106 hospitalized patients with COVID-19, that underwent endoscopy of GI tract, the most prevalent upper GI lesions were ulcers, erosive/ ulcerative gastroduodenopathy, petechial haemorrhagic gastropathy; in lower GI tract ischemic-like colitis was prevalent. Almost half had an acute major GI mucosal injury and over 33, 3% had ischemic colopathy. However no data were available on HP infection and the possible correlation with GI damage; HP was found in one patient in endoscopic biopsy; no other tests were mentioned.

In our study the prevalent GI disorder, in both COVID-19 with or without HP infection, consisted in Microbiota alteration, detected by H2 Breath test or clinical investigation. These data agree with mucosal barrier alteration by SARS-CoV-2 [3].

The morpho-functional changes in the GI epithelium induced by HP, in particular the increased expression of ACE-2 receptors, favour the rooting of the SARS-Co v2 virus, so as to elicit gastrointestinal disorders. Moreover ACE-2 receptors are expressed also on the microvilli of bile canaliculi; Cholangiolitis was also reported in COVID-19 [3]. On the other hand, we can assume that SARS-CoV-2 infection, whether current or previous, could somehow favour the adhesion of HP to host GI cells and HP replication and colonization.

A possible pathogenetic mechanism could be:

SARS-CoV-2 Infection alters the immune system of patients;

The limited availability of Breath Tests during the Pandemic period delayed the diagnosis of HP infection.

SARS- CoV-2 binds to ACE-2 receptors; as concerns the GI tract, the virus can destroy the so-called mucosal barrier, penetrating into the lining epithelium; this also allows HP to penetrate into the damaged cells, colonize and replicate more easily.

It can be assumed that SARS-CoV-2 opens the way to HP to enter GI tract. It can also be supposed that HP could penetrate not only into gastric mucous cells but also into disrupted enterocytes which have lost their mucosal barrier function. Enterocytes deprived of microvilli loss the function of digest and absorb nutrients as disaccharides; lactose intolerance/ malabsorption has been reported in the population under study.

The failure of the mucosal barrier induced by SARS-CoV-2 may also favour other pathogens entering the cells. Microbiota alteration was also found in COVID-19 patients (83%). We report two studies in literature dealing with Microbiota and SARS-CoV-2 infection [12,13].

Conclusion

Both SARS-CoV-2 and HP may influence each other as co-pathogens. HP enhances ACE-2 receptors and could favour SARS–CoV-2 to adhere and penetrate GI cells, disrupting the mucosal barrier. SARS-CoV-2 allows HP enters GI cells, colonize and replicate in them, through the disrupted apical membrane and microvilli. It could be hypothesized that HP enter and damage not only and exclusively gastric mucous cells but also intestinal cells. Further investigation is needed by morpho-functional studies [14].

Evidences in literature [3] demonstrate that fragments of virus and its RNA have been found in bowel and in stools, even after recovery from the disease.

Interesting hypothesis is reported (3) in patients affected by COVID-19:

SARS-COVID-2 as the access door for virus (oro-fecal transmission).

The intestine is like a viral reservoir that causes the so-called long-COVID syndrome.

Other studies are needed by scientists:

To deepen knowledge trying to diagnose COVID-19 even presenting with minimal and or non-respiratory symptoms. Tests are needed to routinely identify viral fragments in stools. This could avoid false negative testing results and the spreading of the infection as well.

It could be very interesting to observe by morphological technique the possible adherence of HP also on intestinal lining epithelium, allowed by SARS-CoV-2 apical cell membrane disruption.

To study the possible invasion across the disrupted mucosal barrier by other pathogens.

To study the relationship between COVID-19 and blood groups (14).

We would like to recommend to the practitioner:

To search for HP infection also in SARS-CoV-2 variants in current Pandemic, remembering the high prevalence of HP over the world and its oncogenic properties [2].

To evaluate mucosal GI lesions by endoscopy, mainly in acute and persistent symptoms, even in COVID-19 Pandemic.

To consider COVID-19 as differential diagnostic for GI symptoms and diseases.

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