Is a bile reflux an additional cancerogenic factor in peptic ulcer, associated with Helicobacter pylori infection?

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Abstract

Purpose: **It's well known that Helicobacter pylori (H.p.) infection plays a leading role in gastric cancer in 70% of patients. A role of bile acids reflux in the stomach as a potentially cancerogenic factor is disputable. As the influence of both factors for malignancy, is still unknown, it was the aim of our investigations in peptic ulcer (PU) patients complicated with duodenogastric reflux (DGR).**

Material and methods: **79 PU patients (49 men, 27 women, aged 18 to 61, middle age – 41.8 yrs) were observed; DGR was found in 40 of them. For all patients endoscopie examination with antral and fundal parts of the stomach mucosa biopsy were performed. The morphological picture was estimated by Dixon's scale.**

Results: **The similar H.p. colonization level of the stomach mucosa independently of DGR presence was shown. A bile reflux co-exists with diminished acute and chronic inflammation activity and atrophy level. The quantity of the patients with complete intestinal metaplasia did not depend of DGR (32.5% vs. 33.3%), but in the patients with DGR it developed 16 years earlier (42.8 and 58.7 yrs, $p < 0.05$).**

Conclusions: **The combination of a bile reflux and H.p. infection may to provide progression to gastric cancer not by traditional stepwise: inflammation – atrophy-metaplasia.**

Key words: duodenogastric reflux, Helicobacter pylori, inflammation, atrophy, intestinal metaplasia.

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Introduction

Yet 10 years ago a Working Group of the World Health Organization (WHO) and the International Agency for Research on Cancer concluded that Helicobacter pylori (H.p.) is a class 1 cancerogen, and it means that the organism plays a causal role in the development of gastric cancer [1]. The prospective studies have confirmed the association between H.p. infection and the subsequent development of gastric cancer [2-4]. Now it is well known that more then 70% of gastric cancers are associated with H.p. infection. H.p. infection induces an infiltration with neutrophils and macrophages – a marker of acute and chronic inflammation of gastric mucosa. The resulting damage of this mucosa is followed by atrophic gastritis and intestinal metaplasia. Now 3 ways of mutagenesis with duodenal ulcer disease (DUD) duodenogastric reflux (DGR) H.p. participation are proposed. The 1st is inflammation-related; the 2nd is based on mitotic errors, and the 3rd underlines importance of dietary mutagens. The direct stimulation of apoptosis by H.p. is not excludes [5].

In 35-70% patients with complicates principal disorder [6]. A role of bile acids in stomach reflux as a potentially cancerogenic factor is under discussing [7]. So, Robbles at al. [8] considers that gastritis symptoms are more caused with DGR then H.p. status. But it's still unknown the influence of both this factors for malignancy.

The aim of our investigations was to value a compatible influence of H.p. infection and a bile factor on the inflammation, atrophy and metaplasia of gastric mucosa by observation of patients with DUD and DGR.

Material and methods

79 DUD patients (49 men, 27 women, aged 18 to 61, middle age – 41.8 yrs) were observed. In all patients endoscopie investigation with antral and fundal part of the stomach mucosa biopsy was performed. The DGR was confirmed by the bile

***Table 1*. Histological changes of gastric mucosa in the duodenal ulcer disease (DUD) patients with (DGR+) and without (DGR-) duodenogastric reflux by Dixon's score (score, M±m)**

Histological changes	Antrum (n=40)			Fundal (n=39)		
	DGR+	DGR–	p	DGR+	DGR–	p
H.p. colonization	2.38±0.10	2.53±0.10	n.s.	1.10±0.10	1.10±0.10	n.s.
Polymorphonuclear neutrophils infiltration	2.45±0.09	2.72±0.08	<0.05	1.15±0.10	1.08±0.10	n.s.
Mononuclear cells infiltration	1.95±0.11	2.22±0.08	<0.05	1.45±0.09	1.75±0.09	<0.05
Atrophy	1.5±0.13	2.08±0.12	<0.001	1.15±0.11	1.81±0.11	p<0.001

H.p. – Helicobacter pylori
n.s. – no significant

presence at the endoscopic examination, pH fluctuation >4 during 24-hours pH-metry and histological picture of reflux gastritis. The morphological signs of acute inflammation, chronic inflammation, atrophies and metaplasia were estimated by Dixon's scale [12]. For all patients the H.p. infection status, using CLO-test, histology and culture methods was assessed.

Result

The results show (*Tab. 1*) that in patient with DGR, H.p. colonization level (HpCL) in antral part of the stomach was 2.4±0.10 points, in fundal – 1.1±0.10. Polymorphonuclear neutrophils infiltration level (PNIL) was 2.4±0.09 and 1.1±0.10 respectively. Mononuclear cells infiltration level (MCIL) was 2.0±0.11 and 1.4±0.09. Atrophy level (AL) was 1.5±0.13 and 1.2±0.11. Complete intestinal metaplasia (CIM) was assessed to be 7.5% and 2.5% of patients and incomplete intestinal metaplasia (IIM) – in 32.5% patients (in antrum only).

In patients without DGR: HpCL in antral part of the stomach was 2.5± 0.10 and in fundal one 1.1±0.10 respectively; PNIL 2.7±0.08 and 1.1±0.10; MCI 2.2±0.08 and 1.8±0.09; AL 2.1±0.12 and 1.8±0.11. CIM was observed in 8.3% of patients (in fundal only), IIM – 33.3% of patients (in antral part of the stomach only). This data show similar H.p. colonization level of the stomach mucosa independently of DGR presence (p>0.05). The intensity of acute and chronical inflammation in gastric antrum mucosa was less in patients with DGR than without it, as well as the intensity of chronical inflammation (mononuclear cells infiltration score) in gastric fundum DGR. The atrophy score as in antrum so in fundal part of the stomach was less too.

Discussion

The role of bile as a potentially cancerogenic factor was studied in many cases. Study on animal's model [9] had show that H.p., especially combined with bile, has an influence on cell kinetics, contributing to the development of gastric cancer. Other histological studies of gastric mucosa suggest that intragastric bile acids may be implicate in premalignant histological changes of gastric mucosa and thus play a part in gastric carcinogenesis [10].

The controversial studying had demonstrated comparable low increase of duodengastric reflux concentration in proximal gastric ulcer and distal gastric carcinoma. That gives no evidence for a main role of reflux in the pathogenesis of gastoduodenal ulcer [11]. But in our results it seems a paradox that a bile reflux promotes diminished acute and chronical inflammation activity and atrophy level of gastric mucosa in H.p. infected patients. Although the quantity of patients with complete intestinal metaplasia does not depend on DGR (32.5% and 33.3%), but in patients with DGR it develops 16 years earlier. The middle age of metaplasia for patients with DGR was 42.8 ±3.0 and 58.7±2.2 yrs without it (p<0.05). It means that a bile reflux could hasten the development of incomplete intestinal metaplasia in H.p. infected patients. Another authors also underlines the danger of both factor (a bile and H.p.) for cancerogenesis [12-14].

It is difficult to explain this result, but there is all reasons to think that the combination of a bile reflux and H.p. infection provides progression to cancer by not traditional stepwise according to Correa but alternative way suggested by Sipponen [15].

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