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Role and clinical importance of *Helicobacter pylori* infection in hemodialysis patients

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SUMMARY: **Role and clinical importance of *Helicobacter pylori* infection in hemodialysis patients.**

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Dyspepsia is an extrarenal symptom frequently found in hemodialysed patients; it is due to chronic renal failure, and uremic gastritis is a specific associated condition in chronic renal failure (CRF). On the other hand, in the general population, Helicobacter pylori infection is an important dyspepsia-related risk factor; its close connections with gastro-duodenal pathology are already known, above all the peptic disease in a really exclusive way.

By observation of a dyalitic group of patients, opportunely matched with a no CRF group, we evaluated CRF-associated uremia and Helicobacter pylori infection which could eventually interact causing symptoms and lesions.

A statistical analysis of obtained data allowed us to conclude that, although there is not, from an epidemiological view-point, a larger diffusion of Helicobacter pylori among dyalitic patients compared to general population, moreover the infection is uremia-synergic in causing gastro-duodenal symptoms and lesions.

These findings, therefore, suggest systematically investigation a possible Helicobacter pylori infection in CRF patients and its relation to gastritis grading, and searching for probable active peptic lesions.

RIASSUNTO: **Ruolo e importanza clinica dell'infezione da *Helicobacter pylori* nei pazienti emodializzati.**

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La dispepsia è un sintomo estrarenale che si osserva frequentemente nei pazienti dializzati a causa dell'insufficienza renale cronica (CRF) e della gastrite uremica. Nella popolazione a generale l'Helicobacter Pylori (HP) è un fattore di rischio per la malattia peptica, le gastriti croniche e la corrispettiva sintomatologia dispeptica.

Nel presente studio vengono osservati un gruppo di pazienti dializzati e confrontati con un gruppo di pazienti con funzione renale normale e con uno con CRF. Viene valutata l'associazione tra l'uremia e l'infezione da HP e l'eventuale correlazione con la sintomatologia dispeptica e le lesioni anatomo patologiche del tratto gastroenterico superiore.

L'analisi statistica ci ha permesso di concludere che dal punto di vista epidemiologico non c'è ampia diffusione dell'infezioni da HP nei pazienti dializzati rispetto alla popolazione normale. Si evince, comunque che l'infezione da HP può essere la causa di lesioni anatomo patologiche del tratto digestivo superiore e della sintomatologia ad essa correlata.

KEY WORDS: Chronic renal failure - *Helicobacter pylori* - Dyspepsia.
Insufficienza renale cronica - *Helicobcter pylori* - Dispepsia.

Introduction

One of the main problems that do not involve the kidney in patients with chronic renal failure (CRF) treated with hemodialysis (HD) is the increase of dyspeptic symptoms. Uremic gastritis can be considered the digestive expression of CRF. Patients treated with HD show a huge incidence of gastritis, peptic ulcer and upper gastrointestinal bleeding.

Helicobacter pylori (Hp) infection is strictly correlated to gastric diseases, even though it has recently shown a negative epidemiologic trend. It has great importance in causing a lot of diseases: gastritis, dyspeptic disease, peptic ulcer, gastric cancer and lymphoma (1, 2).

We must consider that the main factor of endogastric survival of Hp is its intense ureasic activity, creating around the bacterium an alkaline area in the gastric acid, resulting in mechanism which leads to

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produce ammonium ions from the urea. So it may be interesting to hypothesize an association between Hp infection and CRF.

The aim of our retrospective research is to verify the presence of digestive symptoms and signs in CRF patients undergoing with HD, comparing them with a group of dyspeptic subjects with normal renal function, homogeneous for gender, age and environmental conditions. Our aim is also to stress the correlation with different degrees of CRF. At the end, we will hypothesize a pathophysiologic correlation between Hp infection and CRF.

Patients and methods

Our retrospective survey included 274 dyspeptic patients with or without renal failure; 124 of them were women and 150 men, between 42 and 85 years old, which we observed in the last five years. The patients were divided into three groups, homogeneus for gender and age: a) group 1: 132 dyspeptic patients with normal renal function, (control group); b) group 2: 63 dyspeptic patients HD treated for less than 5 years; c) group 3: 79 dyspeptic patients HD treated for more than 5 years.

All patients were investigated with upper gastrointestinal endoscopy searching for Hp by rapid urease test (RUT), both in antral and in body gastric biopsies, and by histologic evaluation (Giemsa). All the patients, before gastrointestinal endoscopy, were questioned about their smoking habit, addiction to alcool and drug, and particurarly about their dyspeptic symptoms according to the symptom score (Tab. 1).

We excluded some patients according to the following criteria: antibiotic therapy, FANS and steroid drug taking, PPI or anti-H2 therapy during the previous two months.

The statistical analysis we used is the comparison between percentage rate, as shown below:

$$p1 - p2 \geq 1{,}96 * \sqrt{\frac{p1 * q1}{N2} + \frac{p2 * q2}{N1}}$$

Results

From the analysis of Table 1 it's clear that the epigastric discomfort (meal-related) plus nausea is more frequent in the patients belonging to group 3, while the epigastric discomfort (meal-related) is more frequent in group 2 and the epigastric pain in addition to the epigastric discomfort meal-related dominates in the group 3.

The statistical analysis points out the significant data as the epigastric discomfort (meal-related) plus nausea in the control group vs group 3, and the epigastric discomfort (meal-related) alone in group 2 vs group 3. The other data are insignificant.

Table 2 quotes the incidence of Hp infection in each group, where we observe that group 3 has a greater incidence of the infection followed by group 2 and by the control group, but these data aren't statistically significant.

Table 3 is about the diagnosis by gastrointestinal endoscopy and points out that both microscopic and macroscopic gastritis dominate in group 3, while gastric ulcer predominates in the control group and in group 2; duodenal ulcer is more frequent in groups 2 and 3. However these data aren't statistically significant.

TABLE 2 - CAUSES OF CRF.

Cause	Pts (N)	Pts (%)
Chronic glomerulonephritis	39	27.5
Nephroangiosclerosis	29	20.5
Diabetes	22	15.4
Policystic kidney disease	17	12.0
Unknown	35	24.6
Total	142	100

TABLE 3 - HP INFECTION INCIDENCE.

GROUP 1 132 pts. with normal renal function	GROUP 2 63 pts. HD treated < 5 years	GROUP 3 79 pts. HD treated ≥ 5 years
N = 59	N = 33	N = 42
44.70%	52.38%	60.76%

TABLE 1 - SYMPTOM SCORE IN PATIENT GROUPS.

SYMPTOM	GROUP 1 132 pts with normal renal function	GROUP 2 63 pts HD treated < 5 years	GROUP 3 79 pts HD treated ≥ 5 years
Epigastric pain plus epigastric discomfort meal-related	N = 42 (31.82%)	N = 8 (12.69%)	N = 12 (15.19%)
Pyrosis plus epigastric discomfort meal-related	N = 7 (5.30%)	N = 1 (1.59%)	N = 8 (12.69%)
Epigastric discomfort meal related plus nausea	N = 10 (7.58%)	N = 18 (28.57%)	N = 6 (36.71%)
Nausea	N = 14 (10.61%)	N = 3 (4.76%)	N = 13 (16.46%)
Epigastric discomfort meal-related	N = 59 (44.69%)	N = 33 (52.38%)	N = 19 (24.05%)

Discussion

In this study we observed that the prevalence of Hp infection in dyspeptic patients with and without CRF is greater in HD patients in therapy for more than five years; however these data are not supported by statistical significance and are confirmed by some authors and denied by others. In fact, Hp infection prevalence among CRF patients is estimated between 21% and 64% (3-5).

Conflicting data can be attributed to different factors, such as infection diagnostic methods, observed population, Hp prevalence in healthy people, clinical and demographic characteristics of the groups studied, and other unknown factors.

On the contrary, Fabrizi et al. (5) observed a lower prevalence of Hp infection among HD patients in relation to patients with normal renal function and they reached the conclusion that patients with CRF could be partially protected against Hp infection. They also thought that an eventual protective factor could be the use of antibiotics and/or PPI in HD patients. Therefore, according to Fabrizi et al., the increased uremia could modify the bacterial colonization of the upper gastrointestinal tract with a bacterial overgrowth of other bacteria and a reduced Hp colonization (5).

Nardone et al. have recently found that uremic patients have a lower prevalence of dyspeptic symptoms, but a higher prevalence of peptic lesions in relation to dyspeptic patients without CRF, with and without Hp infection (6).

Our analysis underlines that Hp infection has a negative effect on both lesions and symptoms of gastric diseases in CRF patients. Urea transformation into ammonium by bacterial urease produces an increase of gastric pH suitable to bacterial survival in this area, and it also produces the increase of ammonium, obviously more toxic compared to urea for gastric epithelium.

Particularly, gastric hyperammonemia changes regular cellular turnover with apoptosis induction and hence with slow repair of mucosal lesions. These phenomena are related to carcinogenesis with other chemotactic factors.

In recent years it has become more evident that Hp is the most important etiologic factor in gastric cancer and that COX2 is implied in gastric carcinogenesis both in early and later phases. A complex phlogistic and immunological reaction caused by Hp in the gastric area damages DNA. One of the earliest and most important molecular alteration is the increase of COX2, involved in the carcinogenetic process through apoptosis inhibition, the modulation of immunological response, the regulation of signal transduction and neo-angiogenesis increase.

In this process there are other carcinogenetic factors as CagA protein, transformed into an unrestrained growth factor of gastric cells and some bacterial enzymes such as phospholipase. This enzyme could modify the phospholipids of the gastric mucosa and consequently it could cause a phlogistic process with a production of interleukines and TNF-α (2, 7-11). Besides these dangerous and rather slow effects, the Hp infection produces immediate consequences too, not correlated to the activity of urease enzyme, such as the cytotoxic effect of bacterial toxins, the beginning of local immunological phenomena, and activation of cytochines. We must carefully observe the data on the greater quantity of endoepithelial urea in CRF patients since this could lead to a more vivid and active Hp infection. Consequently the Hp infection, already dangerous in normal patients, in CRF patients can worsen the gastric condition, either increasing the shift urea ammonium, or harshen the factors connected to optimal bacterial colonization (12).

We can affirm that Hp infection, even if it does not differ among normal and uremic subjects from an epidemiologic point of view, provokes more serious damage in the gastroduodenal mucosa of CRF patients, characterized by a higher incidence of dyspeptic symptoms.

TABLE 4 - ENDOSCOPIC DIAGNOSIS.

DIAGNOSIS	GROUP 1 132 pts with normal renal function	GROUP 2 63 pts HD treated < 5 years	GROUP 3 79 pts HD treated ≥ 5 years
Normal range	N = 35.0 (26.6%)	N = 4.0 (6.3%)	N = 4 (5.06%)
Microscopic gastritis	N = 38.0 (28.70%)	N = 4.0 (6.70%)	N = 26.0 (32.91%)
Erosive (macroscopic) gastritis	N = 48.0 (36.40%)	N = 21.0 (33.40%)	N = 43.0 (64.43%)
Gastric ulcer	N = 2.0 (1.5%)	N = 1.0 (1.5%)	N = 0.0 (0%)
Duodenal ulcer	N = 9.0 (6.8%)	N = 6.0 (9.5%)	N = 6.0 (7.59%)

Conclusions

Because the symptoms do not show Hp infection, we hope CRF patients are investigated with biological and instrumental tests to reveal the gastric bacterial colonization and the histologic staging. We must also verify if there is other damage in evolution. Increasing the concentration of plasmatic urea we can observe an increase of the number of symptoms; it is important to start the above mentioned, diagnostic proceedings, in an early phase of CRF, to avoid the beginning of more serious damages.

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