The histological changes of digestive organs in experimental decreases of hepatic venous outflow at the rat

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Abstract

The hepatic venous outflow may be diminishing in right-sided heart diseases, constrictive pericarditis, obstruction of suprahepatic veins or an inferior vena cave. It was created an experimental model by obstruction of the suprahepatic veins lumen and inferior vena cave, too, at the adult Wistar rats. The animals were sacrificed in the 30 days after operation. At the iterative laparatomy it was found the liver more increased in volume, a little amount of ascites in peritoneal cavity, oedema of the digestive organs walls. Liver and stomach fragments were prelevated and were processed for optic microscopy and electronic microscopy. The morphological study using by usual technics has highlighted vascular stasis in gastric submucosa. In liver it is standed out the pericentrolobular vascular stasis, inflammatory lymphoplasmocytic infiltrate around the end of hepatic vein. In the gastric submucosa have found vascular stasis, and within the chorion mucosa, the high capillary hyperemia. There is a discreet vacuolar feature on epithelium surface of the gastric mucosal in pyloric region. In the other layers, at rats the epithelium multistratum keratinized of the stomach is without changes, in this region is maintaining the hyperemia in mucosal chorion.

Keywords: hepatic venous outflow, portal hypertension gastropathy, gastric antral vascular ectasia (GAVE).

Background

The hepatic venous outflow may be diminishing by the right-sided heart diseases, constrictive pericarditis, obstruction of suprahepatic veins or an inferior vena cave, but also in the portal hypertension syndrome [1].

As part of portal hypertension, two distinct entities have been described recently, the portal hypertensive gastropathy (GPH) and gastric antral vascular ectasia (GAVE) syndrome, with clinical involvements. Both entities can be associated with gastrointestinal hemorrhage at the patients with or without cirrhosis, and the impairment of hepatic venous outflow that are due to anomalies of portal tracts, may mimick the signs of chronic biliary disease [2].

Portal hypertensive gastropathy (GPH) is defined as a congestive modification of gastric mucosa due to increasing of portal pressure and it was first described in 1985. The GAVE syndrome is characterized by the ectasia and dilatation of the vessels from gastric submucosa that have clinical manifestation as an important blood loss.

Gupta R et al. (1996) have shown that in GPH occur physiopathological changes that eventually result in appearance of congestive gastropathy, so GAVE may be considered as a consequence of GPH [3]. The distinction between GPH and GAVE is difficult, but there are some specific features, especially histological features, that distinguish one from the other.

GPH has an incidence up to 65% among the patients with cirrhosis associated with portal hypertension. After Pique JM (1995) 65–90% of these patients suffer from a light form of GPH, while 10–25% shows severe forms dependent of portal hypertension etiology, functional status of liver evaluated through Child scale, and the presence and the size of esophageal varices [4]. The presence of esophageal varices is accompanied in 61% of cases by portal hypertensive gastropathy, while in 14% of cases is accompanied by portal hypertensive duodenopathy. A study realized by Zaman A et al. (1999) on 120 patients endoscopically explored prior to hepatic transplant has shown that among them 73% of patients had esophageal varices, 62% have had GPH and 16% gastric varices [5].

The appearance of GPH represents a marker of severe hepatic impairment. So, Zoli M et al. (1996) have suggested that GPH represent a forerunner of hemorrhagic varices and in spite of the fact that patients with GPH may present gastrointestinal hemorrhage, more frequently they suffer because of the chronic anemia [6].

The histological studies realized on biopsies prelevated from fundus and antrum gastric mucosa at cirrhosis patients has shown that thickness of capillary walls from gastric mucosa represent the histological marker of portal hypertension. Therefore, the capillary diameter from gastric mucosa shows the presence of portal hypertension with an accuracy of 50%, while the thickness of capillary from antrum and fundus gastric...
mucosa shows the portal hypertension with 85% of accuracy. The clinical marker of portal hypertensive gastropathy severity is represented by the presence of bleeding from esophageal and gastric varices. More than that, presence of GPH is associates the worsening of the hepatic disorder.

The studies of Gupta R et al. (1996) have shown that both sclerotherapy and esophageal varices ligation as a prophylactic treatment of bleeding GPH complication do not influence the GPH severity [3]. They also noticed an increase of GPH frequency two years after sclerotherapy. These results have concluded that the increasing frequency of GPH after esophageal varices ligation or after sclerotherapy represents a consequence of hepatic severity evolution.

Another authors (Sarin SK et al. 1997), has shown that recurrence of oesophageal varices complicated by digestive bleeding is higher in patients with oesophageal varices ligation, and GPH was almost 10-fold higher in patients treated with sclerotherapy [7].

In another study, Hou MC et al. (1995) shows that the probability to modify the GPH severity was not correlated with the method of bleeding cease (ligation or sclerotherapy) [8]. However, at the moment, we can not say that variceal obliteration contributes in a higher proportion to increase the GPH development [7].

Because TIPS effectively reduced PVP, this procedure appeared to be effective for the treatment of uncontrollable GPH. (Urata J et al., 1998) [9].

The second clinical entity is represented by GAVE syndrome (gastric antral vascular ectasia) and was described for the first time by Riedel in 1953 and recently characterized by Jabbari in 1985. The GAVE syndrome is present in 70% patients with cirrhosis or portal hypertension, but it may be present in noncirrhotic patients also, but these patients present an autoimmune disease of conjunctive tissue (62% of cases), scleroderma or atrrophic gastritis (Gostout CJ et al., 1993) [10].

The endoscopical characteristic features include hyperemic lesions, often hemorrhages localized predominantly in antral mucosa and it can cause an important bleeding.

The certainty diagnosis and also, clinical differential diagnosis between GPH and GAVE is establishing on the base of endoscopic exploration which allow the visualization of macroscopic characteristic features. Thus, in GPH, in the mild form of GPH, is present the aspect of gastric mucosa mosaic-like pattern similar with snakeskin with edema and hyperemia. In the severe form of GPH the gastric mucosa appears with reddish linear spots, very friable or cherry red spots bleeding during endoscopy. Sometimes even black-brown spots were found (Carpinelli L et al., 1997) [11].

This type of gastric mucosa modifications are localized in fundus and corpus of stomach, but the similar changes „GPH-like” were described in other segments of the gastrointestinal tract, such as rectum, colon, small intestine.

In GAVE syndrome, the gastric mucosa lesions like spots and red points or diffuse pattern achieves the “red-mellow” pattern and is affected more the antral zone of stomach. This vascular ectasia results in an important bleeding.

The purpose of our study is to stand out early histological changes at the stomach and liver level in experimental portal hypertension and the clinical significance of the pathological changes that appears after diminishing of hepatic venous outflow.

Material and methods

It was created an experimental model by narrowing of lumen hepatic veins and also, inferior cava vein at adult Wistar rats. The rats were anesthetized with ether and ketamine. The operatory technique: median celiotomy followed by evidential of the suprahepatic veins and the inferior cava vein, and then obliteration of these veins. After that we applied a metallic clip on the suprahepatic veins – inferior cava vein system and at the last closure the abdominal wall.

At 30 days after the operatory techniques we made an iterative celiotomy under ketamine anesthesia. Intraoperatory, we noticed that the liver had enlarged volume, there was a small amount of fluid in peritoneal cavity and edema in digestive organ walls (stomach, colon, small intestine). It is harvested the liver and stomach fragments which has been analyzed for light microscopy (colored by Hematoxylin–Eosin) and for electronic microscopy, only the liver fragments.

Results

The morphological study through light microscopy from stomach fragments has shown a series of changes at the fundic and antrum mucosa and submucosa level. Therefore, at the gastric mucosa level appears an important capillary dilatation (Figure 1).

At the level of gastric submucosa the morphological changes are dominated by the vascular stasis in submucosa and capillary stasis at the mucosa level (Figures 2–4).

The emphasis of interstitial vascular stasis and mucus dissolution in prismatic epithelium is a direct consequence of the presence of portal hypertension. The vascular stasis is important also in submucosa vessels and in the capillaries from glandular epithelium (Figures 5–8).

The glandular epithelium was modified. This embraces the vacuolar aspects (Figure 9) and connective tissue stroma of submucosa from the proximal site of keratinized epithelium stratum presents dilated vessels with stasis (Figures 10 and 11).

Another morphological aspects observed in gastric submucosa (at proximal extremity) is dominate by dissolution of mucus in the crossing zone between the keratinized epithelium of the rat stomach and prismatic epithelium unistratum and, also, with cleaning of apical extremity (Figure 12).

In the animals sacrificated on the 30 days postoperatory, the light microscopy study shows phenomenos of centrolobular vascular stasis (Figures 13 and 14), pericentrolobular inflammatory infiltrate and appearance moderate pericentrolobular lipidic distrophy (Figure 15).
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Figure 1 – Gastric mucosa with fogging of the covering epithelium at the apical pole and mucus dissolution and capillary dilatation

Figure 2 – Marked vascular stasis in the submucosa, interstitial capillary stasis in the mucosa, lack of mucus in the epithelium

Figure 3 – Vascular stasis in submucosa

Figure 4 – Marked vascular stasis in main vessels of the submucosa

Figure 5 – Junction between keratin epithelium and simple prismatic epithelium. Mucus dissolution in prismatic epithelium

Figure 6 – Stratified keratinized epithelium in the proximal part of the stomach. Inflated vessels in submucosal conjunctive stroma
Figure 7 – Massive vascular stasis in submucosa

Figure 8 – Semifine section with vascular stasis in submucosa

Figure 9 – Ectatic interstitial capillary and vacuolar aspects in glandular epithelium

Figure 10 – Superficial and glandular epithelium with major modifications. Vacuolar aspect in glandular epithelium and fogging of the apical pole through mucus dissolution

Figure 11 – Vascular stasis in main vessels of the stomach

Figure 12 – Vascular stasis in submucosa and partially in muscular layer
The histological changes of digestive organs in experimental decreases of hepatic venous outflow at the rat

Figure 13 – Intense process of sinusoid capillary dilatation in hepatic lobule

Figure 14 – Hepatic lobule: sinusoid capillary stasis and granulo-vacuolar dystrophy

Figure 15 – Centrolobular vein with centrolobular inflammatory infiltration. Hepatocytes with granular and vacuolar degeneration

Figure 16 – Two hepatocytes. Cytoplasm with endoplasmic reticulum modifications. Inflated fragmented endoplasmic reticulum. Mitochondria with homogenous contour and matrix (absence of crysta)

Figure 17 – Hepatocyte: fragmented endoplasmic reticulum, mitochondria with homogenous astructural aspect; rare lipide inclusions

Figure 18 – Hepatocyte with granular cytoplasm with multiple lipidic inclusions inside rough endoplasmic reticulum. Mitochondria with modified structure (homogenous matrix and absence of crysta)
The electronic microscopy study on liver fragments shows details about hepatocytes with cytoplasm that present endoplasmatic reticulum modified (inflated fragmented endoplasmatic reticulum, mitochondria with homogenous contour and matrix and absence of crysta) (Figure 16), hepatocytes with fragmented endoplasmatic reticulum, mitochondria with homogenous anastomotic aspect and rare lipidic inclusions (Figure 17), hepatocytes with granular cytoplasm with multiple lipidic inclusion inside rough endoplasmatic reticulum, mitochondria with modified structure (homogenous matrix and absence of crysta) (Figure 18).

Discussion

The literature experimental data shows histological changes (consequence of reduced venous hepatic outflow) appear early in liver and stomach and they may be correlated with endoscopical aspects. Thus, at the gastric mucosa level is observed the capillary stasis, mucosal disappearance on the surface epithelium. The glands have vacuolar aspect with cleaning of apical extremity, while in submucosa the frame is dominated by vascular dilatation. These characteristics are due to the changes that appear in vascular distribution and also in sanguine flow speed, this being decreased in gastric mucosa and increased in other layers of the wall (submucosa, musculosa and serosa). All of that results in a high susceptibility for aggressions.

The distinguishing histological features in GPH consist in vascular dilatation in gastric mucosa and submucosa congestive gastropathy-like. This congestive gastropathy is different from inflammatory gastritis and it may be put in evidence by means of biopsies prelevated during endoscopy and stained by Hematoxylin–Eosin, and by means of a specific marker for endothelium with a great affinity for vascular wall (Dako Immunoglobuline – antigen dependent of factor VIII).

Foster PN et al. (1989) has shown that capillary dilatation represents a nonspecific sign and all histological features of GPH are highlighted by means of this specific endothelial marker [12].

Also, it is shown that gastric chronic inflammatory infiltrate specific to chronic gastritis is different from the features realized by the ectasia and prominence of mucosa capillary in portal hypertension. These appear irrespective of gastric inflammation.

Sometimes, the histological description in portal hypertension shows the features of reflux gastritis characterized by foveolar hyperplasia, congestion, edema with decrease of inflammatory cells. In spite of all this, it is not known exactly if these changes are consequences of reflux gastritis or it could be because of changes suffered by mucosa in portal hypertension that could mimic reflux gastritis.

The mechanisms involved in GPH syndrome pathogeny are still unclear. However, some factors involved in GPH syndrome pathogeny are known. So, the reduction of gastric mucosa that has an important role in gastric mucosa defense makes it to become more vulnerable. Another factor is represented by the increase level of gastrin serum and also, decrease in the parietal cells mass. It is known that increased nitric oxide (NO) production in cirrhotic patients represents a marked vasodilator which stimulates GPH.

TNF-α has been implicated in impairment of gastric and intestinal mucosa due to his proinflammatory action (Perez-Ayuso RM et al., 1991) [13]. In GPH syndrome has been described the impairments of the growth factors.

Wang JY et al. (1998) has shown on experimental animal that in spontaneous ulcer sites of mucosa there is a significant increase of TGF-α (transforming growth factor) and those of EGF (epidermal growth factor). Also, decrease in prostaglandin activity may cause appearance of gastric disorders (lesions) both in experimental animals and GPH patients [14].

The earlier changes in decreased hepatic outflow are first consequences upon liver and are represented mainly by sinusoidal stasis that can induce pericentrolobular inflammatory infiltrate. Subsequently, the hepatocytes presents marked granulo-vacuolar dystrophy and degenerative impairment in cytoplasm which presents endoplasmatic reticuli broken up and mitochondria with disappearance of the regular structure. The earlier changes are due to the impairment of hepatic outflow and are initiated by the sinusoidal dilatation that may produce congestion, and then haematic extravasations, and eventually, portal and periportal fibrosis. Also, the sinusoidal dilatation and increase of the venous pressure associated with arterial flow impairment may result in ischemic lesions that can produce biliary duct proliferation in association with large regenerative nodules. After appearance of portal hypertension the hepatic changes are early followed by histological changes in the layer of gastric mucosa, capillary stasis in gastric mucosa and submucosa, decrease and disappearance of surface mucosa. After a short period, the glands take a vacuolar aspect and their proximal extremity is modified.

Conclusion

In portal hypertension appear early histological changes in digestive organs, such as stomach, liver, small intestines that may result in severe complications as hemorrhage. The GPH syndrome appears not only in case of cirrhotic patients, but also in non-cirrhotic patients with impairment of hepatic outflow such as in autoimmune disease or in heart disease (constrictive pericarditis, right-side heart disease).

At liver level we noticed aspects of granulo-vacuolar dystrophy and mild lipidic charges, especially pericentro-lobular and inflammatory infiltrate around the suprahepatic veins. Also, in gastric mucosa and submucosa prevails vascular stasis, dilated capillaries and venules and capillary hyerenmia is present in chorion mucosa.

The consequences of changes in sanguine distribution cause the disappearances of mucus, the changes of apical extremity of glands, all predisposing to the appearance of hemorrhagic accidents.
The histological changes of digestive organs in experimental decreases of hepatic venous outflow at the rat

References

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