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Correlation Between Liver Cirrhosis and Benign Prostatic Hyperplasia: A Morphological Study

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Summary. In elderly males hormonal changes occur, that are believed to cause benign prostatic hyperplasia (BPH). These are decreased testosterone production, an increased testosterone SHBG and a slightly increased estradiol production. Liver cirrhosis in males causes similar endocrine changes. We carried out a post mortem study evaluating the prostates of 51 men who died with liver cirrhosis compared with a similar group without any hepatic disease. The occurrence of BPH in cirrhotic subjects was diminished and delayed compared to total population. Furthermore in cirrhotic men BPH is more common as early nodular hyperplasia (early stage) or stromal hyperplasia (suggesting estrogenic prevalence), while in the general population stromal and epithelial hyperplasia (androgenic stimulation), were almost equally present.

Key words: Benign porstatic hyperplasia (BPH), Alcoholic liver cirrhosis, Stromal hyperplasia, Epithelial hyperplasia.

Introduction

It is well known that in liver cirrhosis, among the various disorders, hyperestrogenism occurs, which results in feminization. This situation could be considered to be similar to the changes consequent on ageing. In the latter, however the estrogenic prevalence is the result of a reduction in testosterone production in its free state, while there is an increase of the quota carried by the SHBG. This situation causes reduced virilizing activity. Moreover free estrogens tend to rise, especially estradiol (E_2) [3].

In benign prostatic hyperplasia (BPH), estrogen supports stromal development while androgen causes epithelial hyperplasia. Stromal hyperplasia would be prevalent in the early stages as fibromyomatous periurethral nodes (early nodular hyperplasia); this situation itself could be a factor stimulating the development of epithelial proliferation which, especially in advanced cases, could be predominant on histological specimens [2, 3, 4].

The hormonal changes in the older male are believed to be the pathogenetic factors in the development of BPH. In patients with liver cirrhosis there is a hormonal imbalance, especially in testosterone activity, quite similar to that described above; it is the result of a reduced production of testosterone and of an increase of the SHBG; furthermore there would be a secondary defect of the hypothalamic-pituitary-gonadal axis [5, 8, 9].

Hyperestrogenism is due to an increase of estrone and estriol, that are less femininizing than estradiol, whose production is not very much increased.

Pathogenetic correlations between hormonal changes in liver cirrhosis and in BPH have been studied by several Authors, first of all Wu in 1942 [10], who noted that in a small group of cirrhotic subjects the incidence of BPH (histologically evaluated) was 91%, while it could be exstimated at about 50% in the general population.

IN 9150 Bennet [1] carried out a post mortem study showing an incidence of BPH of 28.6% in cirrhotic subjects, compared to 50% in the total population.

Stumpf [7] in 1953 reported similar results (30% of BPH in people with liver cirrhosis, compared to 53% in the general population).

In 1964 Robson [6] evaluated 205 prostates belonging to cirrhotic subjects and 2,227 prostates of non cirrhotic people; he noted that the incidence of BPH was similar in the two groups (25.4% in cirrhotic people and 30.5% in the control group). Moreover Robson tried to classify the severity of cirrhosis, basing upon some clinical features: jaundice, ascitis, esophageal varicosities, liver enlargement, hepatic coma. If three of these features were present, then cirrhosis was considered "severe". BPH incidence in "severe" cases was 18.4% compared to 27% in "not severe" cases; this difference was considered to be of non statistic significance. The author evaluated the signs of hyperestrogenism too: gynecomastia, testicular atrophy, feminine hair distribution, palmar erythema, spider angiomatas; if two of these

Table 1. Histological assessment of BPH incidence in cirrhotic subjects and in controls, ($p < 0.02$)

	Cirrhotics		Non cirrhotics	
	Cases	%	Cases	%
Absent BPH	18	35.3	7	13.7
Signs of BPH	33	64.7	44	86.3

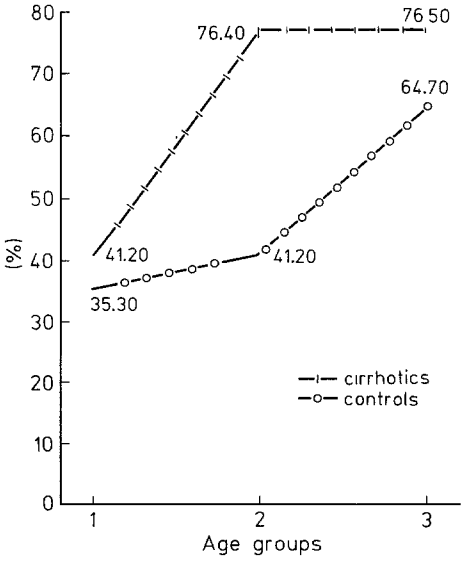

Fig. 1. BPH incidence in the various age groups ($p < 0.05$ in the second age group for evident BPH)

signs were present he assumed that hyperestrogenism existed. But he noted that the difference of BPH incidence in the groups with or without hyperestrogenism was of no statistic significance.

Robson also divided his cases into three different age groups: 50 to 59, 60 to 69, and over 70 years old. He noted that the development of BPH in cirrhotics was "later" compared to the group of non cirrhotics.

Materials and Methods

We carried out a post mortem study on the relationship between BPH and liver cirrhosis documenting the histogical features of the prostates of 51 subjects who died with liver cirrhosis and 51 subjects without any liver disease; the examination was both macroscopic and histological.

All the cases with liver cirrhosis had a pure Laennec' alcholic cirrhosis; we excluded all the other types of cirrhosis and all people who died with primary or secondary liver neoplasms.

Controls were selected in a randomized way, excluding those who presented with any hepatic disease.

Cases and controls were divided in three different age groups: 40 to 59, 60 to 69, 70 to 80 years old.

The macroscopic evaluation of prostates reveated only two groups: BPH presence or absence.

Histological evaluation considered three classes: BPH absence, early nodular hyperplasia, and evident hyperplasia. Early nodular hyperplasia meant the cases with fibromynomatous node, with evidence of periductal, perivascular and intralobular fibrosis. These criteria are considered to be the early stages of BPH.

Moreover we considered, in cases of evident BPH, epithelial or stromal prevalence, according to the pathogenetic hypothesis that the former is the effect of an androgenic stimulation and the latter is due to an estrogenic one. Epithelial hyperplasia meant the presence of glandular epithelial cells disposed in "papillae" without fibrovascular axis. For this purpose we considered sections of the prostates far from periurethral portions, to eliminate the possible confusion with urothelial proliferation originating from urethra itself, which is frequently found in the proximal portions of some glandular ducts.

Results

In Table 1 we report the incidence of BPH in the two groups; it is more frequent in the control group (without any disease of the liver). This different BPH incidence between these two groups is especially evident in the class aged between 60 and 69: 76.4% in controls and 41.2% in cirrhotics. This difference is less evident in the group aged between 70 and 80, however BPH is more common in the group without liever cirrhosis (Fig. 1).

Moreover we can see that there is, among the group of cirrhotics, a large number of subjects who do not present any sign of BPH. If we transfer these results to a graph, we obtain Fig. 2: it shows that the incidence of BPH rises in the second age group (60–69) and becomes steady in the third one; on the contrary, in the group of cirrhotics, it rises only in the third class (70–80) while it remains steady in the first and in the second ones.

These results could mean a slow and delayed development of BPH in people with liver cirrhosis.

In Fig. 3 is showed that there is a prevalence of epithelial hyperplasia in the group of controls (3/4) compared to only 1/2 in cirrhotics. Stromal hyperplasia is abundant in both groups.

Discussion

Our results are similar to those reported by other authors [1, 7]. The higher incidence of BPH in patients without liver diseases was explained by other authors because of the higher age of this group of people. This objection cannot be raised on our series because we have selected our materials coupling each cirrhotic case with a control subject of the same age.

We report a significant diffence in the incidence of BPH between cirrhotics and non cirrhotis (41.2% in the former, 76.4% in the latter) in the class of age between 60 and 69 ($p < 0.05$).

In the first age class (40–59) and in the third one (70–80) the incidence of BPH is not very different between the two groups. This situation could reflect a retardation in the

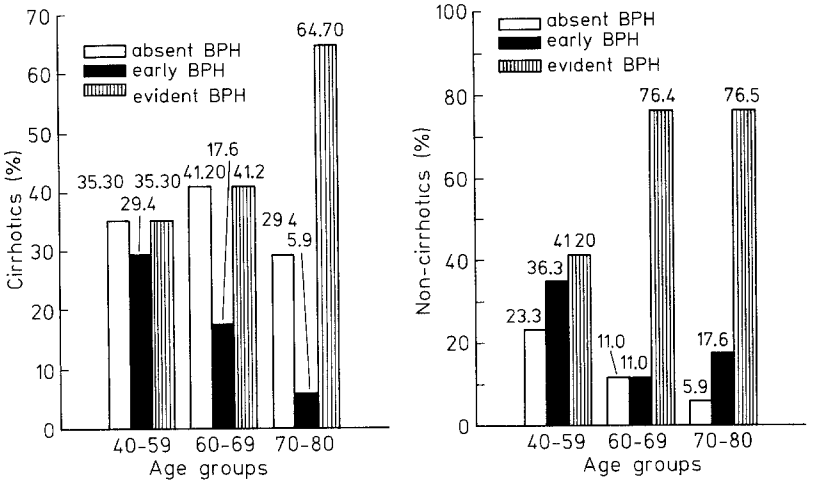

Fig. 2. Evident BPH incidence throughout the three ages in cirrhotics and in non-cirrhotics

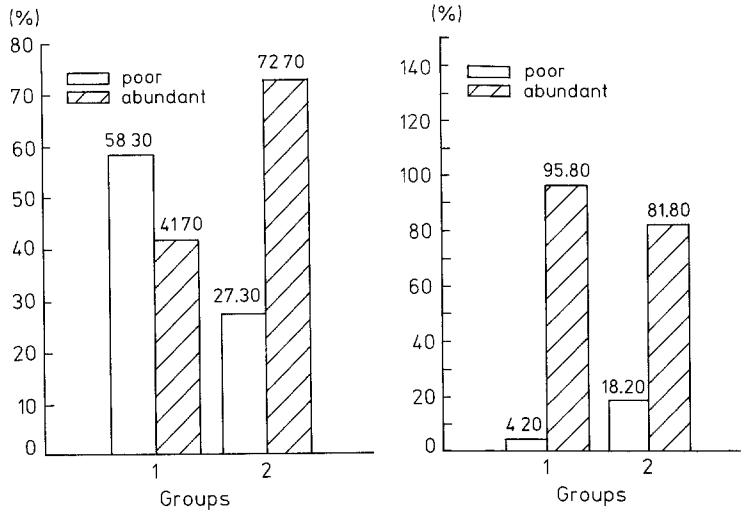

Fig. 3. Stromal versus epithelial hyperplasia incidence in evident BPH. (Group 1 = cirrhotics; Group 2 = non-cirrhotics)

development of BPH in patients with liver cirrhosis, according to Robson [6]. This statement could be strengthened by the finding that early nodular hyperplasia (an early stage of BPH) is slightly more common among cirrhotics.

Moreover epithelial hyperplasia (that seems to be dependent on androgenic stimulation) is quite abundant especially in the group of controls (72.7% compared to 41.7% in the group of cirrhotics), while stromal hyperplasia is present in the prostates of both groups. These results could be related to the hormonial imbalance (elevated estrogen' activity and reduced androgen activity) which occurs in people who suffer from liver cirrhosis.

We did not evaluate the degree of metabolic disorders due to liver cirrhosis damage [6] because we consider the clinical features unreliable, because they are not necessarily correlated with the degree of hepatic dysfunction. In the same way we reject the proposed criteria of evaluation of the presence of hyperestrogenism because they do not reflect its degree and duration.

Conclusions

From macroscopic and histological esamination of the prostates of cirrhotic and non cirrhotic subjects we found that:

- the incidence of BPH is less in cirrhotic population;
- its appearance is delayed in cirrhotic population;
- in cirrhotic males BPH shows poor epithelial proliferation (reduced androgenic stimulation);
- there are no reliable parameters for the post mortem evaluation of the metabolic and hormonal disorders of cirrhotic people so that it would be desirable to run a prospective clinical study, based upon hormonal samples, transrectal prostatic echotomography and prostatic biospy (when possible).

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