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HEPATOCELLULAR CARCINOMA IN BRAZIL: REPORT OF A NATIONAL SURVEY (FLORIANÓPOLIS, SC, 1995)

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SUMMARY

In order to investigate epidemiological aspects of hepatocellular carcinoma (HCC) in Brazil, basic informations about cases diagnosed from January 1992 to December 1994 were requested to several medical centers of different Brazilian States. A simple questionnaire included age, sex, alcohol abuse (over 80g/day), associated liver cirrhosis, persistent HBV infection (HBsAg), HCV infection (anti-HCV) and serum levels of alpha fetoprotein. 287 cases, over 16 years old, from 19 medical centers of 8 States (Pará, Bahia, Minas Gerais, Espirito Santo, Rio de Janeiro, São Paulo, Paraná and Rio Grande do Sul) were analysed. The results showed: (a) Mean age was 56.3 ± 14.4 for men and 54.7 ± 16.8 yr for women and the male/female ratio was 3.4:1. (b) 69.6% were caucasians, 21.8% mullatoes, 4.8% orientals and 3.7% blacks. (c) HBsAg (+) in 77/236 cases (41.6%) without differences between males and females. (d) Anti-HCV (+) in 52/193 cases (26.9%). (e) 7/180 cases were positive both for HBsAg and anti-HCV (3.8%). (f) There was chronic alcoholism in 88/235 cases (37%). (g) HCC was found in cirrhotic livers in 71.2% of 202 cases in which the presence or absence of cirrhosis was reported. (h) Alpha-fetoprotein above 20 ng/ml was found in 124/172 cases (72%) and above 500 ng/ml only in 40 cases (23.2%). These results showed that the HCC in Brazil has an intermediate epidemiological pattern as compared to those from areas of low and high incidence of the tumor. In spite of the high frequency of the association of HCC with the HBV and/or HCV infections, 42% of 180 cases were negative both for HBsAg and anti-HCV, indicating the possible role of other etiological factors. The comparison of data from different States showed some regional differences: higher frequency of associated HBsAg in Pará, Bahia, Minas Gerais and Espírito Santo, higher frequency of associated HCV infection in Rio de Janeiro, São Paulo and States of the Southern region and low frequency of associated liver cirrhosis in Salvador and Rio de Janeiro (55.5 and 50% respectively). Further investigation will be necessary to study the presence of other possible etiological factors as aflatoxins, suggested by the favourable climatic conditions for food contamination by fungi in the majority Brazilian regions.

KEYWORDS: Hepatocellular carcinoma; Liver Tumors; Liver.

INTRODUCTION

A discussion about hepatocellular carcinoma in Brazil, during the XIII Congress of the Brazilian Society of Hepatology (Florianópolis, SC, September, 1995) was based in, at least, two justifications: reports indicating regional differences in the epidemiology of the tumor and a great concern on the study of hepatocellular carcinoma in Brasil in recent years[7]. For these reasons and because there is little information about primary liver tumors in Brazil, we decided to collect data about hepatocellular carcinoma diagnosed in different States in order to compare epidemiological aspects.

METHODS

For collecting the data a simple questionnaire was prepared in which only basic informations about the tumor, available in most medical centers, were requested: identification, age, sex, ethnic group, methods used for diagnosis, serum markers for HBV and HCV infections (HBsAg for HBV and anti-HCV for

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HCV), presence or absence of chronic alcoholic ingestion (chronic alcoholism being considered the ingestion of more than 80g of ethanol daily), associated liver cirrhosis and serum levels of alpha-fetoprotein. Only cases diagnosed from January 1992 to December 1994 were included in order to facilitate data retrieval but also because only after 1991 the accurate serologic diagnosis of HCV infection was widely available in Brazil.

The only criterion for inclusion was age over 16, because of the peculiar characteristics of HCC in children.

An EPIINFO software (version 5.1) was utilized for statistical analysis. For comparison, non-parametric tests were used (Mann-Withney and Kruskal-Wallis) and the frequencies were compared in 2x2 tables using the CHI square test or the Fischer exact test.

RESULTS

Data of 291 cases were received from 19 medical centers of eight States (Table 1). The methods used for diagnosis in the 291 cases are in Table 2. Almost 90% had a histologic diagnosis. Four cases were excluded because the patients were less than 16 years old.

TABLE 1
HCC: Study of 291 cases. Geographical Origin

State	Number of medical centers	Number of cases
Pará	1	9
Bahia	1	24
Minas Gerais	3	40
Espírito Santo	1	25
Rio de Janeiro	2	49
São Paulo	8	125
Paraná	2	9
Rio Grande do Sul	1	10
TOTAL	19	291

TABLE 2
HCC: Methods of diagnosis in 291 cases

Methods	N (%)
Autopsy	7 (2.4)
Biopsy	261 (89.6)
Alfa-fetoprotein	7 (2.4)
Other	16 (5.5)

TABLE 3
HCC: Study of 287 cases. Sex and age

Sex	N	Age (mean ± SD and median)
Male	223	56.3 ± 14.4 (59)
Female	64	54.7 ± 16.8 (59)
TOTAL	287	55.9 ± 15.0 (59)

Male/female Ratio = 3.4:1

The data about age and sex are presented in Table 3.

The distribution by ethnic groups was as follows: 188 (69.6%) caucasians, 10 (3.7%), blacks, 59 (21.8%) mulattoes and 13 (4.8%) orientals. In 17 cases the ethnic group was not identified.

Persistent infection with the HBV determined by the detection of HBsAg in the serum in 236 cases. The results are in Table 4.

HCV infection was diagnosed by the detection of antibodies anti-HCV in 193 cases, without specification of the method used. The results are in Table 5.

In 180 cases HBV and HCV markers were tested (Table 7) and in seven both HBsAg and anti-HCV were positive (3.8%). The mean age in these cases was 66.1 ± 13.4 years. In 76 cases (42.2%) the two serologic markers were negative. The mean age in these patients was 54.9 ± 16 years. 59 cases (32.7%) were only positive for the HBsAg (49.1 ± 16 years) whereas 38 (21.1%) only anti-HCV positive (63.0 ± 9.4 years).

Chronic alcoholism (ingestion of more than 80g of ethanol daily), was investigated in 235 cases, without reference to the mean daily ingestion. The results are in Table 6.

In 102 cases there was an association of alcoholism with and HBV or HCV infection. The results are in Table 8. Although the mean age was lower when there was the association of alcoholism with HBV infection, the differences were not significant.

In 202 cases the presence or abscence of liver cirrhosis was reported. In 144 the tumor was superimposed in a cirrhotic liver (71.2%). The data about age and sex in these cases are displayed in table 9.

Among 132 cases in which there was investigation of alcoholism, HBV and HCV infection, in 70 only one of those factors was present. In these cases it was possible to verify the main etiology of liver cirrhosis in patients with HCC. Liver cirrhosis was present in 62.5% of alcoholics, 88.2% of HBsAg positive and in 83.3% of anti-HCV positive patients (Table 10).

Alpha-fetoprotein was tested in the serum of 172 cases and the results are in Table 11.

For comparison of the data from the different States, Table 12 summarizes the number of cases, sex, age, presence or abscence of alcoholism, HBsAg and anti-HCV, and the frequency of HCC in cirrhotic livers, for each State separately.

DISCUSSION

The 287 cases of hepatocellular carcinoma diagnosed in three years, in different Brazilian states, represented a good sample of HCC in Brazil, although there was not information

TABLE 4
HCC: 236 cases. Frequency of HBsAg. Age and sex distribution

Sex	HBsAg(+)		HBsAg(-)	
	N %	mean±SD (median)	N %	mean±SD (median)
Male	77 (41.6)	52.0±14.5 (53)	108 (58.4)	59.2±13.7 (63)
Female	16 (31.3)	49.1±19.9 (46)	35 (68.7)	56.3±16.0 (58)
TOTAL	93 (39.4)	51.5±15.5 (53)	143 (60.6)	58.0±14.3 (62)
M/F ratio	4.8:1		3.1:1	

for M/R, p = 0.185; for ages; M (+) x (-), p = 0.003; F (+) x (-), p = 0.002

TABLE 5
HCC: 193 cases. Frequency of anti-HCV in the serum and age.

Sex	anti-HCV(+)		anti-HCV(-)	
	N %	mean±SD (median)	N %	mean±SD (median)
Male	39 (24.8%)	61.5±9.8 (63.0)	118 (75.1%)	54.1±15.3 (56.0)
Female	13 (36.1%)	63.6±11.1 (66.0)	23 (63.8%)	46.6±17.3 (44.0)
TOTAL	52 (26.9%)	62.0±10.1 (63.5)	141 (73.1%)	52.9±15.8 (54)
M/F ratio	3.0:1		5.1:1	

M/F ratio, p = 0.170. Mean between (+) and (-), p = 0.0006

TABLE 6
HCC: 235 cases. Chronic alcoholism, sex and age distribution

Sex	Alcoholic		Non-alcoholic	
	N %	mean±SD (median)	N %	mean±SD (median)
Male	81(44.0)	57.1±13.1 (59.0)	103 (56.0)	57.7±14.6 (60.0)
Female	7(13.8)	46.5±14.1 (44.0)	44 (86.2)	56.7±17.3 (60.0)
TOTAL	88(37.4)	56.3±13.4 (44.0)	147 (62.6)	57.3±15.4 (60.0)
M/F ratio	11.5:1		2.3:1	

M/F ratio, p = 0.0001. Ages: alcoholic x non-alcoholic, p = 0.08; alcoholic M x alcoholic F, p = 0.048.

about the tumor from Amazonas and Central states as Mato Grosso and Goiás; in Amazon region there is strong evidence of a significant prevalence of the neoplasm. This sample, including cases from the Southern, Southeastern, Northeastern regions and from one state of the Northern region, may indicate some characteristics of HCC in our country.

The male/female ratio, althought with some variations, is similar to that observed in areas of low or intermediate incidence of HCC[8], and are inkeeping with previous data from 135 cases of HCC diagnosed in different Brazilian states presented in the VII Congress of the Brazilian Society of Hepatology (Porto Alegre, 1981)[5], and isolated reports from São Paulo and Espirito Santo[6]. However these data do not confirm some low male/female ratios (less than 2:1) reported in Minas Gerais and Bahia[2,3,4].

The mean ages were similar in different States and there were no significative differences between the age of males and females, as observed in the state of Espirito Santo [6].

The investigation of possible etiologic factors confirmed what had been reported by isolated observations: a great participation of HBV and HCV infections, with regional differences[7]. The association with HCV infection was more frequent in Southern states and in great urban concentrations as the cities of Rio de Janeiro and São Paulo. Associated persistent HBV infection was more frequent in Minas Gerais and Espirito

TABLE 7
HCC: 180 cases. Association of HBsAg and anti-HCV. Age distribution

Markers	N (%)	mean±SD
HBsAg(+) anti-HCV (+)	7 (3.8)	56.1 ± 13.4
HBsAg(-) anti-HCV (-)	76 (42.2)	54.9 ± 16.0
HBsAg(+) anti-HCV (-)	59 (32.7)	49.1 ± 16.0
HBsAg(-) anti-HCV (+)	38 (21.1)	63.0 ± 9.4

C (+) B (-) x other groups, p = 0.027; B (+) C (-) x B (-) C (-), p = 0.089; B (+) C (-) x B (+) C (+) p = 0.370

TABLE 8

HCC: 132 cases. Association of chronic alcoholism, HBsAg and anti-HCV: sex and age distribution

Associated Factor	Sex	N	mean±SD	M/F ratio
Alcohol	M	28	56.8 ± 14.7	28:1
	F	1	37.0	
HBsAg (+)	M	35	51.9 ± 15.6	5.8:1
	F	6	37.1 ± 15.5	
Anti-HCV (+)	M	11	63.9 ± 9.8	1.5:1
	F	7	65.2 ± 7.4	
Alcohol + HBsAg (+)	M	11	51.4 ± 13.8	-
	F	0	——	
Alcohol +. anti-HCV(+)	M	14	62.6 ± 8.1	7:1
	F	2	54.5 ± 27.5	
AgHBs (+). + Anti-HCV (+)	M	3	60.6 ± 14.3	-
	F	0	——	
Alcohol. + AgHBs (+). + Anti-HCV (+).	M	4	52.5 ± 13.5	-
	F	0	——	
Negative for the three factors	M	31	57.9 ± 15.0	2.3:1
	F	13	52.1 ± 16.9	

B(+) M x B (+) F p = 0.042; B (+) x C (+), p = 0.003

Santo and in the states of Northeastern and Northern regions.

Chronic alcoholism, although in different proportions, was a frequent associated factor, confirming previous observations and showing that this condition is an important factor for chronic liver disease in our country.

One important observation was the fact that among the 180 cases in which there was the investigation both of HBV and HCV, 47% had neither HBsAg nor anti-HCV. Although we can not completely discard viral infection in these cases, they may suggest the existence of other etiological factors for HCC in our country. The high frequency of cases not associated with persistent HBV or HCV infection suggests the participation of other etiologic factors possibly aflatoxins, because the tropical climate all over the Southeastern and the Northern regions favours the contamination of food with *Aspergillus flavus*. In fact studies of cases of hepatocellular carcinoma diagnosed in Recife (Pernambuco) and São Paulo showed 61.5% and 33.3% with p53 mutation[1,9], respectively, indicating possible participation of aflatoxin in the pathogenesis of these tumors.

TABLE 9

HCC: 202 cases. Association with cirrhosis. Sex and age distribution

Liver cirrhosis	N	mean±SD	(median)	M/F ratio
Present Male	119	57.2 ± 13.4	(60.0)	
Present Female	25	59.2 ± 17.6	(65.0)	
TOTAL	144	57.8 ± 14.2	(61.0)	4.7:1
Absent Male	41	57.0 ± 15.3	(59.0)	
Absent Female	17	51.4 ± 15.5	(55.0)	
TOTAL	58	55.3 ± 15.5	(57.5)	2.4:1

M/F cirrhosis present x M/F cirrhosis absent, p = 0.058

TABLE 10

HCC: 70 cases. Cirrhosis and etiologic factors (chronic alcoholism, HBsAg and anti-HCV). Sex distribution

	Sex	Liver cirrhosis	
		Present	Absent
Alcohol	M	15	8
	F	0	1
TOTAL		15	9
HBsAg(+)	M	26	3
	F	4	1
TOTAL		30	4
Anti-HCV(+)	M	5	2
	F	5	0
TOTAL		10	2

Frequency of liver cirrhosis and M/F: Alcohol x HBsAg(+), p = 0.041 and 0.284; Alcohol x anti-HCV (+), p = 0.271 and 0.001; HBsAg (+) x anti-HCV (+), p = 0.491 and 0.028.

TABLE 11

HCC: 172 cases. Serum levels of alpha-fetoprotein

AFP (ng/ml)	N	%
0 to 20	48	27.9
21 to 100	22	12.7
101 to 500	62	36.0
500 or more	40	23.2

The frequency of the association of HCC with cirrhosis was high in all the States, except for the cases reported in Salvador (Bahia) and Rio de Janeiro, where the frequencies of HCC in cirrhotic livers were respectively 55.5% and 50%. More observations are necessary to confirm these data. It is always

TABLE 12

HCC: 287 cases of hepatocellular carcinoma diagnosed in different Brazilian states. Number of cases, M/F ratio, liver cirrhosis, chronic alcoholism, HBsAg and anti-HCV

State	N	M/F	Age (mean±SD)	Cirrhosis %	Alcohol %	HBsAg %	Anti-HCV %
PA	8	7:1	54.4 ± 18.7	NI	25.0 (2/8)	71.4 (5/7)	12.5 (1/8)
BA	23	3.6:1	53.6 ± 16.8	55.5 (5/9)	42.1 (8/19)	45.0 (9/20)	15.3 (2/13)
MG	40	3.4:1	61.2 ± 14.1	73.5 (25/34)	28.2 (11/39)	37.8 (14/37)	8.0 (2/25)
ES	25	7.3:1	55.2 ± 16.2	85.7 (18/21)	4.0 (1/25)	41.6 (10/24)	8.7 (2/23)
RJ	49	2.2:1	56.5 ± 16.0	50 (16/32)	48.4 (16/33)	25.0 (9/36)	34.4 (10/29)
SP	124	3.2:1	53.4 ± 14.9	76.1 (77/88)	52.3 (44/84)	42.2 (41/97)	33.7 (27/80)
PR	9	3.5:1	57.4 ± 13.8	77.7 (7/9)	0.0 (0/9)	44.4 (4/9)	50 (4/8)
RS	9	9:0	62.7 ± 8.6	66.6 (6/9)	66.6 (6/9)	12.5 (1/8)	62.5 (5/8)

possible that some diagnoses of HCC in presumably non cirrhotic liver can be due to sampling errors.

The behaviour of alpha-fetoprotein in cases of hepatocellular carcinoma was similar to that observed in other regions: 28% of the cases had levels less than 20 ng/ml and only in 23% of the cases the levels were above 500 ng/ml.

CONCLUSIONS

The observations about the main epidemiological characteristics of 287 cases of HCC diagnosed in different States of Brazil showed that this tumor has an intermediate epidemiological pattern as compared to other areas of high and low incidence of the tumor.

There are regional differences related to some aspects of the tumor: (a) association with persistent HBV infection was more frequent in Southeastern, Northeastern and Northern regions and association with HCV virus infection more frequent in the South and in large cities of the Southeastern region and (b) low association with cirrhosis in Salvador and Rio de Janeiro.

The high frequency of cases of hepatocellular carcinoma negative for HBsAg and anti-HCV suggests the participation of other etiological factors, possibly mycotoxins. More studies about food contamination by aflatoxin and the presence of aflatoxins - DNA adducts in hepatocytes of people with or without chronic liver disease, living in areas at high risk for aflatoxin ingestion, are necessary to know about the possible role of this carcinogen in the etiology of HCC in Brazil.

RESUMO

Carcinoma hepatocelular no Brasil: relato de um inquérito nacional (Florianópolis, SC, 1995)

Para conhecer as principais características epidemiológicas do carcinoma hepatocelular no Brasil foi feito um levantamento de casos diagnosticados no período compreendido entre Janeiro de 1992 e Dezembro de 1994, em diferentes centros médicos de diferentes Estados. Foi solicitado o preenchimento de um questionário simples que perguntava sobre: idade, sexo, método de diagnóstico, alcoolismo crônico, infecção com vírus B (HBsAg) e vírus C (anti-VHC), cirrose hepática associada e níveis séricos de alfa-fetoproteína. Foram analisados 287 casos, com idade acima de 16 anos, provenientes de 19 serviços médicos dos estados do Pará, Bahia, Espírito Santo, Minas Gerais, Rio de Janeiro, São Paulo, Paraná, e Rio Grande do Sul. Os resultados mostraram: (a) média de idade de 56,3 ± 14,4 e 54,7 ± 16,8 para homens e mulheres respectivamente, com relação masculino feminino de 3,4:1. (b) 69,6% eram caucasianos, 21,8% mulatos, 4,8% orientais e 3,7% negros. (c) HBsAg(+) em 77/236 casos (41,6%). (d) Anti-VHC(+) em 52/193 casos (26,9%), sem diferença significante entre homens e mulheres. (e) 7/180 (3,8%) casos eram HBsAg(+) e anti-VHC(+). (f) Alcoolismo crônico presente em 88/235 casos (37%). (g) Cirrose hepática associada em 71,2% de 202 casos nos quais a presença ou ausência de cirrose foi confirmada. (g) Alfa-fetoproteína acima de 20 ng/ml em 124/172 casos (72%) e acima de 500 ng/ml em 40 casos (23,2%). Estes resultados mostram que o CHC no Brasil tem características epidemiológicas intermediárias entre as observadas nas áreas de baixa e de alta incidência do tumor. Apesar de ser grande a freqüência de infecção associada com os vírus B e C da hepatite, 42% de 180 casos eram negativos para o HBsAg e anti-VHC, indicando a possibilidade da participação de outros fatores na etiologia do tumor. A comparação dos dados dos diferentes estados mostra algumas diferenças regionais: maior freqüência de casos HBsAg(+) no Pará, Bahia, Minas Gerais e E. Santo, maior freqüência de casos anti-VHC(+) no Rio de Janeiro, São Paulo e estados do Sul e menor freqüência de cirrose associada na Bahia e Rio de Janeiro (55,5 e 50% respectivamente). Investigações futuras serão necessárias para se estudar a presença de outros possíveis fatores etiológicos, como as aflatoxinas, tendo em vista as condições climáticas favoráveis à contaminação alimentar com fungos na maioria das regiões do Brasil.

REFERENCES

1. ALVES, V.A.F.; CARRILHO, F.J.; WAKAMATSU, A. et al. - Detecção imunohistoquímica de p53 em carcinoma hepatocelular. In: **CONGRESSO BRASILEIRO DE HEPATOLOGIA**, 12., Salvador, 1993. **Resumos**. p.27.

2. COTRIM, H.P. - Estudo controlado sobre a importância da associação carcinoma hepatocelular e vírus B em Salvador, Bahia. Salvador, 1988. (Tese de Doutoramento - Faculdade de Medicina da Universidade Federal da Bahia).

3. DANI, R. & NUNES, A. - Tumores primitivos do fígado: experiência em 300 laparoscopias. In: **CONGRESSO BRASILEIRO DE HEPATOLOGIA**, 7, Porto Alegre, 1981. **Anais**. p. 71-72.

4. GALLIZI-FILHO, J. - Carcinoma hepatocelular. **Mod. Hepat.**, **9**:9 - 15, 1984.

5. GAYOTTO, L.C.C.; MORAES, C.F.; SILVA, E.F. et al. - Inquérito nacional sobre hepatocarcinoma. In: **CONGRESSO BRASILEIRO DE HEPATOLOGIA**, 7, Porto Alegre, 1991. **Resumos**. p. 75.

6. GONÇALVES, C.S. & PEREIRA, F.E.L. - Carcinoma hepatocelular. **Mod. Hepat.**, **16**: 4-17, 1991.

7. GONÇALVES, C.S. & PEREIRA, F.E.L. - Carcinoma hepatocelular no Brasil: mito ou realidade? (Editorial). **Mod. Hepat., 24**: 3-4, 1996.

8. OKUDA, K. & KONDO, Y. - Primary carcinoma of the liver. In: HAUBRICH, W.S.; SCHAFFNER, F. & BERK, J.E. **Bockus gastroenterology**, 5ª ed. Philadelphia, WB Saunders, 1995. p 2444-2487.

9. PEREIRA, L.M.M., ;MIES, S.; RIDE, S.D. et al. - Mutações do p53 no carcinoma hepatocelular. In: **CONGRESSO BRASILEIRO DE HEPATOLOGIA**, 12., Salvador, 1993. **Resumos**. p 43.

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