Hepatocellular Carcinoma
A REAL PROBLEM IN LATIN AMERICA

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INCIDENCE OF HCC

HIGH
(> 30/100,000/year)
Asia southeast, Africa subsaharian

INTERMEDIATE
(5-20/100,000/year)
South Europe (Italy, Greece, Spain)

LOW
(< 5/100,000/year)
North Europe, Oceania, Americas
# HCC: FEW STUDIES IN LA

## Incidence of HCC Gender, Age / 100,000

<table>
<thead>
<tr>
<th>Geographic Area</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Continents</td>
<td>14.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Eastern Africa</td>
<td>14.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Central Africa</td>
<td>24.2</td>
<td>12.2</td>
</tr>
<tr>
<td>Western Africa</td>
<td>13.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>35.4</td>
<td>12.6</td>
</tr>
<tr>
<td>Western Asia</td>
<td>5.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>5.8</td>
<td>2.5</td>
</tr>
<tr>
<td>North Europe</td>
<td>2.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Western Europe</td>
<td>5.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Caribbean</td>
<td>7.5</td>
<td>4.1</td>
</tr>
<tr>
<td>South America</td>
<td>4.8</td>
<td>3.6</td>
</tr>
<tr>
<td>USA/Canada</td>
<td>4.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Oceania</td>
<td>3.6</td>
<td>1.1</td>
</tr>
</tbody>
</table>
HCC INCIDENCE IN LA, GLOBOCAN 2008, OMS

Estimated age-standardised incidence rate per 100,000
Liver: both genders, all ages

4.9/100,000
ETIOLOGIES OF HCC

- Hemochromatosis
- NASH / ALD
- HBV / HCV
- All CHL

CIRRHOSIS
HCC: HBV AND HCV CONTRIBUTION

Basado en 11 regiones, OMS

Perz et al, J Hepatol 2006
PREVALENCE OF VHB AND INCIDENCE OF CHC

VHB Carriers

HBsAg +
- <2%
- 2–7%
- >8%
- few data

Annual Incidence of CHC

cases/100,000 people
- 1–3
- 3–10
- 10–150
- few data
HBsAg 2-20%

- México: HBsAg = 1.6, Anti-HBs = 11.6
- Costa Rica: HBsAg = 0.6, Anti-HBs = 17.3
- Colômbia: HBsAg = 1.0, Anti-HBs = 25.1
- Equador: HBsAg = 2.0, Anti-HBs = 29.4
- Peru: HBsAg = 2.2, Anti-HBs = 20.2
- Chile: HBsAg = 0.4, Anti-HBs = 3.8
- Argentina/South Brazil: HBsAg = 0.8, Anti-HBs = 14.7
- Brasil: HBsAg = 2.1, Anti-HBs = 26.7
- Suriname: HBsAg = 2.3, Anti-HBs = 28.1
- República Dominicana: HBsAg = 4.1, Anti-HBs = 55.3
- Puerto Rico: HBsAg = 0.2, Anti-HBs = 9.2
- Barbados: HBsAg = 1.4, Anti-HBs = 9.0
- Venezuela: HBsAg = 2.8, Anti-HBs = 11.6

However, in many countries HDV infections are probably underdiagnosed or not diagnosed unless a severe outbreak occurs.

AREAS OF HIGH ENDEMICITY:
- Amazonia
- Central Africa
- Isolated Pacific Islands
PREVALENCE OF HBV AND HDV INFECTION AMONG AUTOCHTHONOUS POPULATIONS IN THE AMAZON AND NEIGHBORING ECOSYSTEMS

<table>
<thead>
<tr>
<th>Country</th>
<th>Area</th>
<th>Anti-HBc</th>
<th>HBsAg</th>
<th>HDV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolivia</td>
<td>Chapare, Santisima Trinidad</td>
<td>34-84</td>
<td>0-4.8</td>
<td>0-2.2</td>
</tr>
<tr>
<td>Brazil</td>
<td>Acre, Amazonas</td>
<td>66.1</td>
<td>0 - 66.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pará</td>
<td>18-85</td>
<td>0-14.4</td>
<td>0</td>
</tr>
<tr>
<td>Colombia</td>
<td>Sierra de Santa Marta</td>
<td>35-93</td>
<td>1.8-23.0</td>
<td>Up to 60</td>
</tr>
<tr>
<td>Peru</td>
<td>Marañón, Madre de Dios</td>
<td>69-74</td>
<td>3.9-12.1</td>
<td>2.5-9.0</td>
</tr>
<tr>
<td>Venezuela</td>
<td>Sierra de Perijá</td>
<td>62-71</td>
<td>5.6-11.1</td>
<td>14.2-42.8</td>
</tr>
</tbody>
</table>

*Among HBsAg carriers

Gaspar et al, 2000
Labrea - Small village

Manaus - big city

Javari Valley - jungle

Different Ethnicities
HBV GENOTYPES/SUBTYPES IN LATIN AMERICA

- Genotype H in Central America
- Genotype F in Amazonian countries
- Genotype F less predominant in Brazil: smaller proportion of Amerindians in total population
HBV IN Amazonia

Genotype F prevails in Amazonia and North of Argentina in isolated populations and Amerindians

- Is Genotype F more carcinogenic?

Around 20% of HBV carriers are infected with HDV Gen III

- Is Genotype III more pathogenic?

Could this combination (HBV Gen F/HDV Gen II) explain the cases of cirrhosis and HCC observed in young people in Amazonia?
PHYLOGENY OF HBV GENOTYPES/SUBTYPES

Phylogenetic tree of orthohednaviruses infecting higher primates

WMHBV, the only hepadnavirus known to infect a New World monkey, is the most divergent. Woolly monkey habitat is the Amazon Basin.

Genotypes F and H are the most divergent of human HBV genotypes. Found mainly in the Amazon Basin and Central America respectively.

All 3 are on the same branch of the phylogenetic tree – zoonotic infection? Possibly, but in which direction?

Amazon River near Manaus
16 November 2007

Genotype III (3) is the most divergent
~ 123 million chronic carriers in the world (WHO, 2004)

It is expected more than 10 million HCV carriers in Latin America

Large majority without diagnosis

70% of Genotype 1 in Latin America
The incidence of new Hep C cases has dramatically decreased. On the other hand, the diagnosis of Cirrhosis due to Hep C is increasing as a consequence of HCV infections acquired during the ’60-’80.
South America is becoming an obese continent. Obesity prevalence from 20 to 40% of adult population.

NASH and NFALD

17 – 33% (USA)

All Continents

Most common liver disease among teenagers (Schweiz Rundsch Med Prax. 2006 Aug 23;95(34):1267-9)

12 -25% Mortality (7 -10 years)

NASH = Main cause of Cryptogenic Cirrhosis
RR OF HCC IS 4.5 IN OBESITY AND OVERWEIGHT

Calle, NEJM, 2003
Higher Risk of HCC in Diabetic patients

173,643 with diabetes and 650,620 without diabetes.
HCC in LA

Descriptive study, multicentric, internacional, supported by ALEH
Online Data Bank with repoted cases from LA countries
n 240 patients
174 males (72.5%) 66 femeles (27.5%)
Male/Female rate 2.6
Median Age 64 yo
Interquartil variation 57-72 YO

Fassio et al, Ann Hepatol 2010
ETIOLOGY OF HCC IN LA
PROSPECTIVE STUDY 18 MONTHS

27 centers of 9 L. A. countries

Fassio et al, Ann Hepatol 2010
### HCC IN LA

#### AGE OF DIAGNOSIS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Median Age ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>64.1 ± 9.9</td>
</tr>
<tr>
<td>Alcohol</td>
<td>64.4 ± 8.8</td>
</tr>
<tr>
<td>Criptogenic</td>
<td>62.2 ± 16.9</td>
</tr>
<tr>
<td>HBV</td>
<td>62.0 ± 11.8</td>
</tr>
<tr>
<td>HCV + alcohol</td>
<td>60.1 ± 11.5</td>
</tr>
</tbody>
</table>

HCC in younger pts in Amazonia

Fassio et al, Ann Hepatol 2010
HCC ETIOLOGY IN ARGENTINA
(N 541, 72% MALE, MEDIAN AGE 62, 93% WITH CIRROSIS)

- Alcohol: 170
- HCV: 157
- HBV: 51
- Criptogenic (NASH ?): 48
- HCV + OH: 35
- HH: 14
- HBV + OH: 12
- PBC: 11
- HCV + HBV: 7

HCV in 39%
Alcohol in 43%

Fassio et al, Acta Gastroenterol Latinoamer 2009
HCC ETIOLOGY IN ARGENTINA
LIVER TRANSPLANTATION CENTER (N 145) VERSUS NO LIVER TRANSPLANTATION CENTER (N 404)

Fassio et al, Acta Gastroenterol Latinoamer 2009
HCC IN MEXICO

Mondragon Sanchez et al, Hepatogastroenterology 2005

- HCV: 50%
- HCV + OH: 17%
- HCV + HBV: 15%
- HBV: 9%
- OH: 9%

n 71 pts
anti-HCV > 70%
HCC IN PERU AND CHILE

Peru
n 136

37%
HBV
63%

Chile
n 50

52%
HCV
48%

Ruiz et al, Rev Gastroenterol Peru 1998
Muñoz et al, Rev Med Chil 1998
BRAZIL AS EXAMPLE

- Continental country
- Many ethnicities
- Many HBV genotypes
- Heterogeneity of HBV Distribution
- Intermediate prevalence for HCV
- Socio-Economic and educational disparities
- Relatively well organized public health system
- High prevalence areas for HDV
- Relatively well organized public health system
RISK FACTORS OF HCC ACCORDING TO BRAZILIAN REGIONS

Carrilho J et al. Clinics 2010;65:1285-1290
HCC STAGE AT DIAGNOSIS ACCORDING TO THE BRAZILIAN REGIONS

Carrilho J et al. Clinics 2010;65:1285-1290
ACCESS TO HCC TREATMENT ACCORDING TO BRAZILIAN REGIONS

CARRILHO J ET AL. CLINICS 2010;65:1285-1290
National Survey on HCC

BRAZILIAN SOCIETY OF HEPATOLOGY

RESULTS

• 29 centers were involved
• PTS ANALYSED: 1405
• Age: median 59 yo
• Variation: 1-92 yo

• Gender
  - Male: 1089 – 78%
  - Female: 314 – 22%
ETIOLOGY OF CLD RELATED WITH HCC IN BRAZIL

- HCV: 39%
- HCV + OH: 15%
- Alcohol: 14%
- HBV: 12%
- HBV + OH: 4%
- 2 virus: 12%
- Criptog: 14%
- EHNA: 15%
- No cirrosis: 4%
- HH: 15%

N = 1308

Carrilho FC & SBH Members, Clinics 2010
HOW ABOUT AFLATOXINA B1 IN LA?
FEW PAPERS

Mutation Ser-249 in TP53 in Brazilian HCC cases

Mutation Ser-249 in gen TP53: is associated to AFB1 exposition studies from China and Senegal observed ~50% in HCCs

Mutation of TP53 is associated to more aggressive HCC

Nogueira et al, BMC Cancer 2009
n 1405 pts

• Cirrhosis in 98% of cases
• Aflatoxina B1 does not seem to be a major problem
• Few Referral centers on Liver diseases
• Most Liver Centers are concentrated in the bigger cities
• Few Hepatologists mainly in remote areas
• (most gastroenterologists are not motivated to face Chronic liver diseases)
• The Cost of HCC management is extremely high for most LA centers
Patients in waiting list for Liver Transplantation get more MELD score and reach priority

- Minimal 20 points
- Within 3 months: 24
- Within 6 months: 29

So, HCC screening is stimulated

The issue is HOW!!!!!!

US recommended every 6 months
Alphafetoprotein not recommended but is still used due to lack of options in many areas
CONCLUSIONS

- The HCC incidence in Brazil is around ~ 5/100,000, but there is no reliable data from Latin America.
- The HCC is surely underestimated in Latin America.
- HCC is clearly related to cirrhosis in Latin America.
- HCV is the major cause, but HBV/HDV may be the most important etiology in highly endemic areas.

The aflatoxina B1 does not seem to play a major role.
To Face HCC in LA we need:

- Cost-Effective diagnostic tools
- Easier access to Image exams
- More Hepatologists and more liver referral centers
- *Capilarization* of liver transplantation center
- Solid policies regarding obesity and HBV vaccination
- Availability of diagnosis and therapy
IMMEDIATE ACTIONS TO PREVENT HCC IN LA

**HCV**
- Easier access to treatment

**HBV**
- Universal vaccination program and easier access to antiviral treatment

**NAFLD**
- Educational activities
- Political actions on industrialized foods
Thank you

Salvador, Northeastern Brazil

Rio Branco –Acre, Amazonia

Thank you