The Immune Response of Prolactin and the Induction of Tumor Necrosis Factor (TNF) in Iraqi Patients Infected with Hepatitis C Virus.

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• Viral Hepatitis Type C is a serious public health challenge throughout the world and remain to be the major causes of chronic hepatitis.

• During the 80s, Iraq had low endemicity among blood donors.

• However its prevalence is now increased with high rate of mortality.
Hepatitis C is a contagious viral disease caused by hepatitis C virus.
Hepatitis C virus (HCV) lipoviral particles (LVPs) attach to the cell surface by interacting with:
- heparan sulphate proteoglycans (HSPGs),
- low-density-lipoprotein receptor (LDLR) and
- scavenger receptor class B member 1 (SRB1).

SRB1 might delipidate HCV-associated lipoproteins and induces conformational changes in the E2 glycoprotein, exposing the CD81-binding site.
(step 2)

- Interaction of E2 with CD81 then activates signal transduction through epidermal growth factor receptor (EGFR) and HRAS, as well as through RHO GTPases.

(step 3)

- These signaling events promote lateral movement of HCV–CD81 complexes to sites of cell–cell contact.
(step 4)

- Interaction of CD81 with claudin 1 (CLDN1), and HCV internalization via clathrin-mediated endocytosis.

(step 5)

- The low pH of the endosomal compartment induces HCV fusion.
• Many cases (two –third) could go through undiagnosed because they might be asymptomatic.

• However the rest one-third of people initially infected with hepatitis C develop symptoms and are more likely to be treatment efficiently with antiviral drugs.
Acute HCV Infection with Recovery

Source: Adapted from MMWR 1998; 47(No. RR19)
Those infected but asymptomatic will develop to chronic HCV and will initiate a broad-based immune response. (adaptive and innate immune response).

**Acute HCV Infection Evolving to Chronic Infection**

- Symptoms +/-
- HCV RNA
- anti-HCV
- ALT

Time after Exposure

: Adapted from MMWR 1998; 47(No. RR19)
Risk Factors Associated with Faster Fibrosis Progression in Chronic HCV

- Disease State Factors
  - Fibrosis stage
  - HCV onset after 40 years of age
  - Persistently elevated ALT

- Host Factors
  - Male gender
  - Age
  - Obesity
  - Diabetes
  - HIV, HBV coinfection
  - Immune system compromise
  - Steatosis
  - Iron overload

- Lifestyle Factors
  - Heavy alcohol consumption
  - Cannabis use
  - Tobacco use

• It is clinically important
  1. to differentiate:
     ▫ incident HCV infections from
     ▫ chronic infections
  2. and to identify
     ▫ primary infections that are asymptomatic.
• Occasional occurrences of acute exacerbation in chronic infection, will complicate decisions regarding whom to treat with the suitable treatment.(1)
Hepatitis C virus-related chronic hepatitis is associated with various immunological disorders example:

- Immuno-endocrine
- Cytokines
- Anti-tissue antibodies
• Interaction of these molecules might trigger a cascade of reaction that will be involved in the progression of the disease.

• And/or might influence the effect of drug of choice that is used for the management of the disease.
Aim of the study:

To evaluate the role of the immunoendocrine system in the pathogenesis of chronic hepatitis C, by measuring serum prolactin and tumor necrosis factor-alpha.
• Subjects involved in the study were selected from Gastrointestinal Hospital in Baghdad, Iraq.
• During the period from July 2014 to September 2014.
• A written consent was taken from each.
Subjects
n = 81

Patients:
n = 61
Median Age = 34.8 yrs.

- Male
  n = 29
- Female
  n = 32

Control:
n = 20
Median Age = 34.6 yrs.

- Male
  n = 10
- Female
  n = 10
• All patients had chronic hepatitis C virus and were on interferon alpha therapy.
• All of them were positive for HCV RNA by means of polymerase chain reaction.
Diagnostic algorithm for hepatitis C

Anti HCV ELISA

Reactive
- Elevated transaminases
- Immuno compromised
  - HCV RNA
    - +ve
    - -ve
    - Consider retesting in six months
  - Non reactive
    - No further investigation
Blood samples were collected between (9.00 a.m - 12.00 p.m).

The blood was allowed to clot in plain tube for 30-45 minutes at room temperature.

Sera were obtained by centrifugation of the collected blood and then stored in plain tubes at -20 c.

ELISA technique was used to measure (TNF and Prolactin)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serum prolactin (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Groups</strong></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>12.54 ± 2.9</td>
</tr>
<tr>
<td>Control</td>
<td>11.50 ± 2.7</td>
</tr>
</tbody>
</table>

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The role of PRL in the immune reactions is stimulating; its presence significantly increases the ability of the immune cells to proliferate and produce cytokines such as TNF-alpha(2)
Recent studies suggest that prolactin is important both for normal liver growth and for regenerating the liver after part of it is removed, with extra prolactin providing a boost for repair mechanisms. Consequently, enhancing prolactin levels could provide a way to improve regeneration when the liver becomes damaged or diseased with viruses, or after surgery.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serum TNF-alpha (ng/ml)</th>
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<tbody>
<tr>
<td>Groups</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>Mean ± SEM</td>
</tr>
<tr>
<td></td>
<td>65.57 x 10^{-3}</td>
</tr>
<tr>
<td>Controls</td>
<td>Mean ± SEM</td>
</tr>
<tr>
<td></td>
<td>7.03 x 10^{-3}</td>
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<tr>
<td></td>
<td>41.52 x 10^{-3}</td>
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<td>1.86 x 10^{-3}</td>
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• HCV infection enhances TNF-α-induced cell death by suppressing nuclear factor NF-κB activation through the action of core, (non structural HCV) NS4B, and NS5B. This mechanism may contribute to immune-mediated liver injury in HCV infection. (4)
Control

- Prolactin ng/ml: 11.5
- ng/ml10-3 TNF x: 41.5

Patients

- Prolactin ng/ml: 12.54
- ng/ml10-3 TNF x: 65.57
Correlation between serum prolactin and TNF in patients group

\[ 41.57x + 1.912y = 0.317 \]

\[ R^2 \]
Parameter: Serum ASMA

Groups:

- Patients: 65.57% +ve, 34.43% -ve
- Controls: 100% -ve
• The result agrees with Clifford et al in their study they reviewed the presence of autoimmune markers in sera of chronic hepatitis C patients.

• Their study showed that treatment with interferon alfa (IFN-alpha) will exacerbate autoimmune hepatitis. (5)

• The pathogenesis of autoimmune hepatitis due to medications is not clear.
Recommendations from an expert panel

• Aiming for treatment optimization by filling some of the gaps of the current guidelines, a group of Italian experts, experienced on treatment of HCV infection, met in Stresa in February 2016.

• The summary of all the considerations arising from this two-day meeting and the final statements are reported in *Digestive and Liver Disease Journal June 2016* [Epub ahead of print]
• “Treatment of chronic HCV (CHC) has been revolutionized in the last few years by the introduction of highly effective and well tolerated direct acting antiviral agents (DAAs) able to achieve >90% rates of sustained virological response (SVR) in many groups of patients, including those previously excluded from interferon-based regimens.

• For such reason interferon-free regimens are now the treatments of choice for all patients.

• Successful anti-HCV treatment can stop liver disease progression and can solve the HCV-related extra hepatic manifestations, eventually reducing both liver-related and overall mortality.”
Conclusions:

• Chronic hepatitis C is associated with an immunological abnormality mainly represented by tumor necrosis factor-alpha and prolactine.

• This might shed a light of the type of therapy and drug of choice when managing the disease.
References:


Any questions?

Thank You