CHRONIC HCV DIAGNOSTIC METHODS IN HUNGARY (1992-2019)

Judit Gervain MD PHD

1st Department of Gastroenterology/Hepato-Pancreateology and Molecular Diagnostic Laboratory, Székesfehérvár, Hungary

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email: jgervain@mail.fmkorhaz.hu

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Chronic HCV diagnosis in Hungary: ORGANISATION

Symptomatic patient → Biochemical and serological examinations → Referral to an accredited Hepatitis Centre (34 centres) → Entry in HCV Register

Blood donor → Biochemical and serological examinations

Other screening programme → Biochemical and serological examinations

Molecular biological tests (3 labs)

Morphological methods

Prognostic score (Child-Pugh (CP) score)

Differential diagnosis (HIV, HAV, HBV/HDV, autoimmune diseases, steatosis, diabetes mellitus, cryoglobulinaemia, etc.)

HCV Therapy & Follow-up

Molecular biological tests (3 labs)

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Chronic HCV diagnosis in Hungary: DETERMINANTS

• The screening of blood donors for HCV infection and further investigation and treatment of infected patients started in 1992 in Hungary

• It is organised jointly by the national hepatologists and infectologists

• Determinants:
  • International guidelines: American Association for the Study of Liver Diseases, European Association for the Study of the Liver
  • National financing landscape: pre-defined diagnostic and therapeutic budget
  • Technological and methodological developments: most specific and sensitive tests are used
  • Annually reviewed Hungarian diagnostic and therapeutic protocol
SCREENING

• **Biochemical tests** *(alanine and aspartate aminotransferase (ALT/AST), alkaline phosphatase (ALP), gamma glutamate dehydrogenase (GGT), lactate dehydrogenase (LDH), creatinine, albumin, total bilirubin, international normalized ratio, haemoglobin, platelet count, glomerular filtration rate)*
  
  • *alanine aminotransferase (ALT) test:*
    – non-specific,
    – first screening test,
    – normal results in 20% of all chronic hepatitis patients

• **Serological tests** *(HCV-antibody)*
  
  • Done in blood transfusion service centres, public and private labs
  • *anti-HCV:*
    – indirect test, **indicator marker**
    – sensitive method: 3. gen. CMIA, ELISA, EIA *(CE IVD tests)*
    – Problem: tests with different sensitivity exist, therefore, often **false positive** test results!
    – If positive: **HCV-RNA PCR test is necessary**!
MORPHOLOGICAL METHODS

• Hepatic imaging:
  • Abdominal and contrast-enhanced ultrasonography (UH, CEUS)
  • Computer Tomography (CT)
  • Magnetic Resonance Imaging (MRI)

• Liver fibrosis:
  • Invasive assessment: liver biopsy (Knodell, METAVIR, Ishak score)
  • Non-invasive assessment: elastography (F0-F4 fibrosis), FibroTests
EXAMINATIONS OF LIVER MORPHOLOGY, HISTOLOGY AND DEGREE OF FIBROSIS

- Transient elastography
  - FibroScan
  - Fibrotouch

- ShearWave elastography

- Ultrasound guided needle biopsy of the liver

- Contrast-enhanced sonography

HCC

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MOLECULAR BIOLOGICAL TESTS

- **Basic method**: reverse transcription polymerase chain reaction (RT-PCR)
- Done centrally in **3 NEAK designated laboratories**:
  - **1992**: Székesfehérvár, Molecular Diagnostic Laboratory
  - **2008**: Budapest „Szent László Hospital”/Central Hospital of Southern Pest
  - **2013**: Semmelweis University, Transplantation and Surgical Clinic
- All 3 labs work with **equipments of the same sensitivity**
- Diagnostic **tests** have the **same sensitivity and specificity** (CE IVD)
- All 3 labs are available for all 34 accredited Hepatology Centres

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MOLECULAR BIOLOGICAL TESTS

1. HCV-RNA detection

- Qualitative method: 1994-1995; Cobas Amplicor HCV 1; 2. gen; 
  \[ LLOD^{1} < 50 \text{ IU/ml} \]

- Quantitative (HCV RNA level) methods:
  - B) real-time PCR: 2004-: CobasAmpliPrep/TaqMan; Cobas 4800 (Roche); m2000 (Abbott); 
    \[ LLOD^{1} < 12-15 \text{ IU/ml} \]

- Measurement time points:
  - PegIFN th.: baseline, W4, W12, EOT (end of treatment), EOT+W24
  - DAA th: baseline, (EOT), EOT+W12/24

\[ ^{1}\text{Lower limit of detection (LLOD)} \]

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MOLECULAR BIOLOGICAL TESTS

2. HCV type/subtype methods

• Serotype (G1-6): 1996-1999; plate enzim-immunoassay
• Genotype (G1-6(7) + a-c subtype):
  A) RT-PCR + reverse hybridisation: 2000-2015; INNO-LIPA HCV II.; VERSANT HCV Genotype 2.0
  B) real-time PCR: 2016; Cobas 4800 (Roche); Abbott HCV Genotype II.
Classification of HCV genotype and subtype 2017.
(International Committee on Taxonomy of Viruses)
## HCV genotype/subtype distribution by different methods in Hungary (n= 5917) (2000-2017)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1a</td>
<td>5,6%</td>
<td>6,1%</td>
<td>3,5%</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>84,6%</td>
<td>83,1%</td>
<td>91,0%</td>
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</tr>
<tr>
<td>1a+1b</td>
<td>5,1%</td>
<td>5,9%</td>
<td>1,7%</td>
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</tr>
<tr>
<td>2</td>
<td>0,1%</td>
<td>-</td>
<td>0,2%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1,8%</td>
<td>1,6%</td>
<td>*2,8%</td>
<td>*2 patients: inj. drug use: 3+1b</td>
</tr>
<tr>
<td>4</td>
<td>*0,1%</td>
<td>*-</td>
<td>0,8%</td>
<td>* G4 + 1a; 1b</td>
</tr>
<tr>
<td>mixed</td>
<td>*1,6%</td>
<td>*1,9%</td>
<td>-</td>
<td>*1a; 1b; 2; 4; mixed</td>
</tr>
<tr>
<td>1</td>
<td>*1,1%</td>
<td>*1,4%</td>
<td>&lt; 0,01%</td>
<td>undifferentiated subtype</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>3 patients</td>
<td>-</td>
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*J. Gervain: Orvosi Hetilap (Hungarian Medical Journal) 2018; 159 (Suppl 2.) 2-8.*
Since 1992, the most specific and sensitive molecular biological tests have been used for the screening and antiviral therapy of HCV infected patients.

Molecular biological tests of all patients from the 34 accredited Hepatitis Centres are done in 3 designated central labs.

Blood samples are transported cooled with specific speed carrier services.

The 3 labs use the same methods and same sensitivity and specificity tests.

Current recommended HCV-antibody test: 3. gen. ELISA, CE-IVD

Currently used HCV molecular biological tests are real-time methods.

The dominant HCV type in Hungary is GT1/b (92%), but the prevalence of GT3 has increased in recent years.

Diagnostic tests defined in the national protocol are available for all infected patient without waiting list thanks to a joint effort of providers, social insurance and the industry.

The author thanks you for your attention and Dr. Mihály Makara for delivering the presentation.

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