

**UNIVERSITY OF MEDICINES AND PHARMACY CRAIOVA
FACULTY OF GENERAL MEDICINE**

**“The Immunological profile at patients with chronic viral hepatitis and
its prognosis value”**

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SUMMARY OF DOCTORAL THESIS

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CONTENTS OF DOCTORAL THESIS

INTRODUCTION

List of abbreviations

Stage of knowledge

Chapter I Hepatitis virus B

- I.1 Epidemiology of virus B infection
- I.2 The genomic structure of virus B
- I.3 Immunological mechanisms in viral B hepatitis
- I.4 The markers of viral B infection and their signification
- I.5. Evolution of viral B infection

Chapter II Hepatitis virus D

- II.1 The structure of virus delta
- II.2 Immunopathological mechanisms involved

Chapter III Hepatitis virus C

- III.1. Epidemiological aspects of virus C infection
- III.2 The structure of virus C
- III.3 The answer of body to the infection
- III.4 Natural evolution of virus C infection

Chapter IV Chronic viral hepatitis

- IV.1. Definition
- IV.2 Lab investigations signification in viral hepatitis
- IV.3 Diagnosis criteria of hepatitis B
- IV.4 Diagnosis criteria in hepatitis D
- IV.5 Diagnosis criteria in hepatitis C
- IV.6 Prognosis factors in chronic viral hepatitis

Chapter V Extrahepatic manifestation in viral hepatitis

Personal contributions

Chapter VI.1. The aim of study

- VI.2. Material and method
- VI.2. Statistical interpretation of dates

Chapter VII Results

- VII.1. Demographic characteristics of patients
- VII.2. Clinical profile of patients
- VII.3. Biological characteristics of patients
- VII.4. Extrahepatic manifestations of patients involved in the study
- VII.5. Histopathological and immunohistochemical characteristics

VII.6. Imunohistochemical study
Chapter VIII. Results discussion
Chapter IX. Conclusions
Bibliography

Key words: chronic viral hepatitis, extrahepatic manifestation, immunohistochemistry, lymphocytes

The doctoral thesis entitled “The Immunological profile at patients with chronic viral hepatitis and its prognosis value” extends for 213 pages and is structured according to criteria in force.

At the beginning I had presented a list of abbreviations and a short introduction where I dot the actual problem of patients with viral hepatitis.

Starting with chapter I to chapter V, I presented “**The Actual Stage of Knowledge**”, regarding the structure of hepatitis virus B, C, D, the actual dates of epidemiology, immunopathological mechanisms involved in extrahepatic manifestations and the diagnosis in viral hepatitis with the role of liver biopsy and anatomic-pathological results.

The immunological mechanisms involved in appearance of extrahepatic manifestations have been largely presented, insisting on the role of humoral and cellular immune answer. The extrahepatic manifestations are as result of immunological implications and are more frequent at patients with virus C hepatitis.

The “**Personal Contributions**” are presented started with chapter VI and extends for 130 pages comprise four great themes: the aim of study, material and methods, results and conclusions.

The idea of this study started from the cases met in general practice where more patients diagnosed with viral hepatitis presented extrahepatic manifestations with severe evolution.

The aim of study was to present the prevalence of extrahepatic manifestation, the immunological modifications at patients with viral hepatitis, any correlations between different parameters and liver fibrosis grade.

In “**Material and Methods**” I have presented the protocol of work, including an exclusion criteria for patients, liver biopsy, cytological, histopathological or immunohistochemical examinations. The data were processed through statistic methods.

The “**Results**” chapter is divided in three sub-chapters. The first sub-chapter has presented the biological and immunological parameters at patients involved in the study.

The second sub-chapter includes the extrahepatic manifestations at patients involved in the study.

The third sub-chapter is based on histopathological aspects and immunohistochemical examinations.

The study involved 637 patients with viral hepatitis with a high prevalence of female sex, with age over 35 years old. The most patients presented asthenia. The patients with viral C hepatitis presented more common cytolysis syndrome, characterized by high level of aminotransferase and low level of AST/ALT index, compared with patients with viral B hepatitis. Cholestasis index was high at

12-15% from patients with viral hepatitis; the more sensitive for virus reactivation index was alkaline phosphatase, gamma-GT.

3/4 (75%) from patients with viral B hepatitis and 20/38 (52.63%) from patients with viral C hepatitis with severe necro-inflammatory activity had high level of immunoglobulins, most patients with high level of immunoglobulins presenting grade of fibrosis F3 and F4 ($p=0.005$).

In this study, the level of gamma-globulins and IgG are correlated with the level of fibrosis grade and necro-inflammatory activity at patients with viral C hepatitis, while IgA are not correlated.

The rheumatoid factor was present at 18 patients with HBV (5.85%) and 49 patients (14.84%) with HCV, and was associated with female sex, over 40 years old, presence of artralgiás, high level of ALT, without a significance correlation between him and grade of liver fibrosis. The level of complement was normal at almost all patients. The median value of serum complement was low more frequent at patients with chronic viral C hepatitis, $p=0.04$, $RR=0.05$. Low values of serum complement was detected at 20 patients with virus B hepatitis (6,5%) and at 43 patients with chronic virus C hepatitis (13,03%) being associated with female sex, age over 35 years old and high level of aminotransferases.

The level of serum complement can be influenced by immunological mechanisms at patients with viral hepatitis. Although in patients with severe hepatitis a little percent had low level of serum complement, this was not correlated with grade of fibrosis.

The immune circulating complexes were present at 4.6% patients with HBV and 10.9% patients with HCV, ($RR=3,72$, $OR=4,27$) and were associated with extrahepatic manifestations like thyroiditis, glomerulonephritis, cryoglobulinemia at 17 patients with HCV and 4 patients with HBV.

The most common autoantibody found at patients was antinuclear antibody and they are not correlated with level of aminotransferase or fibrosis grade.

Cryoglobulines were found at 3 patients with HBV with median age $50,34\pm 7,89$ years old and at 27 patients with HCV, with median age $51,2\pm 7,55$ years old, the associations being more evident in patient with hepatitis C. the presence of cryoglobulines was associated with grade of liver fibrosis.

The extrahepatic manifestations were found at 32.34% patients with a high prevalence to female and older than 35 years; they are more common at patients with virus C hepatitis. It was found the presence of cryoglobulinemia, glomerulonephritis, diabetes mellitus, and rheumatoid syndrome, skin lesions in lichen or psoriasis, autoimmune thyroiditis, lymphoma.

With predictive value are found APRI index, the platelets level, AST/ALT report, which are correlated with fibrosis grade more common than necroinflammatory activity.

The study is focused on histopathological aspect at these patients and on immunohistochemical implications.

Only 421 patients made liver biopsy and I noticed minimal active chronic hepatitis at 6.35%, 44.91% with moderate active chronic hepatitis and 20.76% patients with severe hepatitis.

Immunohistochemical study was made at 100 patients with chronic viral hepatitis, being focused on detection of portal and periportal lymphocytes T (CD4/CD8) and B. The inflammatory infiltrate was composed from specific cells virus elements, lymphocytes T more common than lymphocytes B and other cells (macrophage, dendritic cells).

Patients with moderate/ severe necroinflammatory activity had inflammatory infiltrate with prevalence of lymphocytes T-CD4+(Th1) which was correlated with high level of extrahepatic manifestations and high level of serum virus.

The most patients with CD8+ lymphocytes infiltrate presented high level of AST and gamma GT and low level of fibrosis grade.

The chapter “**Conclusions**” comprises 11 ideas and sustains the following aspects:

- the extrahepatic manifestations are more common at patients with viral C hepatitis
- the changes at immunological aspects at these patients are correlated with grade of fibrosis and appearance of extrahepatic manifestations
- APRI index, level of platelets and AST/ALT ratio have value of predictive factors with liver fibrosis
- The immunological response has an important role in pathogeny of diseases, lymphocytes T-CD4+ is correlated with liver fibrosis.

The “**Bibliography**” chapter totalizes a number of 200 studied works, most of them being published between 2000-2008.

CURRICULUM VITAE

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2. Educational background

2007- Specialist Physician Internal Medicine

2002- Residency, Bucharest, promoted with 728 points

1996-2002- University of Medicine and Pharmacy- Craiova, Faculty of General Medicine

1990-1995- Carol I High school Craiova

1982-1990- Primary and Secondary School, no-22 Craiova

3. Competences, member in societies, courses, congresses, papers

Competences:

- General Ultrasound

Member in societies:

- Romanian Society of Ultrasonography in Medicine and Biology (from 2006)
- Romanian Society of Internal Medicines

Courses:

- 2 long term courses of general ultrasound

Congresses:

- Congresses and Conference organized by National Societies: 11 participations
- Other Medical Symposiums-20 participations

Extensive papers:

- First author :2
- Joint author:1

Summary papers, posters:

- first author:4
- joint author:2