

PREDICTIVE VALUE OF BLOOD AMMONIA LEVELS FOR THE PRESENCE OF OESOPHAGEAL VARICES IN LIVER CIRRHOSIS

Thesis

*Submitted for Partial Fulfillment for the requirement of M.Sc Degree
in Tropical Medicine*

By

Nabil Nassef Sanad Said

(M.B.B.Ch)

Faculty of Medicine - Assiut University

Supervised by

Dr. Iman Ismail Ramzy

Professor of Endemic Medicine

Faculty of Medicine - Cairo University

Dr. Hanan Abdel Hafez Hamed

Assistant Professor of Endemic Medicine

Faculty of Medicine- Cairo University

Dr. Hanan Ali Madani

Assistant Professor of chemical pathology

Faculty of Medicine- Cairo University

Faculty of Medicine
Cairo University
2014

Acknowledgement

*First of all, Thanks to **ALLAH**, without his will, nothing could have been achieved.*

*I would like to express my gratitude and sincere thanks to **Dr. Iman Ismail Ramzy**, Prof. of Endemic Medicine, Faculty of Medicine, Cairo University, for her valuable supervision, constant support, and encouragement in the conduction of this work.*

*I would like to thank **Dr. Hanan Abd El-Hafez Hamed**, Assistant Professor of Endemic Medicine, Faculty of Medicine, Cairo University, for her effort, time and help, without her help this work could not be done.*

*I would like to thank **Dr. Hanan Ali Madani**, assistant professor of chemical pathology, faculty of medicine, Cairo university, for her help.*

I extend my most profound gratitude to all workers in Kasr Al Aini gastrointestinal endoscopy unit, and to all my professors, to whom I have the honor to belong, to my professors who encouraged and supported me, who gave me their confidence and pushed me forwards.

I extend my most profound gratitude to my family for supporting and pushing me.

Last, but certainly not least, I owe to the patients included in this study may Allah alleviate their sufferings and may all our efforts be just for their own benefit.

Abstract

Background:

The current guidelines recommend the screening of all cirrhotic patients by endoscopy, but repeated endoscopic examinations are unpleasant for patients and have a high cost impact and burden on endoscopic units. The aim of this study is to evaluate the accuracy of using ammonia blood level as potential noninvasive predictor of esophageal varices in cirrhotic patients.

Methods:

This prospective study included one hundred fifty subjects. All studied subjects underwent a detailed clinical examination, biochemical workup, upper gastrointestinal endoscopy and abdominal ultrasound. Ammonia blood levels for all patients were calculated.

Results:

Ammonia demonstrated a high statistically significant correlation with the presence and grade of esophageal varices if it is put in a prediction model but ammonia alone we cannot depend on it in diagnosis of esophageal varices.

Conclusion:

The use of ammonia with a prediction model can help physicians by restricting the use of endoscopic screening only to patients presenting a high probability of esophageal varices. This is especially useful in clinical settings where resources are limited and endoscopic facilities are not present in all areas. While ammonia alone can not be used as a non invasive predictor of esophageal varices.

Keywords

- Noninvasive diagnosis of esophageal varices.
- Ammonia.
- Esophageal varices.
- Portal hypertension.
- liver cirrhosis.

Table of Content

Subject	Page
List of Abbreviations	III,IV
List of tables	V,VI
List of Figures	VII,VIII
Introduction	1
Aim of the work	3
Review of literature	4
Chapter (1): Portal Hypertension	4
1. <i>Introduction</i>	4
2. <i>Anatomy of portal venous system</i>	7
3. <i>Causes of portal hypertention</i>	12
4. <i>Pathogenesis of portal hypertention</i>	23
5. <i>Complications of portal hypertension</i>	27
6. <i>Esophageal varices</i>	28
7. <i>management of portal hypertension</i>	31
Chapter (2): Ammonia	
1. <i>introduction</i>	35
2. <i>ammonia metabolism</i>	37
3. <i>Urea cycle and its enzymes.</i>	38
4. <i>Ammonia detoxication by glutamine synthesis:</i>	40
5. <i>the key role of ammonia</i>	45
6. <i>Glutamate metabolism alteration</i>	47
7. <i>The NMDA receptor</i>	47
8. <i>The glutamate-glutamine cycle</i>	49
9. <i>Glutamine and its relation with brain edema:</i>	50
10. <i>Glutamine synthetase:</i>	51

11. ammonia and esophageal varices	52
Patients and Methods	55
Results	63
Discussion	88
Summary	97
Conclusion	99
Recommendations	100
References	101
Protocol	
Arabic summary	

List of Abbreviations

ASL	Argininosuccinate lyas.
ASS	Argininosuccinate synthetase.
BBB	Blood brain barrier
CNS	Central nervous system
CPS 1	Carbamoylphosphate synthetase I.
CT	Computed tomography.
EHPVO	Extrahepatic portal vein obstruction.
eNOS	Endothelial nitric oxide synthase
EVL	Endoscopic variceal ligation.
EV	Esophageal Varices.
FHVP	Free hepatic vein pressure.
HCC	Hepatocellular carcinoma.
HE	Hepatic encephalopathy.
HSC	Hepatic stellate cells.
HVPG	Hepatic vein pressure gradient.
iNOS	Inducible nitric oxide synthase
LSS	Large Spontaneous Shunts.
MHE	Minimal hepatic encephalopathy.
MOHP	Ministry Of Health and Population.
MPT	Mitochondrial permeability transition
NASH	Nonalcoholic steatohepatitis.
NCPF	Non-cirrhotic portal fibrosis
NH ₄	Ammonia.
NNT	Number needed to treat.
NO	Nitrous oxide.
NSCP	National Schistosomiasis Control Programme.

OTC	Ornithine transcarbamyase.
OV	Oesophageal varices.
PHC	Portal Hypertensive Colopathy.
PHG	Portal Hypertensive Gastropathy.
PLTS	Platelets count.
PSE	Portal-Systemic Encephalopathy.
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
ROS	Reactive oxygen species
SEC	Sinusoidal endothelial cells.
SLD	Spleen Longitudinal Diameter.
SRS	Spleno-Renal Shunt.
US	UltraSonographic.
VEGF	Vascular endothelial growth factor.
WHVP	Wedged hepatic vein pressure.

List Of Tables

Review of literature:		
No	Table	Page
I	Causes of portal hypertension	13
II	Risk factors for variceal hemorrhage	29
Results:		
No	Table	Page
1	The age, sex and residence distribution of the studied groups	64
2	Clinical data for the studied patients:	66
3	Results of haemogram of the studied groups	68
4	Laboratory findings for the studied patients	71
5	Abdominal ultrasonographic findings in the different groups	73
6	Upper gastrointestinal endoscopic examination	76
7	Comparison of ammonia among patients and control	77
8	Comparison between subgroups of group I (IA,IB)	78
9	Comparison between ammonia levels in different grades of oesophageal Varices in group I	79
10	Comparison between group II, group IA group IB regarding ammonia Levels	79
11	Comparison between groups I,II at ammonia levels above and below 47 $\mu\text{mol/l}$	80
12	Relationships in the esophageal varices group (group I N=100)	81

13	The correlation in the cirrhotic group both with and without varices n=130	82
14	Comparison between splenic vein diameter in group IA,IB patients	84
15	Prediction model (I) including NH4, platelets, age, PT, PC, RBC for prediction of esophageal varices	85
16	Prediction model (II) including NH4, PC, PT, RBC, PV, liver size for prediction of esophageal varices	86

List Of Figures

No	Figures	Page
Review:		
I	From Thieme Atlas of Anatomy: Neck and internal organs page: 274	7
II	The tributaries of the portal vein	8
III	Schematic representation of the pathophysiology of portal hypertension	23
IV	Algorithm for primary prophylaxis of variceal bleeding (Nina Dib, Frédéric Oberti, Paul Calès. Current management of the omplications of portal hypertension: variceal bleeding and ascites. CMAJ • May 9, 2006 • 174(10)	31
V	Algorithm for the treatment of variceal bleeding. TIPS = transjugular intrahepatic portosystemic shunt. *The therapeutic option depends on what was done in primary prophylaxis. Nina Dib, Frédéric Oberti, Paul Calès. Current management of the complications of portal hypertension: variceal bleeding and ascites. CMAJ • May 9, 2006 • 174(10)	32
VI	Algorithm for screening endoscopy.	34
VII	Schematic representation of the glutamate-glutamine cycle	49
Results:		
1	The age in the three studied groups.	65
2	Male and female percent in the three studied groups.	65
3	Ascites percent in the three studied groups	67
4	Liver size percent in the three studied groups.	68
5	RBC in the three studied groups.	70
6	Platelets in the three studied groups.	70

7	Portal vein diameter in the three studied groups	75
8	Splenic vein diameter in the three studied groups.	75
9	NH4 in the three studied groups.	77
10	Chart representing the correlation between the NH4 and the splenic vein in group I cirrhosis with varices	81
11	Chart representation of the correlation between the NH4 and the splenic vein in group 11 cirrhosis with no varices	83
12	Chart representation of the correlation between the NH4 and the splenic vein in group 111 (normal).	83



INTRODUCTION

Esophageal varices are the most critical portosystemic shunts that develop secondary to portal hypertension, which is considered a main complication of liver cirrhosis (**Imperiale and Chalasani, 2001**). The development of esophageal varices in cirrhotic patients can transform the disease from a pre-clinical to a clinical stage (**Biecker, 2013**) and the use of endoscopic prophylactic band ligation and non-selective beta blockers can decrease the risk of esophageal bleeding by 50% (**Giannelli et al., 2014**).

Variceal bleeding occurs in 20–40% of cirrhotic patients with esophageal varices and is associated with a high morbidity and mortality (**Chang, 2006**) The mortality associated with each episode of variceal bleeding ranges from 17% to 57% (**Jensen, 2002**) The current guidelines recommend screening of all liver cirrhosis patients by endoscopy to identify those at risk of bleeding so that they can be administered prophylactic therapy (**Addley et al., 2012**).

Endoscopically, the presence of large varices and/or red spots on the varices indicates a high risk of bleeding (**Bhasin and Malhi, 2002**) Patients who do not have varices with compensated cirrhosis should receive an endoscopic examination every 2–3 years. Those with small varices should receive an examination every 1–2 years (**Grace et al., 1998**). The recommendation for patients with decompensated cirrhosis is an endoscopic examination every year even if there are no varices present (**De Franchis, 2000**).



The prevalence of esophageal varices among cirrhotic patients is variable, ranging from 24% to 80%. Therefore, endoscopic screening of all patients with liver cirrhosis would result in a large number of unnecessary endoscopies and additional burden to endoscopic units(**De Franchis, 2006**) . Repeated endoscopic examinations are unpleasant for the patients and result in a high cost. In addition, patient compliance with the screening program may be reduced.

For these reasons, several studies have examined how to identify patients with varices using non-invasive or minimally invasive methods to avoid endoscopy in patients with a low risk of varices. These studies include biochemical, clinical and ultrasound parameters, transient elastography, computerized tomography (CT) scanning and video capsule endoscopy (**De Franchis, 2008**).



AIM OF THE WORK

To test the accuracy of using ammonia blood levels as non- invasive predictor of oesophageal varices in cirrhotic patients, for restriction of performance of screening endoscopy.

PORTAL HYPERTENSION

Introduction:

Portal hypertension, a major hallmark of cirrhosis, is defined as a portal pressure gradient exceeding 5mmHg (**Bosch & Carlos, 2000**). In portal hypertension, portosystemic collaterals decompress the portal circulation and give rise to varices. Successful management of portal hypertension and its complications requires knowledge of the underlying pathophysiology, the pertinent anatomy, and the natural history of the collateral circulation, particularly the gastroesophageal varices (**Toubia & Sanyal, 2008**).

Portal pressure is most commonly determined by the hepatic vein pressure gradient (HVPG), which is the difference between the wedged hepatic venous pressure (reflecting the hepatic sinusoidal pressure) and free hepatic vein pressure (**Pagan et al., 2005**).

An increase in portal pressure can be detected by the measurement of HVPG already in patients with histologically defined advanced fibrosis. However, complications of portal hypertension, i.e. development of esophageal

Varices, ascites, hepatic encephalopathy, bleeding, and renal impairment, Occur over a threshold value of 10-12mmHg. Over these limits cirrhosis becomes clinically decompensated and bleeding from ruptured esophageal or gastric varices constitutes the major clinical event causing death (**Amico et al., 2006**).