THE INFLUENCE OF THE OXIDATIVE STRESS ON THE EVOLUTION OF PORTOSYSTEMIC ENCEPHALOPATHY

Petrişor Diana, Szegedi Ladislau, Iovan Ciprian

University of Oradea, Faculty of Medicine and Pharmacy, First December Square, No 10, Oradea, Romania, e-mail: petrisordiana@yahoo.com

Abstract

The oxidative stress tends to become a subject more and more approached by numerous authors because it has been noticed that it is involved in several pathologies positively correlating with their evolution.

It was noticed that the portosystemic encephalopathy, a complication of the hepatic cirrhosis, may be ameliorated even by small therapeutic interventions without any etiopathogenetic intention.

This study tries to emphasize the fact that even though the etiologic factor of the basic disease is not eliminated, only by applying the standard therapy for the hepatic cirrhosis, an improvement in the clinical and, bioumoral state and consequently of the oxidative stress markers may be obtained.

Key words: oxidative stress, portosystemic encephalopathy, hepatic cirrhosis

INTRODUCTION

The oxidative stress represents that unbalance between the oxidation products and the antioxidant capacity of the body. (1) It gets involved in a series of pathologies including the chronic hepatic disease, no matter the aetiology.

This study tries to follow the evolution of the oxidative stress under treatment, on a group of patients with portosystemic encephalopathy developed on a hepatic cirrhosis basis.

The hepatic cirrhosis represents one of the final stages of numerous pathologies which can affect the function and morphology of the liver. It may have different etiologies, amongst which, the most frequent are: the infection with the hepatic virus C, B, B+ delta, ethanolic, autoimmune, and primitive biliary, etc. It presents in its evolution several complications like portosystemic encephalopathy, a group of disorders of different severity, of the psychomotor, intellectual, cognitive, emotional affective, behavioural, and motor functions.

The portosystemic encephalopathy sometimes associates a triggering factor: the infectious intercurrence, constipation, diarrhea, electrolytic imbalance, hypoxia, hypovolemia, benzodiazepine consumption.

In the case of the selected patients, the decompensation of the disease came due to: a viral respiratory intercurrence (2 patients), an acute diarrheic

syndrome (2 patients) and because of the inobservance of the hygienic-nutritional and life regime, as well as to a previous treatment (4 patients).

MATERIAL AND METHOD

We selected 8 patients with portosystemic encephalopathy on a hepatic cirrhosis basis hospitalized in the Internal Medicine ward of the Clinical Municipal Hospital ”Dr. G. Curteanu” Oradea, between May 2010- May 2011.

There were 3 women and 5 men. The age limit was between 43 and 67 years, with an average of 55 years. After aetiology the cirrhoses were classified as follows: - 5 patients with viral C etiology, 2 patients with viral B etiology and one patient with hepatic cirrhosis on a chronic consumption of ethanol.

All the patients were submitted to an initial evaluation, at start, consisting in a clinical examination, abdominal ultrasound, superior digestive endoscopy, usual bioumoral tests, and specific for the oxidative stress. After 12 months of standard treatment, with hepatoprotectors, membrane stabilizers, diuretics, beta blockers, inhibitors of the ammoniogen flora, etc., were submitted to the same evaluation. None of the patients with viral etiology of the basic disease received antiviral treatment.

The markers of the oxidative stress were determined through the following methods:

- Chromatography of the liquids under high pressure (HPLC) with detection by fluorescence for malondialdehyde (normal values: 0,36 -1,24 μmol/l.
- Photometric method, by which the enzymatic activity in erythrocytes for the glutathione peroxidase is analyzed (normal values: 4 171 -10 881) and for superoxide dismutase (normal values: 1 200 – 1 800 U/gHb).

RESULTS AND DISSSIONS

In what concerns the etiology of the portosystemic encephalopathy cases, 62,5% were caused by hepatic cirrhosis with hepatic C virus, 25 % were caused by viral B hepatic cirrhosis, and 12,5 % were caused by chronic consumption of alcohol.

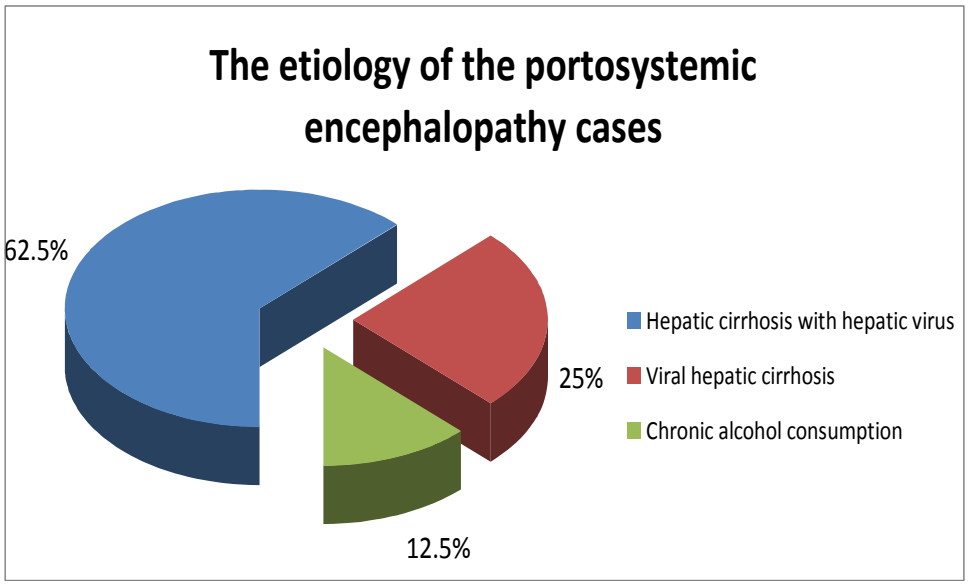

Fig.1. The etiology of the portosystemic encephalopathy cases

The assessment of the encephalopathy degree was made on the basis of the clinical picture of the neuropsychic manifestations according to West Haven classification, as follows:

Table 1.

West Haven classification of portosystemic encephalopathy

Degree 0	normal neuropsychic picture
Degree 1 (prodromal)	asthenia with apathy or euphoria, with or without neurologic modifications (dysarthria, hyper-reflexion, disorders in the sleeping rythm). Often paranoid or megalomanic tendencies
Degree 2	Modifications of personality and neurologic alterations (hypertonia, hyper-reflection, dysarthria, flapping tremor), psychomotor disorders (excitation or apathy). Flapping tremor, increasing sleepiness, the finger-nose sign changed, EEG modifications
Degree 3	Advanced state of confusion and disorientation is added, ataxia, spastic rigidity, increased osteotendinous reflexes, discrete hepatic factor

Degree 4	stupor appears, but with response to stimuli, hypotonia hypo-reflection
Degree 5	Profound coma with hypothermia, sometimes convulsions, loss of tonus, areflexia, lack of reaction to pain stimuli, lost corneal reflex.

Dependent on this classification, at the beginning, the 8 patients were classified as follows:

- 2 patients stage I
- 5 patients stage II
- 1 patient stage III

The hepatocytolitic syndrome with average values of the transaminases of 54 U/L for 50% of the patients and of 108 U/L for 50% of the patients for GPT. In the case of GOT the average value was of 52,5 U/L for 37,5 % of the patients and 105 U/L for 62,5% patients, which shows that besides the hepatic fibrosis process, cytolysis appeared and the inflammatory process confirmed by a leucocytosis of > 8 000/mm^3 in 65,5% of the patients at the beginning and 50% at the end of the study.

The most important marker of the low intensity inflammation, specific to hepatic events, is reactive C proteine with values between 1-3 mg/dl, respectively between 3-10 mg/dl, and which shows general inflammatory character, associated to some more complex events linked to the oxidative stress.

Malondialdehyde as an expression of the presence and activity of the oxidative stress in hepatic encephalopathy is found with values of 2,12 μmol/L in 62,5% of the patients with neuropsychic symptoms, come under II stage West Haven. They presented personality changes, agitation alternating with sleepiness, flapping tremor. After a year of monitoring under the complex conventional treatment, the value of the oxidative stress in some of the patients increased, the malondialdehyde reaching a sanguine level of 7 μmol/l for 50% of the patients.

In the same time, the antioxidant defence of the body has decreased, the superoxide dismutase reaching under the inferior limit of the normal interval, respectively from 37,5% patients at the beginning, to 62,25% of the patients after one year's monitoring. The glutathione peroxidase presented more and more decreased values, from 25% of the patients to 37,5% of the patients, which shows how much, under the influence of the oxidative stress, the capacity of the body to fight the local and general phenomena associated to the basic disease is surpassed. This is how, the increase in the number of patients whose neuropsychic symptomatology became more complicated, increased from 12,5% to 37,5%, increasing from stage II to III, together with the increase of the serum level of the protein C-reactive, and

of the alkaline phosphatase to over 180 U/L from 12,5% to 25% of the patients.

The fact that the self antioxidant defence is a little reactive, and the contribution of the antioxidants administrated in the current therapy is little intense, emphasizes the aggressiveness of the oxidative stress, expressed by the number of patients with values of the protein C-reactive greater than 6 mg/dl at the end of the monitoring period (25%) as compared to 12,5% at the beginning.

Table 2.

Bioumoral examinations and West Haven stage of the patients with portosystemic encephalopathy at the beginning and at the end of the monitoring.

Biologic Marker Average Values	**At the beginning**		**At the end**	
	No. of affected patients	**West Haven Stage**	**No. of affected patients**	**West Haven Stage**
Malondialdehyde				
0,36-1,24= 0,80 µmol/l	2 (25%)	I	1 (12,5%)	I
1,24-3,00 = 2,12 µmol/l	5 (62,5%)	II	2 (25%)	II
3,00-9 = 7 µmol/l	1 (12,5%)	III	4 (50%)	III
GPT U/L 4-36 U/L				
36-72 = 54 U/L	4 (50%)	I	3 (37,5%)	I
72-144 = 108 U/L	4 (50%)	II	2 (25%)	II
144-320 = 232 U/L	-	-	3 (37,5%)	III
GOT U/L 10-35 U/L				
35-70 = 52,5 U/L	3 (37,5%)	I	4 (50%)	I
70-140 = 105 U/L	5 (62,5%)	II	3 (37,5%)	II
140-280 U/L= 220 U/L	-	-	1 (12,5%)	III
Protein C-reactive				
Interval normal < 1 mg/dl	2 (25%)	I	-	
1-3 mg = 2 mg/dl	5 (62,5%)	II	6 (75%)	II
3-10 mg = 6,5 mg/dl	1 (12,5%)	III	2 (25%)	III
Alpha-fetaprotein				
< 40 ng/ml	4 (50%)	I	3 (37,5%)	I
40-100 = 70 ng/ml	3 (37,5%)	II	4 (50%)	II
100- 300 ng/ml	1 (12,5%)	III	1 (12,5%)	III
Total Bilirubin				

0,3-1 mg/dl	6 (75%)	I	4 (50%)	I
1-25 mg/dl-2,75 mg/dl	2 (25%)	II	4 (50%)	II
Time for prothrombin 11-12,5 sec	3 (37,5%)	I	2 (25%)	I
> 12,5 sec	5 (62,5%)	II	6 (75%)	II
Superoxide dismutase 1200-1800 U/gHg	-	-	-	-
< 1200 U/gHg	3 (37,5%)	III	5 (62,5%)	III
> 1800 U/gHg	5 (62,5%)	I	3 (37,5%)	II
Glutathione peroxidase 4171-10881 U/L	-	-	-	-
< 4171 U/L	2 (25%)	III	3 (37,5%)	III
> 10881 U/L	6 (75%)	I	5 (62,5%)	II
Alkaline Phosphatase 30-120 U/L				
120-180 U/L	7 (87,5%)	I	6 (75%)	I
> 180 U/L	1 (12,5%)	II	2 (25%)	II
Ag HBs	2 (25%)	I	2 (25%)	I
Ac Anti VHC	5 (65,5%)	II	5 (65,5%)	I
Leucocytes > 8 000/ mm^3	5 (65,5%)	II	4 (50%)	II

CONCLUSIONS

Within the portosystemic encephalopathy, the increased level of the oxidative stress is positively associated to 5 (62,5%) from the 8 (100%) with a degree of neuropsychic impact, so that they were classified as I-II stage West Haven at the beginning of the study, and respectively II-III stage West Haven at the end of the study, as compared to the rest of 3 patients (37,5%), whose serum level of the malondialdehyde stayed lower, and the neuropsychic classification remained at stage I West Haven after one year's monitoring.

As by definition the portosystemic encephalopathy represents a potentially reversible state, the possible identification and annihilation of the etiologic factor of the basic disease or of the determining one of the encephalopathy, would determine the annihilation of the effects of the oxidative stress. Where the antioxidant reaction expressed by self active enzymes is increased, the oxidative stress is annulled, and the value of the normal cellular and tissular functions re-establish the normal.

The impossibility of administrating a curative treatment of the basic disease (hepatic cirrhosis) explains why after a year's monitoring of the patients under conservative treatment, it couldn't avoid the increase of the encephalopathy degree. In the same time with the neuropsychic degradation, with the increase of the malondialdehyde, as a marker of the oxidative stress, the antioxidant enzymes had decreased (superoxide dismutase and glutathione peroxidase).

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