Original article

A pilot study using lactulose in management of minimal hepatic encephalopathy in children with extrahepatic portal vein obstruction

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Background: **Minimal hepatic encephalopathy (MHE) is not associated with overt neuropsychiatric symptoms but rather with subtle changes in psychometric and/or neurophysiologic tests. We aimed to diagnose MHE in children with extrahepatic portal vein obstruction (EHPVO) and to evaluate the effect of lactulose on MHE.**

Methods: **A prospective study was carried out on 30 patients with EHPVO (21 males; mean age 10±2.5 years). The study was carried out in the Pediatric Hepatology Unit, Cairo University Pediatric Hospital, Cairo, Egypt, between 2011 and 2013. All patients were subjected to clinical and laboratory assessment, neuropsychmetric testing using the arabic version of Wechsler intelligence tests, neurophysiological testing by visual electroencephalogram and P300 event related potentials (ERP).**

Results: **The prevalence of MHE among children with EHPVO was 20% (6/30). After randomization to treatment and no-treatment groups using lactulose, all tests were repeated after three months. Among four patients with MHE who received lactulose, three (75%) improved. On the other hand, one of the patients in the no-treatment group developed MHE. Only one patient in the treatment arm had to discontinue lactulose because of severe diarrhea.**

Conclusions: **This pilot study revealed that the prevalence of MHE was 20%. Improvement on psychometic tests was seen in 75% of our patients (3/4) after treatment with lactulose. Lactulose treatment was well tolerated.**

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Key words: **children;**
extrahepatic portal vein obstruction;
lactulose;
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neuropsychometric tests;
P300 event-related potential

Introduction

Extrahepatic portal vein obstruction (EHPVO) is a common cause of non cirrhotic portal hypertension[1] and upper gastrointestinal bleeding in children[2,3] in developing countries.[1] The most common presentation in children with EHPVO is upper gastrointestinal bleeding and splenomegaly.[1,4]

In contrast with children with portal hypertension secondary to cirrhosis, children with EHPVO have primarily normal liver functions and parenchyma.[5] Because of the high pressure in the obstructed splanchnic bed and normal hepatic sinusoidal pressure, multiple hepatopetal collaterals develop to "cavernomatous transformation". However, these hepatopetal collaterals are not sufficient and hepatofugal collateral vessels develop at the sites of normal porto-systemic communications.[1] The portal blood thus bypasses the liver, carrying toxic substances to the systemic circulation.[6,7]

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting. It manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.[8,9] Minimal hepatic encephalopathy (MHE) and covert hepatic encephalopathy is defined as the presence of test-dependent or clinical signs of brain dysfunction in patients with chronic liver disease who are not disoriented or display asterixis. Testing strategies can be divided into two major types: psychometric and neurophysiological.[10,11] Because MHE affects several components of cognitive functioning, which may not be impaired to the same degree, the International Society for Hepatic Encephalopathy and Nitrogen

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Metabolism (ISHEN) suggests the use of at least two tests, depending on the local population norms and availability, and preferably with one of the tests being more widely accepted so as to serve as a comparator.

Patients with EHPVO may be vulnerable to mild cognitive and psychomotor deficits in absence of liver diseases.[12]

This study aimed to diagnose MHE in children with EHPVO and to evaluate the effect of lactulose on MHE.

Methods

The study was carried out in the Pediatric Hepatology Unit, Cairo University Pediatric Hospital, between January 2011 and December 2013. This study was approved by the Ethics Committee of Kasr Alainy Medical School, Cairo University, Egypt, according to the ethical guidelines of the 1975 Declaration of Helsinki. An informed consent was obtained from each patient included in the study. All EHPVO patients aged above 6 years who agreed to be participate into this study were included. Exclusion criteria included: 1) evidence of primary intrinsic liver disease; 2) overt hepatic encephalopathy; 3) profound mental retardation, and 4) neurological disease. Finally, a total of 30 patients were included in this study.

Clinical and laboratory assessment

Proper history taking including onset of the illness, presenting complaint, history of esophageal bleeding, neurological symptoms (with special stress on insomnia, disturbed sleep rhythm, drowsiness, confusion, impaired memory, bizarre behavior, irritability and tremors), symptoms of hepatic dysfunction in the form of jaundice, edema, bleeding tendency, past history of hepatic encephalopathy and full clinical examination especially for signs of hepatic dysfunction such as jaundice, palmar erythema, edema, hepatomegaly, splenomegaly and ascites. Blood total and direct serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin, international normalization rate (INR), complete blood count and ammonia were all examined.

Neuropsychometric testing

All patients were tested using the arabic version of Wechsler Intelligence Tests.[13,14] Tests were performed at the Psychiatry Department, Kasr Alainy Medical School, Cairo University, by a psychologist. The tests included the following: Information Test and Digit Span (representing verbal scale), Coding Test, Block Design Test and Object Assembly Test (representing performance scale).

Calculation of results was done in the following sequence: 1) The raw score for each individual subtest was transformed to scaled score (age and sex matched) using standardized tables. 2) The scaled scores of performance subtests and verbal subtests were summated to obtain the performance and verbal scaled score. 3) The performance and verbal scaled score were summated to obtain the full-scaled score. 4) The full-scale, performance and verbal scaled scores were transformed to full scale, performance and verbal IQ respectively. Abnormal performance of any given result was considered if the score was more than -2SD below the mean.[14]

Neurophysiologic testing in the form of Visual electroencephalogram (EEG)

All subjects underwent an EEG recording at the Pediatric Neurology Unit, Department of Pediatrics, Kasr Alainy Medical School, Cairo University. Electrodes were attached to the scalp according to the international 10-20 system of electrode placement. P300 event related potentials (P300 ERP) recordings were performed at the Neurophysiology Department, Kasr Alainy Medical School, Cairo University. The P300 responses were elicited by the standard auditory "oddball paradigm".

Waveform identification: The P300 was identified as the positive peak or series of peaks in the vicinity of 300 ms which was presented in the waveform evoked by the infrequent (target) tone.[15] If a single peak was present after 250 ms in the anticipated target window, it was identified as the P300. The latency in this condition was taken at the middle of that peak. If two peaks were present, the latency was measured by taking the average values calculated from values obtained at each peak.[15]

Management of MHE with lactulose

After the aforementioned steps were done, patients were randomly assigned into two groups. Group A included 15 patients who received lactulose at a dose of 0.3 ml/kg three times daily for 3 months; Group B included 15 patients who did not receive any intervention.

All patients were followed up every month for checking adherence to treatment and development of complications. Adherence to lactulose intake was assured by increased frequency of stool and changing to a softer consistency and by counting the number of bottles consumed. Only one patient in group A developed severe diarrhea from lactulose after one month and had to discontinue it.

Three months later, re-evaluation was done in 27 patients. Two patients dropped to follow up (one from Group A and one from Group B). Re-evaluation included

blood ammonia, neuropsychometric tests, EEG and P300ERP.

Statistical analysis

Quantitative variables were presented as mean and standard deviation (SD), or median (min-max), and qualitative data as number and percentage. Student's *t* test was used to compare mean±SD between the groups. Repeated measures of quantitative variables in the different groups were analyzed by general linear model. *P* within groups was for significant difference on repeated measures for each group separately; *P* between groups was for significant difference in changes between groups. They were compared by Chi square or Fisher's exact test when appropriate. In all tests, a *P* value of less than 0.05 was considered statistically significant.

Results

This study included 30 patients with an age range between 6 and 15 years (mean 10±2.5 years), including 21 males (70%) and 9 females (30%). The mean age of disease onset ranged from 3 months to 8.5 years (mean 3.3±2 years).

The main complaint was gastrointestinal bleeding in 16 patients (53.3%), abdominal distension in 6 (20%), accidently discovered splenomegaly in 6 (20%), purpuric eruption in 1 (3.3%) and epistaxis in 1 (3.3%).

All patients had no history of neurological symptoms or hepatic dysfunction. None experienced any episode of HE. By examination, 29 patients had splenomegaly (96.6%), 1 (3.3%) was splenectomized. None had hepatomegaly or ascites, and all patients were neurologically-free.

All patients had normal liver function tests including ALT, AST, total and direct serum bilirubin, serum albumin and INR, except two patients who had mildly elevated ALT, AST and serum bilirubin, with normal serum albumin and INR. All patients had elevated blood ammonia levels. Normocytic normochromic anemia was found in 13 patients (43.3%), leucopenia in 3 (10%) and thrombocytopenia in 6 (20%), and pancytopenia was present in 3 (10%) (Table 1).

Neuropsychometric testing

Results of neuropsychometric tests were considered normal if the score ranged between 7 and 13 with a mean of 10. Borderline results were considered if the score ranged between 4 and 7 expressed as -1SD to -2SD below mean. A score below 4 was considered abnormal and expressed as more than -2SD below mean. We found that object assembly and block design tests were the most affected (30% and 36.7% abnormal respectively) (Table 2).

The definition of MHE is based on psychometric test results more than two standard deviations below mean in at least two of these tests.[16] Accordingly, Six of our patients met the criteria of MHE, as 3 patients had 2 abnormal tests and the other 3 had 3 abnormal tests.

History of gastrointestinal bleeding was positive in 21/24 patients without MHE (87.5%) and in 5/6 (83.3%) with MHE. All patients were managed endoscopically with band ligation. Baseline liver function tests and ammonia were compared between patients with MHE and patients without MHE and none of studied parameters showed statistically significant difference between the two groups (Table 3).

Neurophysiological testing

All cases showed no abnormality by EEG except two cases. One showed high voltage slow activity asymmetric record, and the other showed oligorythmic monotonous EEG. Both changes were not attributed to HE. A typical response peaks within 250-500 ms after the stimulus. A delay greater than 2.5 SD of the age-controlled mean indicates a dysfunctional response.[17]

Table 1. Laboratory data of studied patients with extrahepatic portal vein obstruction (*n*=30)

Biochemical tests	Mean±SD	Abnormal, *n* (%)
Total serum bilirubin (mg/dL)	0.88±0.66	2 (6.7)
Direct serum bilirubin (mg/dL)	0.22±0.15	2 (6.7)
Serum albumin (g/dL)	3.85±0.43	0 (0)
ALT (IU/L)	28.65±13.09	2 (6.7)
AST (IU/L)	36.74±16.24	2 (6.7)
INR	1.24±0.20	0 (0)
Blood ammonia (μmol/L)	438.27±272.65	30 (100)
Hemoglobin (g/dl)	10.30±1.80	16 (53.3)
Total leucocyte* count/mm^3	4000 (1500-14 800)	6 (20)
Platelet* count/mm^3	100 000 (2500-240 000)	9 (30)
Pancytopenia	Not applicable	3 (10)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalization rate. *: median (min-max).

Table 2. Results of neuropsychometric tests of studied patients with extrahepatic portal vein obstruction (*n*=30)

Psychometric tests	*n** (%)		
	Normal	Borderline	Abnormal
Information test	22 (73.3)	6 (20.0)	2 (6.7)
Digit span test	11 (36.7)	18 (60.0)	1 (3.3)
Coding test	14 (46.7)	12 (40.0)	4 (13.3)
Block design test	4 (13.3)	15 (50.0)	11 (36.7)
Object assembly test	13 (43.3)	8 (26.7)	9 (30.0)

*: Number of patients with normal, borderline or abnormal results.

Our study showed no delay in P300 wave latency in all patients with EHPVO, including the six cases who had MHE as evidenced by psychometric tests.

Lactulose administration

Our patients were categorized into two groups. Group A included 15 patients who received lactulose, and group B included 15 patients who did not receive lactulose. Comparisons between baseline liver function tests and blood ammonia between groups A and B are shown in Table 4.

Both groups were re-evaluated 3 months later for blood ammonia, neuropsychometric tests, EEG and P300 ERP. One patient from each group dropped out on follow-up and thus each group ended with 14 patients. One case in group A was diagnosed with MHE discontinued treatment due to severe diarrhea.

Comparisons between baseline and follow-up ammonia level between groups A and B showed that baseline blood ammonia level was comparable in both groups (P>0.05). After 3 months, both groups showed significant reduction in ammonia level (P<0.01) with no significant difference (P>0.05).

In both groups, significant improvement was noted in information test and object assembly tests after 3 months (P=0.03 and 0.01 respectively) with no significant difference between both groups (Table 5).

Table 3. Biochemical tests between patients with and without minimal hepatic encephalopathy

Biochemical test	Patients without MHE (n=24)	Patients with MHE (n=6)	P value
Total serum bilirubin (mg/dL)	0.94±0.69	0.63±0.53	0.316
Direct serum bilirubin (mg/dL)	0.24±0.15	0.15±0.12	0.211
ALT (IU/L)	28.69±13.84	28.50±10.60	0.975
AST (IU/L)	37.43±17.72	34.00±8.67	0.652
Serum albumin (g/dL)	3.88±0.45	3.77±0.36	0.592
INR	1.25±0.20	1.19±0.18	0.490
Blood ammonia (μmol/L)	411.54±281.30	545.17±223.64	0.291

MHE: minimal hepatic encephalopathy; ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalization rate; IU: international unit.

Table 4. Baseline laboratory data of the patients

Biochemical test	Group A (n=15)	Group B (n=15)	P value
Total bilirubin (mg/dL)	0.71±0.36	1.05±0.84	0.155
Direct bilirubin (mg/dL)	0.16±0.09	0.28±0.17	0.280
ALT (IU/L)	26.47±9.09	30.84±16.18	0.369
AST (IU/L)	35.73±10.82	37.75±10.82	0.741
Serum albumin (g/L)	3.85±0.43	3.86±0.45	0.934
INR	1.21±0.13	1.27±0.24	0.379
Blood ammonia (μmol/L)	504.47±261.12	372.07±276.42	0.188

ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalization rate; IU: international unit. Group A received lactulose, and group B did not receive lactulose.

Discussion

To our knowledge, this is the first study on diagnosis and treatment of MHE in children with EHPVO. Because psychometric tests were the basic test used for diagnosis, we could not include cases below 6 years of age. None of our patients had a history of overt HE, or any neurological symptoms such as insomnia, disturbed sleep rhythm, drowsiness, confusion, impaired memory, bizarre behavior, irritability or tremors. In contrast to overt HE, in which a physical and mental status examination shows clear evidence of impairment, the diagnosis of MHE is less apparent.[18] None of the patients with EHPVO experienced overt HE in our center, even during episodes of bleeding.[19]

All our patients had normal liver function tests including ALT, AST, total and direct serum bilirubin, serum albumin and INR except two patients who had elevated ALT, AST and serum bilirubin with normal serum albumin and INR. Elevated aminotransferase levels can be attributed to the prolonged decrease in portal circulation and/or to the development of portal biliopathy, which shows that the disease may have a progressive course.[19,20]

All patients included in our study had elevated plasma ammonia level despite that none of them had any hepatic dysfunction or neurological symptoms or a history of HE. In EHPVO, despite normal hepatocellular function, portal-systemic shunts and liver bypass causes a rise of plasma ammonia level. This may impair cognitive functions in these patients with advancing age.[21]

Using neuropsychometric tests, we diagnosed 6 patients (20%) with MHE as having at least 2 tests more than two standard deviations below mean.[16] The prevalence of MHE in our study group was lower than previous studies.[22,23] This may be attributable to the lower age of our patients (mean 10±2.5 years *vs*. 23.2±10.8 and 28.2±8 years respectively) as compared to previous studies.

Table 5. Baseline and follow-up psychometric tests for the patients

Parameters		Baseline	Follow up	P value
Group A	Information test (mean±SD)	8.36±3.18	2.50±8.86	0.03
	Digit span (mean±SD)	6.50±2.31	6.71±2.30	0.19
	Coding test (mean±SD)	6.36±1.65	6.14±2.35	0.82
	Object assembly (mean±SD)	6.36±2.62	6.71±2.30	0.01
	Block design test (mean±SD)	4.14±1.88	4.36±1.99	0.07
Group B	Information test (mean±SD)	8.64±3.41	9.43±2.95	0.03
	Digit span (mean±SD)	6.36±2.41	6.64±2.27	0.08
	Coding test (mean±SD)	6.29±2.81	6.36±2.82	0.18
	Object assembly (mean±SD)	4.64±2.76	6.07±2.79	0.04
	Block design test (mean±SD)	3.79±2.08	4.79±1.48	0.21

SD: standard deviation. P<0.05 is considered significant. Group A received lactulose, and group B did not receive lactulose.

Although there is international consensus that psychometric tests are the gold standard in the diagnosis of MHE, no agreement exists as to what combination of tests should be carried out, and what the threshold value is at which MHE may be reliably diagnosed. This central problem is reflected in the varying reported prevalence for the disease, which ranges from 22% to 74% depending on which tests were chosen and where the threshold was defined.[16]

In our study visual EEG was done for all patients, None of them showed evidence of encephalopathic changes whether at baseline or on follow up. Revising the literature revealed scarcity of data about EEG findings in children with EHPVO. Results in cirrhotic adults revealed significant slowing of EEG background by visual analysis of EEG records in 17%,[24] and in 21%-38% by automated EEG analysis.[25,26]

In the present study there was no statistically significant delay in P300 ERP wave latency in patients with MHE as compared to patients without MHE. This was previously reported in adult cirrhotics younger than 40 years of age.[26] Our results revealed that amongst the various diagnostic tests used, only psychometric tests were impaired in MHE.

Up to the present time, there are no studies on treatment of MHE in children with EHPVO. Most studies have tried various therapies including lactulose, rifaximin, L-acetyl carnitine, fermentable fiber and probiotics in adult patients with liver cirrhosis,[27-31] with an exception of a single study in adults with EHPVO.[23] They utilized lactulose in the treatment of MHE and improvement was reported in 53% of their patients.

All cases in the treatment group tolerated lactulose, except one patient (17.6%) with MHE who developed severe diarrhea and had to discontinue treatment. The adverse effects of lactulose include alteration of taste perception, bloating and overdosing causes diarrhea which can result in severe dehydration and hyponatremia, and may lead to worsening of HE.[32]

Strangely enough, ammonia level showed statistically significant reduction three months later in comparison to baseline levels in both treatment and no-treatment groups. However, it is also important to note that correct measurement of the blood ammonia concentration requires a venous blood sample obtained without using a tourniquet and immediate laboratory analysis within 20 minutes. Ammonia concentration is also influenced by factors such as renal function, nicotine consumption, and muscle mass.[33] Severity of MHE was independent on levels of blood ammonia, but markers of inflammation (higher neutrophil counts, C-reactive protein levels, and interleukin-6 levels) were significantly higher in those with MHE compared to those without MHE.[34]

Out of the four patients with MHE who were randomized to the treatment group and continued treatment for three months, three patients (75%) improved on re-assessment of psychometric tests, as compared to 53% in the results by Sharma and Sharma.[23] It was also important to note that one of the patients in the no-treatment group developed MHE on re-assessment of his psychometric tests.

One limitation of our study is the small number of patients with EHPVO, as we had to exclude cases below 6 years of age. The number of cases with MHE studied was also small, which reflected the lower prevalence of MHE among EHPVO patients in the pediatric age group.

In conclusion, despite the small sample size, improvement after lactulose treatment for MHE was seen in children with EHPVO. Lactulose was well tolerated in 83% of our patiets. However, further larger studies are needed to determine the duration of therapy.

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