Med. J. Cairo Univ., Vol. 92, No. 2, Accepted 21/1/2024
DOI: 10.22608/MJCU. 549-557, June 2024
www.medicaljournalofcairouniversity.net

Cognitive Dysfunction in Children with Chronic Liver Diseases and Portal Vein Thrombosis

MOHAMMED A.E. EL-GUINDI, M.D.*; MAGDY A. SABER, M.D.*; NAHLA M.S. ABDELHADY, M.D.**; MOHAMED G. HENIDY, M.Sc.*** and OLA A. FOUAD, M.D.*

The Department of Pediatric Hepatology, Gastroenterology & Nutrition, National Liver Institute, Menoufia University, Department of Pediatric, Neurology Unit**, Faculty of Medicine, Menoufia University and Pediatric Department, Ministry of Health, Kafr EL-Sheikh, Egypt****

Abstract

Background: Chronic liver diseases (CLD) are a common cause of morbidity and mortality in children. Neurologic affection in CLD may be due to brain accumulation of ammonia and lactate; altered permeability of the blood-brain barrier and neuroinflammation. Chronic portal vein thrombosis (PVT), with a development of Porto-systemic shunts through which several neurotoxins can pass to the systemic circulation, may affect the neurocognitive functions.

Aim of Study: The aim of this study was to assess and manage the cognitive dysfunction in children with CLD and in those with chronic PVT.

Patients and Methods: The study was a cross sectional one that included 150 children, recruited over a period of three years (August, 2020 – August, 2022), who were categorized into three groups, group 1 included 60 patients with CLD, group 2 included 30 patients with chronic PVT and group 3 which included 60 apparently healthyage matched children. All children underwent assessment of the cognitive performance using the Arabic Version of the Revised Wechsler Intelligence Scale for Children (WISC-IV) followed by treatment of patients showed cognitive dysfunction by either lactulose or rifaximin for three months duration. The cognitive performance of affected children was reassessed after the end of treatment.

Results: 98.3% of the healthy control group had normal intelligence versus 70% of PVT group and 63.3% among those with CLD. The presence of CLD significantly increases the risk of below normal intelligence scale by 34.16 folds while PVT significantly increases that risk by 25.29 folds. After treatment with lactulose, the cognitive performance of 50% of CLD patients and 66.7% of PVT patients have been improved with a statistically significant difference (*p*-value=0.011 and *p*-value =0.034 respectively). While after treatment with rifaximin, the cognitive performance of 16.7% of CLD group have been improved with non-significant (*p*-value=0.317).

Conclusion: Chronic liver diseases and PVT in children significantly increase the risk of cognitive dysfunction which can be improved with lactulose.

Key Words: *Chronic liver diseases – Portal vein thrombosis – Cognitive dysfunction – Lactulose – Rifaximin.*

Introduction

THE term chronic liver disease (CLD) implies a long standing irreversible change in the hepatic structure that may end in complications like cirrhosis leading to premature death **[1]**. Liver disease chronicity is determined either by duration of the liver disease (>6 months) or by evidence of physical stigmata of CLD, clubbing, spider telangiectasia and hepatosplenomegaly **[2,3].**

The causes of liver disease in pediatric patients vary with age. Some are associated with certain age groups, such as biliary atresia (BA) and idiopathic neonatal hepatitis, which are observed only at birth or shortly thereafter **[2,3,4]**. Conversely, Wilson disease is typical of older children, especially adolescents **[4]**. Chronic viral hepatitis specially hepatitis B and C viruses (HBV) and (HCV) are the most common causes prevalent in children between 1 year to 12 years of age. They are important public health problems with broad clinical spectrums, from asymptomatic infection to cirrhosis and hepatocellular carcinoma **[5].**

The major cause of deaths in patients with CLD is due to end stage liver disease and hepatic failure and the only way to treat these patients is by liver transplantation **[1].**

In children, PVT is a significant clinicopathologic entity that all physicians should be aware with

Correspondence to: Dr. Ola A. Fouad,
E-Mail: ola29594@gmail.com

[6,7]. Several etiological causes, either of local or systemic origin, might be responsible for PVT development, although more than one factor is often identified. Furthermore, PVT clinical presentation is different in the context of acute or chronic onset and depends on the development and the extent of a collateral circulation. Intestinal congestion and ischemia, with abdominal pain, rectal bleeding, abdominal distention, and splenomegaly are common features of acute PVT. In contrast, chronic PVT can be completely asymptomatic, or characterized by splenomegaly, pancytopenia, varices, and, rarely, ascites **[6].**

Neurologic damage in CLD seems to be multifactorial primarily attributable to the following: brain accumulation of ammonia, manganese, and lactate; altered permeability of the blood-brain barrier; recruitment of monocytes after microglial activation; and neuroinflammation, that is, direct effects of circulating systemic proinflammatory cytokines such as tumor necrosis factor, IL-1β, and IL-6 **[8].**

Two types of neurological dysfunction can occur in CLD: 1) Extrapyramidal signs related to the accumulation of manganese in the basal ganglia and 2) Milder degrees of cognitive impairment known as minimal hepatic encephalopathy (MHE) **[9].**

The diagnosis of MHE may have clinical importance, as its presence may result in substantial impairment in occupational and psychosocial functioning, activities of daily living and overall quality of life. Moreover, MHE could be a preceding stage of overt neurological manifestations of hepatic encephalopathy **[10].**

Patients and Methods

The present study was conducted as a prospective cross-sectional studyin Pediatric Hepatology, Gastroenterology and Nutrition Department of National Liver Institute, Menoufia University. Informed written consent was obtained from legal guardians. The study procedures were carried out and approved by the Ethical Committee of National liver institute and in accordance with the declaration of Helsinki. The present study included included 150 children recruited over a period of three years (August, 2020 – August, 2022). The children were divided into three groups; group (1) included 60 patients with CLD, group (2) included 30 patients of chronic PVT and group (3) which included 60 apparently healthy children with matched age and sex.

Children with previous or current hepatic encephalopathy, Children with neurological or psychiatric disease, children with Wilson's disease, children with Endocrinal disorders e.g. Diabetes mellitus and hypothyroidism, Children with chronic hematological conditions e.g. β-thalassemia and sickle cell anemia andchildren on intestinal antiseptics therapy were excluded from the study. Each patient underwent: Full history taking, thorough clinical examination, laboratory investigations, abdominal ultrasonography (US) which was performed using Xario and Nemio US devices (Toshiba, Tokyo, Japan).

The study was carried out through two stages:

Stage 1: Assessment of the cognitive performance using The Arabic Version of the Revised Wechsler Intelligence Scale for Children WISC-IV; **[11],** which comprises 10 subsets, grouped into two general areas: Verbal scales and performance scales. The verbal scales measure general knowledge, language, reasoning, and memory skills, while the performance scales measure spatial, sequencing, and problem-solving skills **[12,13].** (Table 1).

Table (1): Indexes of the Wechsler Intelligence Scale for Children **[13]**.

Verbal Index	Performance
1- Information	1- Picture Completion
2- Comprehension	2- Matrix Reasoning
3- Similarities	3- Visual Puzzles
4- Vocabulary	4- Symbol Search
5- Arithmetic	5- Coding

The tests were carried out by a specialist, using a complex set of test materials. Testing requires approximately ninety minutes. Raw scores on each test converted to standard scores with a mean of 10 and a standard deviation of 3. Scale scores in the Verbal battery will be summed and converted to a Verbal IQ score; the same was done for the Performance scale scores which yield the Performance IQ score. In turn, the Verbal and Performance IQ scores summed and converted to obtain the Full-Scale IQ score which is considered average if the score is 90-109, high Average 110-119, very high 120-129, extremely high more than 130, low average 80-89, very low 70-79 and extremely low if the score less than 69 **[13].**

Stage 2: Management of the cognitive dysfunction:it included children with CLDs and those with chronic PVT who showed cognitive dysfunction in the stage one. These children were randomly divided into two groups: Lactulose group: Received Lactulose, manufactured by E.P.I.CO. (0.3ml/kg/ 8 hours) for 3 months duration **[14]** and Rifaximin group: Received rifaximin, Gastrobiotic manufactured by Al Andalous company (20mg/kg/day into 2 doses) for 3 months duration **[15].** At the end of the three months duration, the cognitive performance of those children was reassessed in the same way in stage one.

The duration of the treatment regimen was decided as 3 months because it`s the adjusted period of lactulose and rifaximin to be effective for primary prevention of HE in patients with CLD **[16-20]** and in those with PVT **[14].**

Statistical analysis:

Data was collected and entered to the computer using SPSS (Statistical Package for Social Science) program for statistical analysis, (version 13; Inc., Chicago. IL).

Types of statistics were used:

a- Descriptive statistics e.g., number (N) and percent (%) for qualitative data, mean and standard deviation (SD) for quantitative data.

b- Analytic statistics e.g. Chi-square test has been used to measure association between qualitative variables. Student *t*-test has been used to compare mean and SD of 2 sets of quantitative normally distributed data, while Mann Whitney test will be used when this data is not normally distributed. One-way analysis of Variance (ANOVA) test has been used for comparison between three or more groups having quantitative normally distributed data, while Kruskal-Wallis test has been used when this data is not normally distributed. Pearson's correlation has been used to study correlation between two variables having normally distributed data, while Spearman's correlation has been used when this data is not normally distributed. Fisher exact test has been used for 2x2 qualitative variables when more than 25% of the cells have expected count less than 5. Probability of error (*p*-value): Is considered statistically significant when it is less than 0.05.

Results

Children in this study were divided into three main groups namely: Group 1 (60 patients with CLD, Their mean of age was 10.38±2.19 years and 56.7% were females), group 2 (30 patients with chronic PVT, Their mean of age was 7.87±2.86 years and 70% were females) and 60 apparently healthy children as group 3, Their mean of age was 9.3±2.57 years and 60% were females. Analysis of children with CLD revealed that cryptogenic liver diseases, Autoimmune hepatitis (AIH) and congenital hepatic fibrosis (CHF) were the most detected causes (30%, 25% and 11.7% respectively). (Fig. 2).

This study showed a statistically significant difference between the studied groups regarding (WIS-IV). 98.3% of the healthy control group had normal intelligence versus 70% of PVT group and 63.3% among those with CLD. The presence of CLD significantly increases the risk of below normal intelligence scale by 34.16 folds while PVT significantly increases that risk by 25.29 folds. (Table 2).

Table (2): Comparison between studied groups regarding Wechsler Intelligence Scale-IV (WIS-IV).

Parameter	CLD group N=60 (%)	PVT group N=30 (%)	Control group N=60 (%)	$\chi 2$	*p*
WIS-IV:					
Extremely low	5 (8.3%)	1 (3.3%)	0 (%)	MC	<0.001
Very low	2 (3.3%)	0 (0%)	0 (0%)		
Low average	15 (25%)	8 (26.7%)	1 (2%)		
Average	37 (61.7%)	21 (70%)	52 (86.7%)		
High average	1 (1.7%)	0 (0%)	7 (11.7%)		
Normal	38 (63.3%)	21 (70%)	59 (98.3%)	MC	<0.001
Below normal	22 (36.7%)	9 (30%)	1 (1.7%)		
COR	34.16	25.29	1 (reference)		
95% CI	4.42 – 264	3.02 – 211.76			

CI : Confidence interval.
CLD: Chronic liver disease.
COR: Crude odds ratio.
MC : Monte Carlo test.
NS : Not statistically significant ($p>0.05$).
PVT: Portal vein thrombosis,
$p\leq0.001$: Is highlystatistically significant.
WIS-IV : Wechsler intelligence scale for children.
$\chi 2$: Chi square test.

There was a statistically significant positive correlation between WIS-IV and alkaline phosphatase, while there was a statistically significant negative correlation between WIS-IV and all of urea, creatinine, serum ferritin and ammonia.

The total number of patients who had a below normal IQ scale was 31 patients (22 in CLD group an 9 in PVT group), But the total number of patients who agreed to continue the treatment regimen through the next 3 months of the study was only 24 patients (16 in the CLD group and 8 patients in the PVT). One of the CLD patients has been died before starting the treatment plan while the families of the other 6 patients refused to involve their children in any treatment trials. 16 patients received lactulose (10 patients with CLD and 6 patients with PVT) while 8 patients received rifaximin (6 patients with CLD and 2 patients with PVT) (Fig. 1).

After treatment with lactulose, there was non statistically significant difference between the 2 patients groups, but at the same time, the patients in both groups were improving. In CLD group (50%)

of the cases have been improved with significant (*p*-value=0.011) while in the PVT group, (66.7%) of the patients became normal with significant (*p*-value=0.034). (Table 3).

There was no statistically significant difference between both groups regarding (WIS-IV) testing neither before nor after the treatment regimen with rifaximin. In CLD group (16.7%) of the cases have been improved with non-significant (*p*-value =0.317) while in the PVT group, none of the patients became normal with also non-significant (*p*-value=1.000) (Table 4).

There was non-statistically significant difference between lactulose and rifaximbin groups regarding (WIS-IV) testing before treatment, however, there was a statistically significant difference between them regarding (WIS-IV) after treatment. All patients before treatment had below normal intelligence while after therapy, 56.3% of the patients within lactulose group have been improved versus 12.5% within rifaximin group. In lactulose group, there was a significant improvement in WIS-IV (*p*-value=0.003) while the rifaximin group showed non-significant change (*p*-value=0.317). (Table 5).

Serum ammonia significantly decreased after treatment in CLD group while there was non statistically significant difference of serum ammonia before and after treatment in PVT group (Table 6).

Table (3): Comparison between patient groups regarding Wechsler Intelligence Scale (WIS-IV) after treatment with lactulose.

Parameter	CLD group N = (10%)	PVT group N = (6%)	χ^2	*p*
WIS-IV before:				
Below normal	10 (100%)	6 (100%)	–	–
WIS-IV after:				
Normal	5 (50%)	4 (66.7%)	0.423	FEp=
Below normal	5 (50%)	2 (33.3%)		0.633
P (Wx)	0.011	0.034		

CLD : Chronic liver disease.
FE : Fisher Exact.
PVT : Portal vein thrombosis.
p (wx) : p for Wilcoxon signed rank test.
WIS-IV : Wechsler intelligence scale for children.
χ^2 : Chi square for trend test.

Table (4): Comparison between patient groups regarding Wechsler Intelligence Scale (WIS-IV) after treatment with rifaximin.

Parameter	CLD group N = (10%)	PVT group N = (6%)	χ^2	*p*
WIS-IV before:				
Below normal	6 (100%)	2 (100%)	–	–
WIS-IV after:				
Normal	1 (16.7%)	0 (0%)	0.381	FEp=
Below normal	5 (66.7%)	2 (100%)		1.000
P (Wx)	0.317	1.000		

CLD : Chronic liver disease.
FE : Fisher Exact.
PVT : Portal vein thrombosis.
p (wx) : p for Wilcoxon signed rank test.
WIS-IV : Wechsler intelligence scale for children.
χ^2 : Chi square for trend test.

Table (5): Comparison between patient groups regarding Wechsler Intelligence Scale (WIS) before and after treatment.

Parameter	Lactulose group N=16 (%) (10CLD+6 PVT)	Rifaximbin group N=8 (%) (6CLD+2PVT)	χ^2	*p*
WIS-IV before:				
Below normal	16 (100%)	8 (100%)	–	–
WIS-IV after:				0.04
Normal	9 (56.3%)	1 (12.5%)	4.2	
Below normal	7 (43.7%)	7 (87.5%)		
P (Wx)	0.003	0.317		

CLD : Chronic liver disease.
FE : Fisher Exact.
PVT : Portal vein thrombosis.
p (wx) : p for Wilcoxon signed rank test.
WIS-IV : Wechsler intelligence scale for children.
χ^2 : Chi square for trend test.

Table (6): Comparison of serum lactate and ammonia between before and after treatment.

		Before Treatment	After Treatment	*t*	*p*
CLD	Lactate Mean ± SD. Median (Min. – Max.)	(n = 60) 2.86±3.06 2.10 (0.60 – 18.30)	(n = 16) 2.90±1.11 2.88 (1.11 – 5.33)	0.828	0.421
	Ammonia Mean ± SD. Median (Min. – Max.)	(n = 60) 45.37±16.55 43.50 (21.0 – 94.0)	(n = 16) 39.13±9.41 42.50 (24.0 – 59.0)	3.624*	0.003*
PVT	Lactate Mean ± SD. Median (Min. – Max.)	(n = 26) 2.91±6.27 1.02 (0.50 – 33.0)	(n = 8) 2.90±1.18 2.53 (1.30 – 4.55)	1.134	0.294
	Ammonia Mean ± SD. Median (Min. – Max.)	(n = 30) 33.73±9.42 33.50 (19.0 – 55.0)	(n = 8) 32.38±6.57 33.50 (22.0 – 40.0)	0.521	0.618

SD: Standard deviation. *t*: Paired *t*-test. *p*: *p*-value. *: Statistically significant at $p \leq 0.05$.

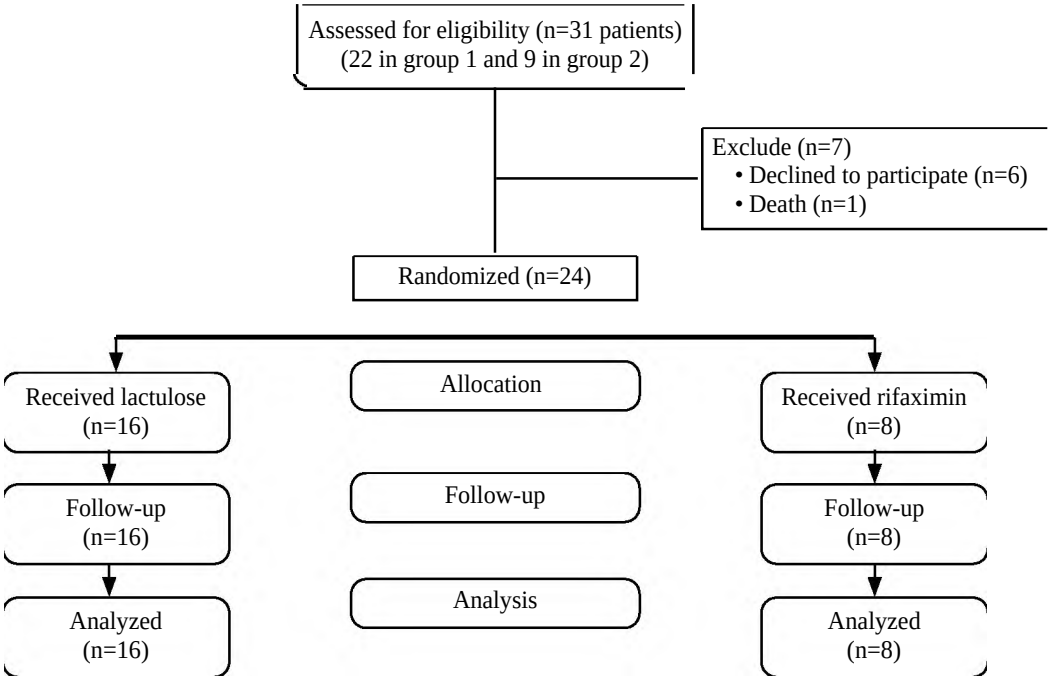

Fig. (1): Consort flow chart.

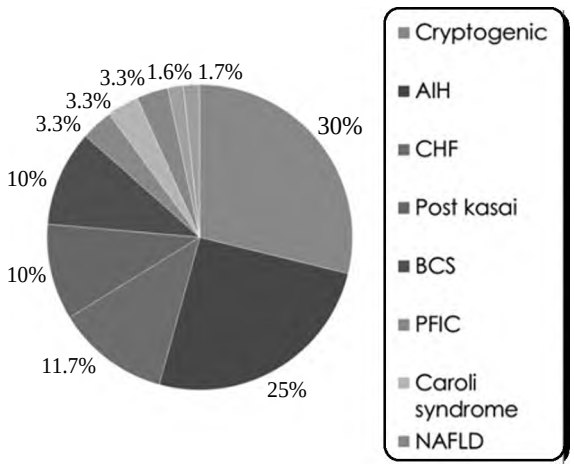

Fig. (2): Simple Pie chart showing the etiology of chronic liver diseases.

AIH: Autoimmune Hepatitis,
BCS: Budd Chiari Syndrome.
CHF: Congenital Hepatic Fibrosis.
NAFLD: Non Alcoholic Fatty Liver Disease.
PFIC: Progressive Familial Intrahepatic Cholestasis.

Discussion

Cognitive functions are group of functions including memory, general intelligence, learning, language, orientation, perception, attention and concentration, judgment. Some medical conditions could lead to cognitive impairment in the children for example epilepsy, cerebral palsy, Diabetes mellitus, β-thalassemia, and CLD *[23-25]*.

Cognitive deficits have tremendous consequences for future development and well-being, especially in children, as cognitive performance impacts daily life as well as educational success. Therefore, cognitive performance should be regarded as equally important measure of therapeutic success in addition to medical outcomes *[26]*.

Liver diseases during early life have pernicious effects on intellectual function and linear growth. Careful monitoring of the mental status of children with early-onset liver disease and aggressive nutritional, medical and psychological support beginning at the time of diagnosis may help reduce delays in growth and mental development *[27]*. Children with early onset of liver disease are at high risk for cognitive impairment *[28]*.

Chronic PVT is a common cause of chronic portal hypertension in children with a development of Porto-systemic shunts through which several neurotoxins can pass to the systemic circulation and bypass the detoxification process by the liver. These neurotoxins affect the neurocognitive functions which can be improved by restoration of porto-portal flow by Rex Shunt *[29-31]*.

Early screening for and identification of neurodevelopmental deficits in children with CLDs should prompt therapies that can maximize developmental outcomes. Further, attention and executive functioning should be closely monitored across disease groups since these domains can significantly impact learning and everyday functioning *[32]*.

We aimed in this study to assess the cognitive function of children with CLD and those with PVT in the absence of clinical signs of encephalopathy then to assess the efficacy of lactulose and rifaximin in improving the cognitive functions of the affected patients. The patients are recruited from the National liver Institute, Menoufia University. The study included 150 children, 60 patients with CLD, 30 patients with PVT and 60 as healthly controls.

The current study showed a statistically significant difference between the studied groups regarding Wechsler intelligence scale (WIS-IV). (98.3%) of healthy control group had normal intelligence versus 70% with PVT group and 63.3% among those with CLD. (Table). Presence of CLD significantly increases the risk of blow normal intelligence by 34.16 folds while PVT significantly increases that risk by 25.29 folds.

Children with a history of CLD may experience increased risk of long-term deficits in cognitive skills and decreased quality of life, even following liver transplantation. Data suggest that CLD during early life has pernicious effects on intellectual function and linear growth. Even asymptomatic liver disease can be associated with altered brain biochemistry and cognition *[33]*.

Factors that appeared to be associated with neurodevelopmental outcomes were variable to some extent. Cognitive outcomes were more impaired in children with metabolic disorders than in children with biliary atresia or other cholestatic diseases. We have to bear in mind that in some liver diseases, for example, the metabolic-induced liver diseases, impaired neurodevelopment might be explained by brain damage because of the underlying disease. Poor adherence to therapy could also influence neurodevelopmental outcome *[34]*.

Apart from hyperammonemia in patients with liver cirrhosis, the increased plasma levels of proinflammatory cytokines in those with CLD, with or without liver cirrhosis, leads to variable degrees of neuro-inflammation which leads to altered neurotransmission and impairment of neurocognitive functions *[35]*.

The results are in agreement with Leung et al., *[32]* who started the first and largest prospective multi-center analysis of neurodevelopmental status in children with inherited cholestatic liver disorders who had not undergone liver transplantation. Full Scale Intelligence Quotient (FSIQ) was analyzed continuously and categorically (>100, 85–99, 70–84, <70). Frequency of FSIQ < 85 (>1 standard deviation [SD] below average) was highest in Alagille syndrome (ALGS) (29%) versus 18.6% in progressive familial intrahepatic cholestasis (PFIC) and 12.8% in alpha 1 antitrypsin deficiency (A1AT), and was greater than expected in ALGS based on normal distribution (29% vs 15.9%, $p = 0.003$).

This is also in agreement with Elisofon et al., *[36]* who assessed in their cross-sectional study the health-related quality of life (HRQOL) in children with AGS in comparison with a normative population. They also examined the effect of AGS-specific morbidities on HRQOL. The study demonstrated that children with AGS had significantly lower HRQOL ($p<0.05$) compared with the normative sample indicating a significant burden of chronic disease in both physical and psychosocial health.

In this study there was non-statistically significant difference between lactulose and rifaximin groups regarding WIS-IV before treatment, however, there was a statistically significant difference

between them regarding WIS-IV after treatment. All patients before treatment had below normal intelligence while after therapy, 56.3% within lactulose group versus 12.5% within rifaximin group had normal intelligence. In lactulose group, there was a significant improvement in WIS-IV while rifaximin group showed non-significant change.

Several treatment modalities that reduce ammonia level have been tried in order to treat this condition, for example, dietary protein manipulation, branched-chain amino acids, L-ornithine L-aspartate, lactulose, and probiotics. Most of the studies of these treatment modalities have found improvement in psychometry, ammonia level, and cerebral edema **[17].** This is in agreement with our results which revealed significant decrease in serum ammonia levels after treatment with lactulose and rifaximin in CLD group with improvement of cognitive function.

Prasad et al., **[17]** measured psychometric performance by of 90 patients with CLD on inclusion into the study and 3 months after treament with lactulose and The study concluded that treatment with lactulose improves both cognitive function in patients with CLD. Sharma et al., **[19]** concluded that lactulose improved MHE in 66% of patients with CLD.

Rifaximin is a novel anti microbiological agent with wide spectrum of activity that has shown promise as an alternative option for hepatic encephalopathy **[37].** It has been reported to decrease the occurrence of HE and also improve cognitive function in studies from Europe and the United States of America **[38].**

Zacharias, et al., **[39]** concluded that compared to placebo/no intervention, rifaximin likely improves health-related quality of life in people with minimal hepatic encephalopathy, and may improve hepatic encephalopathy, particularly in populations with minimal hepatic encephalopathy and when it is used for prevention. Kawaratani et al., **[40]** concluded that the long-term rifaximin treatment was effective and safe for patients with HE, including Child−Pugh C. There were no serious adverse events after rifaximin administration Liver enzymes, renal function, and electrolytes did not change after rifaximin administration.

Conclusions:

Chronic liver diseases and PVT in children significantly increase the risk of cognitive dysfunction which can be improved with lactulose.

References

1- DHOLE S.D., KHER A.S., GHILDIYAL R.G. and TAMBSE M.P. : “Chronic Liver Diseases in Children: Clinical Profile and Histology.” J. Clin. Diagn. Res., 9 (7): Sc04-07, 2015.

2- TAHIR A., MALIK F.R., AHMAD I. and AKHTAR P.: “Aetiological factors of chronic liver disease in children.” J. Ayub. Med. Coll. Abbottabad, 23 (2): 12-14, 2011.

3- HADHOD S.E., MOURAD M.Z., RADWAN A.M. and AHMED O.A.: “Epidemiology and Laboratory Investigations in Children with Chronic Liver Diseases in Sohag University Hospital.” The Egyptian Journal of Hospital Medicine, 85 (2): 4003-4006, 2021.

4- HANIF M., RAZA J., QURESHI H. and ISSANI Z.: “Etiology of chronic liver disease in children.” JPMA. The Journal of the Pakistan Medical Association, 54 (3): 119-122, 2004.

5- VILLAR L.M., AMADO L.A., DE ALMEIDA A.J., DE PAULA V.S., LEWIS-XIMENEZ L.L. and LAMPE E.: “Low Prevalence of Hepatitis B and C Virus Markers among Children and Adolescents.” BioMed Research International, 2014: 324638, 2014.

6- WANG J.-T., ZHAO H.-Y. and LIU Y.-L.: “Portal vein thrombosis.” Hepatobiliary & amp; pancreatic diseases international: HBPD INT, 4 (4): 515-518, 2005.

7- OGREN M., BERGQVIST D., BJÖRCK M., ACOSTA S., ERIKSSON H. and STERNBY N.H.: “Portal vein thrombosis: Prevalence, patient characteristics and lifetime risk: A population study based on 23,796 consecutive autopsies.” World J. Gastroenterol., 12 (13): 2115-2119, 2006.

8- ARDIZZONE G., ARRIGO A., SCHELLINO M.M., STRATTA C., VALZAN S., SKURZAK S., ANDRUETTO P., PANIO A., BALLARIS M.A., LAVEZZO B., SALIZZONI M. and CERUTTI E.: “Neurological Complications of Liver Cirrhosis and Orthotopic Liver Transplant.” Transplantation Proceedings, 38 (3): 789-792, 2006.

9- JOVER R., COMPAÑY L., GUTIÉRREZ A., ZAPATER P., PÉREZ-SERRA J., GIRONA E., APARICIO J.R. and PÉREZ-MATEO M.: “Minimal hepatic encephalopathy and extrapyramidal signs in patients with cirrhosis.” The American Journal of Gastroenterology, 98 (7): 1599-1604, 2003.

10- KULLMANN F., HOLLERBACH S., HOLSTEGE A. and SCHÖLMERICH J.: “Subclinical hepatic encephalopathy: The diagnostic value of evoked potentials.” Journal of Hepatology, 22 (1): 101-110, 1995.

11- LYNN R., EL-GHMARY ABDALLA S. and AL-SHAHOMEE A.A.: “Intelligence in Libya: Norms for the verbal WISC-R.” Mankind Quarterly, 49 (3/4): 292-300, 2009.

12- Abu-Hilal M.M., Al-Baili M.A., Sartawi A., Abdel-Fattah F. and AL-QARYOUTI I.A.: “Psychometric Properties of the Wechsler Abbreviated Scale of Intelligence (WASI) with an Arab Sample of School Students.” Individual Differences Research, 9 (4), 2011.

13- WECHSLER D.: “Wechsler preschool and primary scale of intelligence—fourth edition.” The Psychological Corporation San Antonio, TX, 2012.

14- EL-KARAKSY H.M., AFIFI O., BAKRY A., KADER A.A. and SABER N.: “A pilot study using lactulose in manage-

ment of minimal hepatic encephalopathy in children with extrahepatic portal vein obstruction." World Journal of Pediatrics, 13: 70-75, 2017.

15- EL-SHABRAWI M.H.F. and KAMAL N.M.: "Medical Management of Chronic Liver Diseases (CLD) in Children (Part II)." Pediatric Drugs, 13 (6): 371-383, 2011.

16- DHIMAN R.K., SAWHNEY I.M.S., CHAWLA Y.K., DAS G., RAM S. and DILAWARI J.B.: "Efficacy of lactulose in cirrhotic patients with subclinical hepatic encephalopathy." Digestive diseases and sciences, 45: 1549-1552, 2000.

17- PRASAD S., DHIMAN R.K., DUSEJA A., CHAWLA Y.K., SHARMA A. and AGARWAL R.: "Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy." Hepatology, 45 (3): 549-559, 2007.

18- SHARMA B.C., SHARMA P., AGRAWAL A. and SARIN S.K.: "Secondary prophylaxis of hepatic encephalopathy: An open-label randomized controlled trial of lactulose versus placebo." Gastroenterology, 137 (3): 885-891, 891. e881, 2009.

19- SHARMA B.C., SHARMA P., LUNIA M.K., SRIVASTAVA S., GOYAL R. and SARIN S.: "A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy." Official journal of the American College of Gastroenterology| ACG, 108 (9): 1458-1463, 2013.

20- Yokoyama K., FukudaH. , Yamauchi R., Higashi M., Miyayama T., T. Higashi, Y. Uchida, K. Shibata, N. Tsuchiya, A. Fukunaga, K. Umeda, K. Takata, T. Tanaka, S. Shakado, S. Sakisaka and F. Hirai (2022). "Long-Term Effects of Rifaximin on Patients with Hepatic Encephalopathy: Its Possible Effects on the Improvement in the Blood Ammonia Concentration Levels, Hepatic Spare Ability and Refractory Ascites." Medicina (Kaunas) 58(9).

23- SHEHATA G.A. and BATEH A.E.-A.M.: "Cognitive function, mood, behavioral aspects, and personality traits of adult males with idiopathic epilepsy." Epilepsy & Behavior, 14 (1): 121-124, 2009.

24- SHEHATA G. and ELTAYEB A.: "Cognitive function and event-related potentials in children with type 1 diabetes mellitus." Journal of Child Neurology, 25 (4): 469-474, 2010.

25- EL-TALLAWY H.N., FARGHALY W.M., SHEHATA G.A., BADRY R. and RAGEH T.A.: "Epileptic and cognitive changes in children with cerebral palsy: An Egyptian study." Neuropsychiatric disease and treatment, 971-975, 2014.

26- KALLER T., LANGGUTH N., PETERMANN F., GANSCHOW R., NASHAN B. and SCHULZ K.H.: "Cognitive Performance in Pediatric Liver Transplant Recipients." American Journal of Transplantation, 13 (11): 2956-2965, 2013.

27- STEWART S.M., UAUY R., KENNARD B.D., WALLER D.A., BENSER M. and ANDREWS W.S.: "Mental Development and Growth in Children With Chronic Liver Disease of Early and Late Onset." Pediatrics, 82 (2): 167-172, 1988.

28. STEWART S.M., CAMPBELL R.A., McCALLON D., WALLER D.A. and ANDREWS W.S.: "Cognitive Patterns in School-Age Children with End-Stage Liver Disease." Journal of Developmental & Behavioral Pediatrics, 13 (5): 331-338, 1992.

29- MACK, C.L., ZELKO F.A., LOKAR J., SUPERINA R., ALONSO E.M., BLEI A.T. and WHITINGTON P.F.: "Surgically restoring portal blood flow to the liver in children with primary extrahepatic portal vein thrombosis improves fluid neurocognitive ability." Pediatrics, 117 (3): e405-e412, 2006.

30- MÍNGUEZ B., GARCÍA-PAGÁN J.C., BOSCH J., TURNES J., ALONSO J., ROVIRA A. and CÓRDOBA J.: "Noncirrhotic portal vein thrombosis exhibits neuropsychological and MR changes consistent with minimal hepatic encephalopathy." Hepatology, 43 (4): 707-714, 2006.

31- SEIJO S. and PLESSIER A.: "Noncirrhotic nontumoral portal vein thrombosis." Clinical Liver Disease, 3 (6): 118, 2014.

32- LEUNG D.H., SORENSEN L.G., YE W., HAWTHORNE K., NG V.L., LOOMES K.M., FREDERICKS E.M., ALONSO E.M., HEUBI J.E., HORSLEN S.P., KARPEN S.J., MOLLESTON J.P., ROSENTHAL P., SOKOL R.J., SQUIRES R.H., WANG K.S., KAMATH B.M. and MAGEE J.C.: "Neurodevelopmental Outcomes in Children With Inherited Liver Disease and Native Liver." J. Pediatr. Gastroenterol. Nutr., 74 (1): 96-103, 2022.

33- TALCOTT J.B., BEATH S.V., PATEL T., GRIFFITHS G. and KELLY D. A.: "Long-term Effects of Cholestatic Liver Disease in Childhood on Neuropsychological Outcomes and Neurochemistry." Journal of Pediatric Gastroenterology and Nutrition, 69 (2): 145-151, 2019.

34- GILMOUR S., ADKINS R., LIDDELL G., JHANGRI G. and ROBERTSON C.M.: "Assessment of psychoeducational outcomes after pediatric liver transplant." American Journal of Transplantation, 9 (2): 294-300, 2009.

35- MONTOLIU C., LLANSOLA M. and FELIPO V.: "Neuroinflammation and neurological alterations in chronic liver diseases." Neuroimmunology and Neuroinflammation, 2: 138-144, 2015.

36- ELISOFON S.A., EMERICK K.M., SINACORE J.M. and ALONSO E.M.: "Health status of patients with Alagille syndrome." J. Pediatr. Gastroenterol. Nutr., 51 (6): 759-765, 2010.

37- AHIRE K. and SONAWALE A.: "Comparison of Rifaximin Plus Lactulose with the Lactulose Alone for the Treatment of Hepatic Encephalopathy." J. Assoc. Physicians India, 65 (8): 42-46, 2017.

38- NISHIDA S., HAMADA K. , NISHINO N. , FUKUSHIMA D., KOYANAGI R., HORIKAWA Y., SHIWA Y. and SAITOH S.: "Efficacy of long-term rifaximin treatment for hepatic encephalopathy in the Japanese." World J. Hepatol., 11 (6): 531-541, 2019.

39- ZACHARIAS H.D., KAMEL F., TAN J., KIMER N., GLUUD L.L. and MORGAN M.Y.: "Rifaximin for prevention and treatment of hepatic encephalopathy in people with cirrhosis." Cochrane Database Syst Rev., 7 (7): Cd011585, 2023.

40- KAWARATANI H., KONDO Y., TATSUMI R., KAWABE N., TANABE N., SAKAMAKI A., OKUMOTO K., UCHIDA Y., ENDO K., KAWAGUCHI T., OIKAWA T., ISHIZU Y., HIGE S., TAKAMI T., TERAI S., UENO Y., MOCHIDA S., TAKIKAWA Y. , TORIMURA T., MATSUURA T., ISHIGAMI M., KOIKE K. and YOSHIJI H.: "Long-Term Efficacy and Safety of Rifaximin in Japanese Patients with Hepatic Encephalopathy: A Multicenter Retrospective Study." J. Clin. Med., 11 (6), 2022.

اعتلال الوظائف الادراكية فى الاطفال المصابين بالامراض الكبدية المزمنة والاطفال المصابين بالجلطات المزمنة بالوريد الكبدى البابى

تعتبر الامراض الكبدية المزمنة من الامراض الشائعة لدى الاطفال والتى قد تتسبب فى زيادة معدل الوفيات. وعادة ما يتاثر الجهاز العصبى فى حال الاصابة بالامراض الكبدية المزمنة نتيجة ارتفاع مستوى الامونيا وحمض اللاكتيك ومعاملات الالتهاب فى الدم.كما قد تتسبب الجلطات بالوريد الكبدى البابى فى مرور السموم العصبية مباشرة الى الدورة الدموية دون المرور بالكبد لتنقية الدم من هذه السموم.

الهدف من البحث: يهدف هذا البحث الى تقييم الوظائف الادراكية والمعرفية فى الاطفال المصابين بالامراض الكبدية المزمنة والاطفال المصابين بالجلطات المزمنة بالوريد الكبدى البابى ومعالجتهم.

ادوات وطرق البحث: تم اجراء هذا البحث على ١٥٠ طفل وتم تقسيمهم الى ثلاث مجموعات على النحو التالى:

المجموعة الاولى: شملت ٦٠ حالة من الاطفال ذوى الامراض الكبدية المزمنة وذلك من جناح المرضى الداخلى والعيادة الخارجية بقسم الاطفال والجهاز الهضمى والتغذية بمعهد الكبد القومى-جامعة المنوفية

المجموعة الثانية: شملت ٣٠ حالة من الاطفال المصابين بالجلطات المزمنة بالوريد الكبدى البابى من جناح المرضى الداخلى والعيادة الخارجية فى قسم الاطفال والجهاز الهضمى والتغذية بمعهد الكبد القومى-جامعة المنوفية.

المجموعة الثالثة: ضمت ٦٠ طفل يتمتعون بصحة جيدة.

خضع جميع الاطفال لمايلى:

١- أخذ التاريخ المرضىبدقة.

٢- الفحص السريرى والاكلينيكى الشامل.

٣- مقياس ويكسلر للذكاء فى الاطفال النسخة العربية الطبعة الرابعة (٢٠٠٣).

تم استبعاد الاطفال المصابين بغيبوبة كبدية او الذين تعرضوا للاعتلال الكبدى الدماغى والاطفال المصابين باضطرابات نفسية وعصبية والاطفال الذين يعانون من مرض ويلسون . كما تم استبعاد الاطفال الذين يعانون من امراض الدم المزمنة مثل انيميا البحر المتوسط والاطفال الذين يتعاطون المطهرات المعوية اثناء فترة البحث.

تمت الدراسة على مرحلتين: المرحلة الاولى شملت تقييم الاداء المعرفى والادراكى للاطفال قيد البحث. والمرحلة الثانية شملت معالجة الخلل الادراكى فى الاطفال المصابين بواسطة عقار اللاكتيلوز او الريفاكسمين لمدة ٣ اشهر واعادة تقييم الاداء المعرفى بعد انتهاء فترة العلاج.

وقد اظهرت النتائج وجود فرق ذو دلالة احصائية بين المجموعات قيد البحث فيما يتعلق بمقياس ويكسلر للذكاء . كما اظهرت كفاءة عقار اللاكتيلوز فى تحسن الحالة الادراكية للمصابين.