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Electroencephalogram in Cirrhotic Children without Clinical Encephalopathy

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Abstract

Background: This study aimed to determine the electroencephalogram (EEG) findings in children with hepatic cirrhosis, which occurred without clinical encephalopathy.

Methods: The present study was conducted in an observational-analytical way at Amir-al-momenin Zabol Hospital, Zabol University of Medical Sciences, Iran. In this study, 50 children with hepatic cirrhosis without encephalopathy symptoms and 50 healthy children were evaluated and studied regarding abnormal findings in EEG. Finally, the data were analyzed using SPSS V22 software.

Results: The mean and standard deviation of the age of the studied population was 57.6 ± 76.17 months. Out of a total of 50 children with hepatic cirrhosis, 21 children (42%) had abnormal findings in EEG, while none of the children in the healthy group had abnormal findings in EEG. There was a significant relationship between abnormal EEG findings and older age (P=0.001), underlying autoimmune hepatitis disease (P=0.011), and abnormal (increased) serum levels of Alanineamino Transferase (ALT) (P=0.030) and aspartate amino transferase (AST) (P=0.010) enzymes. Children with cirrhosis who had abnormal EEG findings had a higher average Pediatric End-Stage Liver Disease (PELD) score (18.1 ± 4.1) than patients with normal EEG findings (17.2 ± 3.7), but these findings were not statistically significant and noticeable (P=0.073). The sensitivity of EEG for predicting the severity of cirrhosis was estimated to be 70% and its specificity was 65%.

Conclusion: The results of the present study indicated that the higher sensitivity of EEG compared to the specificity in predicting the severity of cirrhosis indicates that EEG is more useful to rule out severe cirrhosis or to screen cirrhosis patients at risk of deterioration than to confirm its diagnosis.

Key Words: Child, Electroencephalography, Hepatic cirrhosis.

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1- INTRODUCTION

Hepatic cirrhosis is the final stage of chronic liver diseases with different etiologies, including more than one million yearly deaths worldwide (1). Hepatic cirrhosis is an important health problem that only in 2017, about 160 million people suffered from it. Today, the prevalence of this disease is increasing, and the highest annual incidence is in Eastern Asia (2, 3). Among the most common causes of chronic liver disease in children are neonatal liver disease, alpha-1-antitrypsin deficiency, autoimmune liver diseases, cystic fibrosis, chronic viral hepatitis (hepatitis B), non-alcoholic fatty liver disease (NAFLD), metabolic liver diseases (galactosemia, fructosemia), and Wilson's disease (4-7).

Hepatic cirrhosis often accompanies portal hypertension, which is the most common cause of gastroesophageal varices, with a prevalence of 40-85% in cirrhotic patients. Also, visceral bleeding is one of the severe complications associated with cirrhosis and portal hypertension, with a prevalence of 20-76% (8). However, cognitive dysfunction is also mentioned in this disease. Psychological function in hepatic cirrhosis is related to brain atrophy. It has been reported that cerebral atrophy and Electroencephalography (EEG) changes can independently predict cognitive dysfunction in patients with cirrhosis (9).

EEG is a sensitive and fast method to identify brain disorders by recording brain electrical signals. Evidence has shown that EEG can be used as a sensitive and reliable method for screening brain and nerve disorders (10). Many studies have mentioned EEG abnormality as a primary diagnostic sign for brain dysfunction in the absence of Overt Hepatic Encephalopathy (OHE) or Minimal Hepatic Encephalopathy (MHE)(11, 12). MHE is the mildest form of hepatic encephalopathy in which patients do not have obvious symptoms; but may have subtle and mild motor deficits along with cognitive impairment and impairment in neuropsychological tests. Studies have shown that more than 50% of children with chronic liver disease have MHE, which in turn, has a negative effect on brain function and their activity in school. So these cases suggest the need for early identification and treatment (13, 14). The evidence shows that even in milder types of HE, the quality of life pattern, sleep and wakefulness pattern, balance, and interpersonal relationships of the patient are affected (15). However, although several strategies are available to describe HE in the early stages, there is limited data to predict OHE, and many of them are impractical in clinical practice (16). However, some studies have shown that performing EEG as patient follow-up has a prognostic value for the occurrence of OHE attacks and mortality in cirrhotic patients (17). Since in patients with hepatic cirrhosis, changes in EEG are significantly associated with the severity of liver disease and the occurrence of HE, it may be possible to use EEG in determining the prognosis of patients (18).

However, studies have also shown that despite EEG being widely studied and used in clinical practice, we see typical EEG changes only in patients with severe HE; so this clinical tool is not useful for the early detection of HE. It should also be noted that these changes are not specific to HE and are also observed in other metabolic diseases, such as hyponatremia and uremic encephalopathy (19, 20).

Therefore, the present study was conducted with the aim of investigating EEG changes in children with hepatic cirrhosis and without clinical encephalopathy.

2- MATERIALS AND METHODS

2-1. Design and Participants

The present study was conducted in an observational-analytical manner at

Amir-al-momenin Hospital, Zabol University of Medical Sciences, Zabol, Iran, from March 2022 to January 2022. All children with hepatic cirrhosis who visited the hospital's pediatric clinic during this period were evaluated.

2-1.1. Inclusion and exclusion criteria

Inclusion criteria included age groups under 18 years, hepatic cirrhosis confirmed based on clinical examinations, biochemical findings, ultrasound and liver biopsy, absence of symptoms in favor of hepatic encephalopathy, and personal consent of the patient to perform EEG.

Children with chronic pulmonary diseases or other pulmonary diseases with respiratory failure (PaO2 < 60 mmHg and/or PaCo2 > 50 mmHg), renal failure (serum creatinine level > 200 µmol/L), heart disease of any cause, history of focal neurological episodes or any type of neurological disease, psychiatric diseases, use of neuropsychiatric drugs in the last 6 months, various metabolic disorders such as hyponatremia and uremic encephalopathy, and lack of consent for EEG were excluded from the study.

2-2. Procedure

Finally, 50 children with hepatic cirrhosis were included in the study. At the same time, 50 healthy children were also evaluated in the control group. The Pediatric End-Stage Liver Disease (PELD) scoring system was used to determine disease severity and predict survival in patients. PELD score was calculated based on age, bilirubin, albumin, and INR for each patient. Patients with a score of 20 and above were included in the severe cirrhosis group, and patients with a score below 20 were included in the non-severe cirrhosis group. Also, the project manager collected the demographic and anthropometric information, comorbidities, necessary laboratory information, and supplementary information of the patients using the prepared checklist and entered them into the questionnaire.

2-2.1. EEG assessment

EEG was performed in rest condition while the patients were awake and closed-eyes using Neurofax EEG-4518, as previously described. The 10-20 international system was applied. Five electrodes were attached to the skin surface at T3, T4, O1, O2, and Cz locations. The assessment was carried out at 0.53-35 Hz frequency for 100 seconds.

2-4. Data Analysis

After collecting the data, SPSS 22 software was implemented to describe the data in frequency format, percentage, the mean, and standard deviation. Chi-square and Independent Sample Student t-test were used for inferential statistics. A significance level of 0.05 was considered.

3- RESULTS

In the present study, 50 children with hepatic cirrhosis were studied in the intervention group and 50 healthy children in the control group.

The mean and standard deviation of the age of children with hepatic cirrhosis and healthy children were 65.4 ± 83.0 and 48.3 ± 69.2 months, respectively, which were not significantly different. Also, 24 children with hepatic cirrhosis and 18 healthy children were boys. The mean and standard deviation of the PELD score among children with hepatic cirrhosis was 17.6 ± 3.8. The lowest and highest PELD scores were 12 and 27, respectively. The results of the study showed that the most common etiologies of hepatic cirrhosis in the studied children were genetic-metabolic diseases (13 patients, 26%), Wilson disease (11 patients, 22%), and autoimmune hepatitis (10 patients, 20%). Also, 7 patients (14%) were diagnosed with cryptogenic cirrhosis, 6 patients (12%) were diagnosed with biliary atresia, and finally, 3 patients (6%) were

diagnosed with pancreatic cancer with metastasis to the liver. Also, in this study, it was found that the serum levels of Aspartate-amino Transferase (AST), Alanine-amino Transferase (ALT), Alkaline Phosphatase (ALK P), total bilirubin, direct bilirubin, albumin, total protein, Prothrombin Time (PT), and Partial Thromboplastin Time (PTT) were significantly different between cirrhotic and healthy children (Table 1).

Table-1: Baseline and demographic characteristics of children with cirrhosis and their controls

Parameters	Cirrhotic Children (N=50)		Healthy Children (N=50)		P Value
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	
Age (mon)	83.0(65.4)	2-204	69.2(48.3)	2-156	0.233
PELD score	17.6(3.8)	12-27			
Aspartate amino transferase (IU/L)	232.5(121.8)	38-419	32.5(9.6)	20 – 45	0.001
Alanine amino transferase (IU/L)	171.3(116)	42-366	23.6(7.5)	12 – 38	< 0.001
Alkaline phosphatase (IU/L)	877.6(619.5)	141-2060	389(123.8)	211 - 575	< 0.001
Total bilirubin (mg/dL)	16.2(14.3)	1.5-39	0.9 (0.4)	0.5 – 2	< 0.001
Direct bilirubin (mg/dL)	5.7(5.7)	0.7-15	0.29 (0.25)	0.1 - 1	< 0.001
Albumin (g/dL)	2.8(0.6)	1.7-3.8	4.4 (0.5)	3.2 - 5	0.027
Total protein (g/dL)	5.0(0.8)	4-6.3	7 (0.8)	5.8 - 8.2	0.006
Prothrombin time (s)	27.6(9.3)	15-41	12.6 (1.07)	10 - 14	0.04
Partial thromboplastin time (s)	49.8(12.1)	28-66	33.7 (4.9)	30 - 45	0.01

Out of a total of 50 children with hepatic cirrhosis, 21 children (42%) had abnormal findings in EEG, while none of the children in the healthy group had abnormal findings in EEG. Irregular spikes along with alpha waves were the most common EEG findings reported in 8 patients (16%). After that, fast waves (4 patients, 8%), slow and high voltage (4 patients, 8%), and slow with frequent epileptic discharge (2 patients, 4%) were the most frequent among the EEG findings in the studied patients. Also, irregular spikes along with delta and triphasic waves were observed in 4% and 2% of children with hepatic cirrhosis, respectively.

Patients with abnormal EEG patterns had a significantly higher average age (62.1±117.19 months) than patients with normal EEG (56.9±58.3) (P=0.001). It was also observed that among children with abnormal EEG findings, there were 16 children (76.1%) at 7 years old and older, and only 5 children (23.8%) were less than 7 years old. Abnormal EEG findings had no statistically significant relationship with patients' gender (P=0.578). Children with cirrhosis who had abnormal EEG findings had a higher average PELD score (18.1±4.1) than patients with normal EEG findings (17.2±3.7). Also, the results showed that 70% (7 patients) of patients with a PELD score of 20 and higher had abnormal EEG findings, but these findings were not statistically significant (P=0.073). The sensitivity of EEG for predicting the

severity of cirrhosis was estimated to be 70% and its specificity was 65%.

A significant percentage of patients with abnormal EEG findings had abnormal serum levels of AST (13 patients, 61.9%) and ALT (47.6%). The mean serum levels of AST and ALT in patients with abnormal EEG findings (140.3 ± 256.5 and 135.3 ± 190.5) were significantly higher than those in patients with normal EEG findings (135.4 ± 215.1 and 130.5 ± 157.3) (P=0.010 and P=0.030). Also, the results indicated that there is a statistically significant relationship between abnormal EEG findings and serum levels of ALK P (P=0.464), Bili T (P=0.774), D (P=0.774), and Alb (P=0.686). T.Pro (P=0.549), PT (P=0.171), and PTT (0.243) did not exist (Table 2).

Table-2: A Comparison of different clinical and laboratory parameters between cirrhotic children with normal and abnormal EEG profiles

Parameters		Electroencephalography		P value
		Normal(N=29)	Abnormal(N=21)	
Age (years)	7 >	21	5(23.8%)	0.001
	7 ≤	8	16(76.1%)	
Sex	Male	15(51.7%)	9(42.8%)	0.578
	Female	14(48.2%)	12(57.1%)	
PELD score	20 >	26(89.6%)	14(66.6%)	0.073
	20 ≤	3(10.3%)	7(33.3%)	
Aspartate amino transferase (IU/L)	Normal	22(75.8%)	8(38.09%)	0.010
	Abnormal	7(24.1%)	13(61.9%)	
Alanine amino transferase (IU/L)	Normal	24(82.7%)T	11(52.3%)	0.030
	Abnormal	5(17.2%)	10(47.6%)	
Alkaline phosphatase (IU/L)	Normal	25(86.2%)	16(76.1%)	0.464
	Abnormal	4(13.7%)	5(23.8%)	
Albumin (g/dL)	Normal	16(55.1%)	14(66.6%)	0.686
	Abnormal	13(44.8%)	7(33.3%)	
Total protein (g/dL)	Normal	24(82.7%)	18(85.7%)	0.549
	Abnormal	5(17.2%)	3(14.2%)	
Total bilirubin (mg/dL)	Normal	18(62.06%)	14(66.6%)	0.774
	Abnormal	11(37.9%)	7(33.3%)	
Direct bilirubin (mg/dL)	Normal	18(62.06%)	14(66.6%)	0.774
	Abnormal	11(37.9%)	7(33.3%)	
Prothrombin time (s)	Normal	24(82.7%)	17(80.9%)	0.117
	Abnormal	5(17.2%)	4(19.04%)	
Partial thromboplastin time (s)	Normal	27 (93.1%)	18(85.7%)	0.243
	Abnormal	2(6.8%)	3(14.2%)	

By examining the etiology of hepatic cirrhosis in the studied patients, it was found that among the patients with abnormal EEG findings, 8 patients (38%) were suffering from Autoimmune Hepatitis. In fact, 80% of the patients with autoimmune hepatitis had abnormal findings in EEG (P=0.011). No significant statistical relationship was observed between other types of hepatic cirrhosis etiology and abnormal EEG findings (Table 3).

Table-3: A comparison of different etiology of cirrhosis between cirrhotic children with normal and abnormal EEG profiles

Etiology of Cirrhosis		Electroencephalography		P value
		Normal (N=29)	Abnormal (N=21)	
Genetic-Metabolic diseases	YES	11(37.9%)	2(9.5%)	0.095
	NO	18(62.06%)	19(90.4%)	
Wilson	YES	5(17.2%)	6(28.5%)	0.491
	NO	24(82.7%)	15(71.4%)	
Autoimmune Hepatitis	YES	2(6.8%)	8(38.09%)	0.011
	NO	27(93.1%)	13(61.9%)	
Cryptogenic cirrhosis	YES	5(17.2%)	2(9.5%)	0.684
	NO	24(82.7%)	19(90.4%)	
Biliary atresia	YES	5(17.2%)	1(4.7%)	0.380
	NO	24(82.7%)	20(95.2%)	
Pancreatic cancer with metastasis to the liver	YES	1(3.4%)	2(9.5%)	0.565
	NO	28(96.5%)	19(90.4%)	

4- DISCUSSION

Hepatic cirrhosis is one of the leading causes of hospitalization and death in children, and prevention of progressive liver damages such as HE is of great importance in them. In addition, Overt HE, SHE, and MHE are stages of HE that can only be diagnosed with psychometric and neurophysiological tests, and their early diagnosis and treatment can improve the daily functioning of the patients (21, 22). Therefore, this study aimed to determine the EEG findings in children with hepatic cirrhosis without clinical encephalopathy.

Many studies have shown that EEG is a targeted and quantitative tool for diagnosing and evaluating treatment response in patients with hepatic cirrhosis with MHE, which improves the diagnosis of MHE by providing quantitative parameters of brain dysfunction (23). Little information is available on EEG findings in children with hepatic cirrhosis. In the present study, out of a total of 50 children with hepatic cirrhosis, 21 children (42%) had abnormal EEG findings. The results of this study indicated that abnormal EEG findings in children with hepatic cirrhosis were significantly related to older age, underlying autoimmune hepatitis, and abnormal and elevated serum levels of liver enzymes AST and ALT. In line with the findings of the present study, Amodio et al. (17), in their study, evaluated 296 patients with hepatic cirrhosis and showed that abnormal EEG findings were observed in 38% of patients; and there was no significant relationship between abnormal EEG findings and the etiology of hepatic cirrhosis. In this study, EEG was introduced as a suitable tool to predict the occurrence of overt HE and mortality. Also, Quero et al. (24), in their study, showed the frequency of abnormal EEG findings in patients with hepatic cirrhosis to be about 17%. In this study, the occurrence of SHE and abnormal EEG findings had a significant relationship with the severity of liver disease and the older age of the patients. Formentin et al. (25) also showed in their study that neuro-psychological tests, including EEG, can play a significant role in predicting HE. In this study, it was observed that patients with a previous history of HE had significantly more severe liver dysfunction.

EEG findings in children with hepatic cirrhosis showed that irregular spikes along with alpha waves (8 patients, 16%)

were the most common abnormal EEG findings. Also, slowing of Alpha waves was observed in 6 patients (12%). 8% of patients (4 patients) had a fast background, and 4% of patients (2 patients) had epileptiform discharges.

Consistent with the above findings, Patel et al. (26) showed in their study that the changes in frequency and amplitude of alpha waves in patients with hepatic cirrhosis were significantly higher than those in the control group. In this study, it was found that slowing of Alpha waves on EEG can be considered as the first finding of MHE. In fact, one of the earliest findings of HE is the loss of the alpha rhythm frequency, which gradually leads to the onset of slower rhythms. Marchetti et al. (18) also showed that patients with overt HE had a much slower average frequency than patients with MHE. Also, Assem et al. (27) showed in their evaluations that the frequency of EEG slowing in patients with hepatic cirrhosis was about 30%, and a significant relationship between the severity of EEG slowing, and the duration and severity of liver disease was observed.

Generally, EEG changes in HE may be in the form of increased amplitude, low-frequency waves, and triphasic waves. However, in the present study, only 2% of patients had triphasic waves.

Despite the mentioned cases, reports have been presented on the manifestation of HE in the form of generalized seizures (28, 29). The frequency of non-convulsive status epilepticus in patients with hepatic cirrhosis is rare; however, evidence has shown that it is important to consider the possibility of non-convulsive status epilepticus, especially in HE with high degrees (30-32). Also, studies have shown that cerebral dysrhythmias in EEG often appear as focal or generalized spikes/sharp wave discharges, which are similar to epileptiform discharges. Mitra et al. (33) also showed in their study that the frequency of cerebral dysrhythmias in patients with hepatic cirrhosis was about 24%.

Children with hepatic cirrhosis who had abnormal EEG findings had a higher mean PELD score (18.1 ± 4.1) than patients with normal EEG findings (17.2 ± 3.7). Also, the results showed that 70% (7 patients) of patients with PELD scores, 20 and higher, had abnormal EEG findings, but these findings were not statistically significant.

Mitra et al. (33) by examining patients with hepatic cirrhosis and HE, showed that EEG findings could have an effective relationship with the severity of liver disease, and therefore it was found that patients with abnormal EEG had a significantly higher Model for End-stage Liver Disease (MELD) scale than patients with EEG was normal. Dasgupta et al. (34) also showed that EEG as an available and low-cost diagnostic tool could be used in MHE and has a positive relationship with the severity of CTP-Class and higher MELD scores. Also, Montagnese et al. (35) revealed that performing EEG in patients with hepatic cirrhosis in combination with MELD can increase the prognostic accuracy of the MELD score; therefore, combining EEG and MELD score in patients with hepatic cirrhosis can be a suitable option.

Contrary to the studies mentioned above, Yoo et al. (36) evaluating patients with hepatic cirrhosis, showed that there is a weak correlation between MELD score and HE; in fact, in many patients with HE and ascites, if only based on MELD score used to receive a liver transplant, they may not succeed in receiving a liver transplant in time.

5- CONCLUSION

Overall, this study indicated that although with this limited sample size, we did not see a high specificity of EEG, but the higher sensitivity of EEG compared to the specificity in predicting the severity of

cirrhosis indicates that EEG is more useful to rule out severe cirrhosis or to screen cirrhosis patients at risk of deterioration than to confirm its diagnosis.

Also, the results of the present study indicated that performing EEG as a useful and targeted tool along with clinical examinations and biochemical tests can be a suitable option for evaluating and following up children with hepatic cirrhosis.

6- ETHICAL CONSIDERATIONS

This project was approved by the ethics committee of Zabol University of Medical Sciences. The methodology of the study was explained to all subjects and/or parents. And their written consent was obtained.

7- ACKNOWLEDGEMENTS

We would like to thank the patients and their families.

8- CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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