Optic Nerve Sheath Diameter Measured by Trans-Cranial Ultrasound in Children with Acute Liver Failure

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ABSTRACT

Background: The early diagnosis of elevated intracranial pressure (ICP) improves the prognosis of acute liver failure (ALF). Invasive monitoring (intracranial bolts) is the gold standard approach for measuring ICP, however it comes with problems. **Objective:** This study aimed to evaluate the role of bedside, ultrasound (US) guided measurement of optic nerve sheath diameter (ONSD) in ALF children. **Methods:** 36 ALF and 21 healthy children (0-18 years) were enrolled. All patients had undergone full history taking, thorough clinical examination, and routine investigations. ONSD was measured for each on admission, with any change of consciousness and at recovery in ALF, and once in controls. **Results:** Both groups were age- and sex-matched. The ALF group showed significant increase in ONSD than in healthy controls (P 0.008). On admission, the mean of ONSD in resolved group (4.13 ± 0.573 mm) was lower than that of died group (4.57 ± 0.64 mm) but without statistical significance (P = 0.082). ONSD before discharge significantly increased in died group 5.07 ± 0.44 mm than in living group (3.98 ± 0.354 mm, P<0.0001). ONSD was significantly higher in ALF patients with disturbed conscious level (5.16 ± 0.45 mm) than in conscious patients (4.007 ± 0.34 mm, P <0.0001). ONSD at a cut-off value of > 4.82 mm showed accuracy of 88.7% in discriminating between resolving and vanishing ALF patients (P =<0.0001)**. Conclusions:** ONSD is a safe bedside method that may be used to serially monitor children with ALF. It is an excellent predictor of patient outcomes.

Keywords: ALF, ICP, ONSD.

INTRODUCTION

ALF in pediatric is a complicated, rare disease that can quickly lead to multisystem organ failure and death. Acute hepatocellular damage or death that causes a rapid loss of hepatic function, multisystem involvement, and ultimately failure are its defining characteristics [(1)]. In the absence of an urgent liver transplant, mortality remains high (50%) even with the best medical care [(2)]. In patients with ALF, cerebral edoema (CE)-related intracranial hypertension (ICH) is one of the comorbidities and leading causes of death. Timely intervention and improved result are dependent on the early diagnosis of ICH, which is a sign of brain edoema [(3)]. The most effective way to track ICP is invasive monitoring, or intracranial bolts, however this approach is not without risk, particularly in ALF due to underlying coagulation disorders. Although non-invasive methods such as head CT scans and MRIs have been used to diagnose ICP, it can be challenging to get critically ill patients to radiology suites [(4)]. Ultrasonography (USG) has been employed as a non-invasive technique for measuring ICP by measuring optic ONSD. Leptomeninges, which are contiguous with the dura mater, envelop the optic nerve. Any change in ICP causes distension and an increase in ONSD because it is instantly reflected to the potential space underneath the ONS. In the front portion of the nerve directly behind the globe, this alteration is more pronounced [(5)]**.** The current study's objective was to evaluate the role of bedside, US guided measurement of ONSD in pediatric ALF.

PATIENTS AND METHODS

Study Population: This study involved 36 children with ALF. ALF was diagnosed according to the pediatric ALF study group (PALFSG) criteria. Patients were recruited from the Department of Pediatric Hepatology, Gastroenterology and Nutrition, National Liver Institute, Menoufia University, Egypt. Another group of healthy children (n =21) served as healthy controls.

Clinical evaluation: All patients had undergone full history taking, thorough clinical examination, and 3.0623 routine investigations. Specific investigations according to suspected etiology were done. Routine investigations included T. bilirubin and D. bilirubin, total serum proteins, albumin, ALT, AST, ALP, GGT, PT, CBC, urea, creatinine, blood electrolytes (Na, K & Ca), serum ammonia, and lactate. Viral markers for hepatotropic (HAV, HBV, HCV & HEV) and non-hepatotropic (EBV, CMV & herps) viruses, abdominal ultrasound and Doppler examination were done on admission. The clinical symptoms of ICH and the grade of HE were assessed at arrival and then every 12 hours until the patient either recovered or passed away. The West Haven Classification was used to grade him. Also Glasgow coma scale was assessed for patients. The apparently healthy controls were investigated for serum albumin, ALT, AST, PT and CBC.

ONSD measurement: An experienced radiologist used a SonoScape E1EXP USG equipment to do bedside ultrasonography assessment of ONSD. Both the patients and the controls were assessed while lying down, with their heads in the middle and 30 degrees above the floor. A lot of ultrasound gel was administered, along with a sterile dressing over the closed eye. The closed eye was then covered with the high-frequency ultrasound transducer in the transverse plane, making little to no contact with the sterile dressing. The patient's forehead, midface, or nose

Received: 30/10/2023
Accepted: 28/12/2023

served as the sonographer's non-compressible surface to prevent direct globe pressure, pain, and anatomical deformation.

To prevent the picture from tilting, slight movements were made in the nasal and temporal directions to capture the ONS in the same plane as the anterior chamber, posterior chamber, and lens. Following the visualisation of the anechoic streak posterior to the optic disc, measurements were obtained from the stored picture. An electronic caliper placed 3 mm behind the globe and positioned perpendicular to the optic nerve's long axis was used to quantify ONSD. Electronic calipers were utilised to quantify the distance of decreasing echogenicity between the hyperechoic sheath demarcations after measuring 3 mm posterior to the globe (Figure 1).

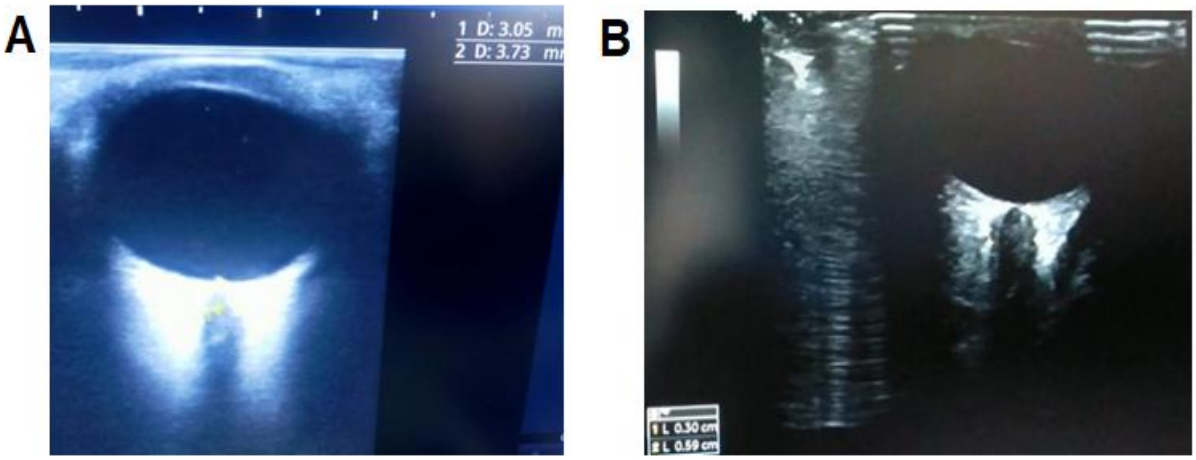

Figure (1): Two-dimensional ocular sonography for measurement of ONSD in control **(A)** and in patient with acute hepatitis and hepatic encephalopathy grade II **(B).**

Three readings were obtained for each eye at a time, and the final ONSD for that eye at that point was determined by averaging the three values. In the end, the ONSD value was determined by averaging the data from both the left and right eyes. Every patient had an ONSD measurement upon admission. Additionally, it was assessed before to death, throughout discharge, and whenever the patient's state of awareness changed.
Exclusion criteria: Patients having a history of ocular injuries, vitreous haemorrhage, central nervous system (CNS) infection such as meningitis and hydrocephalus, or prior neurosurgery using a ventriculoperitoneal shunt.

Ethical considerations: Prior to the patients and controls being enrolled in the trial, written informed permissions were acquired from their parents or legal guardians. The Research Ethics Committee of Menoufia University, Egypt's National Liver Institute, gave its approval to the study. Throughout the course of the investigation, the Helsinki Declaration was adhered to.

Statistical analysis

Version 23.0 of SPSS was used for statistical analysis. The descriptive findings were presented as number and percentage, or as mean ± SD and range. When evaluating the significance between two groups in quantitative data, the Mann-Whitney U test or the student t-test was used, depending on the situation. The difference in ONSD was evaluated using a paired t-test. The X^2-test or Fisher's exact test was used to determine the significance of the data, both qualitative and categorical. Using Spearman's test, correlation was examined. By computing the area under the ROC curve, the value of ONSD at which outcome discrimination was possible was determined. The ROC curves were used to calculate the ONSD cutoff value for ideal clinical performance. The sensitivity, specificity, PPV, and NPV of the diagnostic performance were calculated and reported as percentages. P-values ≤ 0.05 were used to indicate significance.

RESULTS

Study Population's Characteristics:

The current study included 36 infants and children with ALF and 21 infants and children as healthy controls. Both groups were age- and sex-matched. The age in the ALF group ranged from 2-17 years (mean; 8.86 ± 4.56 years) while the age in the healthy controls ranged from 3-16 years (mean; 8.57 ± 3.65 years) (P=0.947). The ALF group included 18 (50%) males and 18 (50%) females and the control group included 11 (52.4%) males and 10 (47.6%) females (P=0.862).

One hundred percent of the ALF patients presented with jaundice. Constitutional symptoms as fever, nausea and vomiting, abdominal pain, anorexia and diarrhea were present at 47.2%, 33.3%, 36.1%, 11.1% and 2.8% respectively. 25% of patients developed disturbed consciousness level. None of the patients presented with hematemesis or melena. Positive consanguinity was present in 10 (27.8%) of patients and 2 (5.6%) patients had history of HAV

infection in their families. History of NSAIDs intake was present in just 1 case. On clinical examination, 100% of patients were jaundiced. Pallor was present in 11.1%. 25% had encephalopathy, their GCS ranged from 10-15. Hepatomegaly and splenomegaly were present in 66.7% and 5.6% of the patients, respectively. 2.8% of patients were ascetic. The most common etiologies of ALF among patients were hepatitis A, 16 (44.4%) followed by indeterminate hepatitis; 13 (36.1%). 6 (16.7%) of patients suffered from fulminant Wilson and 1(2.8%) had fulminant AIH.

Table (1): Demographic data and symptoms

	Children with ALF (n=36)	**Healthy controls (N=21)**	**P value**
Age Mean±SD	2-17 8.86±4.56	3-16 8.57±3.65	P=0.947
Sex Male Female	 18 (50%) 18 (50%)	 11 (52.4%) 10 (47.6%)	P=0.862
Symptoms Fever Nausea and vomiting Abdominal pain Anorexia Diarrhea	 47.2% 33.3% 36.1% 11.1% 2.8%		
The most common etiologies of ALF among patients Hepatitis A Indeterminate hepatitis Suffered of fulminant Wilson Fulminant autoimmune hepatitis	 16 (44.4%) 13 (36.1%) 6 (16.7%) 1 (2.8%)		

The ALF group showed significant increase in ONSD than healthy controls (P 0.008). The ONSD in ALF ranged from 3.4-5.95 mm (mean, 4.29 ± 0.629) while in control group ranged from 3.55-4.3 mm (mean, 3.98 ± 0.205) (Figure 2). Out of the 36 patients with ALF, 23 (63.9%) resolved, 8 (22.25%) died and 5 (13.9%) had undergone liver transplantation. Of the 5 transplanted patients, 2 patients had survived and 3 patients passed away.

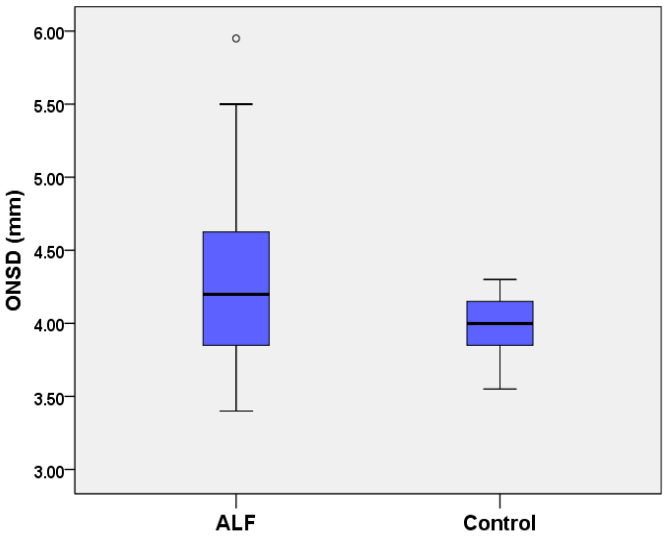

Figure (2): Box and whiskers plot showing comparison of the ONSD between ALF patients and controls.

Comparison of the clinical data between died and resolved ALF patients:

On admission, jaundice and constitutional manifestations were comparable between resolved and died groups (P>0.05), while the Glasgow coma scale was significantly lower in died ALF group than in resolved group (P = 0.026). The total bilirubin, direct bilirubin and total leucocytic count showed significant elevation in died ALF group (P<0.05) than in resolved patients, while the other laboratory investigations did not show significant difference between both groups (P>0.05). There was no significant statistical difference between both regarding other parameters. Abdominal ultrasound features weren't discriminating between both groups (P>0.05). None of the survived patients showed brain edema in CT brain while 1 patient in died group was having brain edema as demonstrated by CT (Table 2). There was no significant statistical difference between the different etiological diagnoses regarding the outcome of ALF (P=0.634). On follow up of patients, total bilirubin showed significant increase in the died group (23.9 ± 9.78 mg/dl) than in the living group (9.38 ± 5.89 mg/dl, P = 0.001). AST, ALT, ALP, serum albumin, total protein, ammonia and serum lactate were comparable between both groups on follow up (P>0.05). GGT showed significant decrease in died than survived (57 ± 47.2 vs 129 ± 125 U/L respectively, P = 0.013). Prothrombin time significantly prolonged in died group (41 ± 15 sec) than in survived (15 ± 5.76 sec, P <0.0001). The mean of INR in died group was 3.76 ± 1.45, which was higher than that in living group (1.35 ± 0.56, P<0.0001). Partial thromboplastin time also showed significant prolongation in died group 54.3 ± 10.5 sec in comparison with survived group 38.6 ± 10.4 sec (P = 0.001).

Table (2): Comparison of the clinical presentations, clinical examination, laboratory and radiological investigations between the resolved and died ALF patients

		Outcome		P
		Resolved (N=23)	**Died (**N=8)	
Clinical presentations	Jaundice	23 (100%)	8 (100%)	----
	Disturbed Consciousness level	2 (8.7%)	5 (62.5%)	**0.006**
	Fever	10 (43.5%)	6 (75%)	0.220
	Nausea and/or vomiting	8 (34.8%)	2 (25%)	1
	Abdominal pain	9 (39.1%)	1 (12.5%)	0.222
	Anorexia	2 (8.7%)	2 (25.0%)	0.268
	Diarrhea	0 (0.0%)	1 (12.5%)	0.258
	Hematemesis	0 (0%)	0 (0%)	---
	Melena	0 (0%)	0 (0%)	---
Clinical examination	Jaundice	23 (100%)	8 (100%)	----
	Pallor	1 (4.3%)	1 (12.5%)	0.456
	hepatomegaly	15 (65.2%)	5 (62.5%)	1
	Splenomegaly	2 (8.7%)	0 (0%)	1
	Ascites	0 (0%)	1 (12.5%)	0.258
	Glasgow coma scale	15±0.92	13±1.69	**0.026**
	MAP	85.6±6.79	84.3±8.63	0.672
	Pulse	100±17.3	116±16.4	**0.039**
	Respiratory rate	27±4.93	30±5.65	0.236
	Temperature	37.08±0.24	37.2±0.51	0.550
Laboratory investigations	Total bilirubin(mg/dl)	18±8.22	26.1±7.05	**0.016**
	Direct bilirubin(mg/dl)	11.1±5.04	17.5±5.29	**0.010**
	Alanine aminotransferase(U/L)	1497±1290	680±623	0.095
	Aspartate aminotransferase (U/L)	1382±341.3	871±241.1	0.149
	Albumin(g/dl)	3.37±0.69	3.07±0.58	0.279
	Total protein(g/dl)	6.11±0.81	6.33±0.95	0.533
	Alkaline phosphatase (U/L)	255±62.1	218±12	0.367
	Gamma glutamyl transferase (U/L)	74.9±17.5	88.75±21.8	0.982
	Prothrombin time (second)	29±7.2	43.4±10.2	0.071
	Partial thromboplastin time(second)	50.5±11.8	60.1±14.8	0.125
	International Normalized Ratio	2.69±0.31	3.61±0.41	0.104
	Hemoglobin (g/dl)	10.9±2.29	10.7±1.94	0.964
	Total leucocyte count x10^3/µL	7.69±1.81	16.6±3.81	**0.003**
	Platelets x10^3/µL	259±62.7	278±67.8	0.527
	Sodium (mmol/L)	136±3.30	137±4.73	0.928
	Potassium (mmol/L)	4.06±0.43	3.93±0.51	0.341
	Calcium (mmol/L)	1.12±0.08	1.12±0.06	0.742
	Urea (mg/dL)	16±3.82	14.6±3.42	0.469
	Creatinine (mg/dL)	0.44±0.11	0.36±0.07	0.305
	Random blood sugar	156±37.6	106±14.9	0.699
	Ammonia (n=33)	112±2	106±15	0.241
	Lactate (n=29)	32.8±8.1	41±9.9	0.069
	Phosphorus (n=28)	2.95±0.72	2.68±0.66	0.664
Arterial blood gas	Normal Respiratory alkalosis Metabolic acidosis	20 (87.0%) 1 (4.3%) 2 (8.7%)	6 (75.0%) 2 (25.0%) 0 (0.0%)	0.1
Radiological investigations	Hepatomegaly	15 (65.2%)	6 (75.0%)	1
	Splenomegaly	13 (56.5%)	4 (50.0%)	1
US Ascites	NO ascitis Minimal/mild Moderate	13 (56.5%) 10 (43.5%) 0 (0%)	4 (50.0%) 3 (37.5%) 1 (12.5%)	0.226
CT brain on admission	Brain edema Normal Brain atrophy	0 (0%) 21 (100%) 0 (0%)	1 (14.3%) 5 (71.4%) 1 (14.3%)	**0.040**

Comparison of ONSD in the resolved and died groups:

On admission, the mean of ONSD in resolved group 4.13 ± 0.573 mm (range; 3.4 to 5.95 mm) was lower than that of died group (4.57 ± 0.64 mm, range; 3.45 to 5.25 mm); but without statistical significance (P = 0.082). ONSD before discharge significantly increased in died group (5.07 ± 0.44 mm) than in living group (3.98 ± 0.354 mm, P<0.0001) (Figure 3).

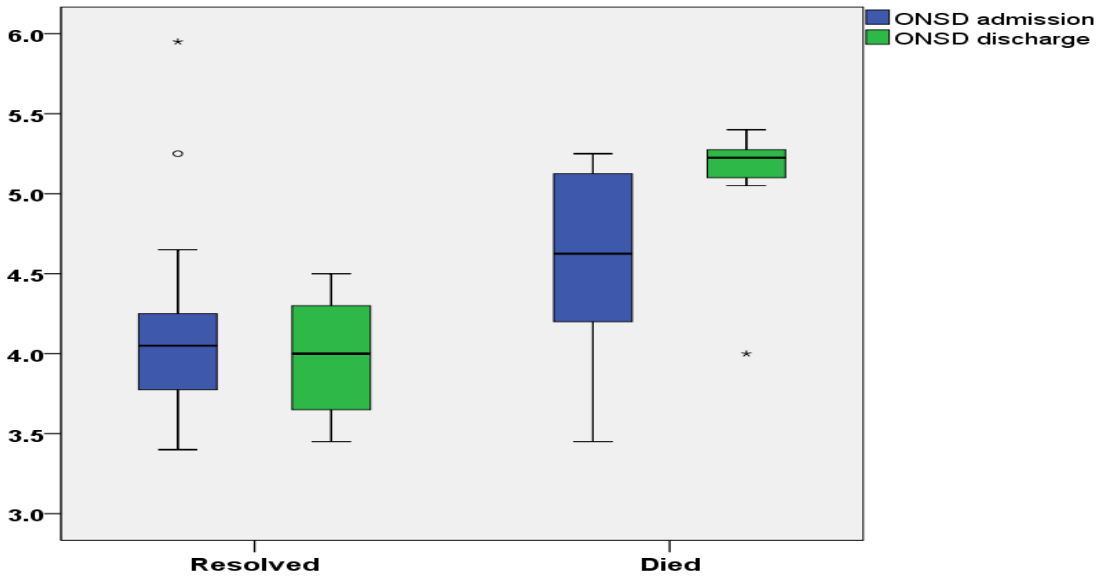

Figure (3): Box and whiskers plot showing comparison of the ONSD in resolved and died ALF patients on admission and before discharge.

On comparing the ONSD between conscious and unconscious patients on admission, the ONSD was significantly higher in ALF patients with disturbed conscious level (5.16 ± 0.45 mm, range, 4.25 to 5.95 mm) than in conscious patients (4.007 ± 0.34 mm, 3.4 to 4.65 mm, P <0.0001). The measurements of ONSD on change of conscious level was significantly higher in died group (5.25 ± 0.097 mm, range; 5.15 to 5.4 mm) than that in survived (4.42 ± 0.106 mm, range; 4.35 to 4.5 mm, P <0.0001). The delta change of ONSD between admission and discharge showed significant reduction in survived group (- 0.14 ± 0.49 mm, range; - 1.8 to 0.15 mm) while it was significantly elevated in died group (0.5 ± 0.43 mm, 0.05 to 1.05 mm, P = 0.001). The performance of ONSD in predicting the patients' outcome was assessed using the ROC curve. ONSD at a cut-off value of > 4.82 mm had 68.8% sensitivity, 95.7% specificity and accuracy of 88.7% in discriminating between resolving and vanishing ALF patients (P =<0.0001) (Figure 4).

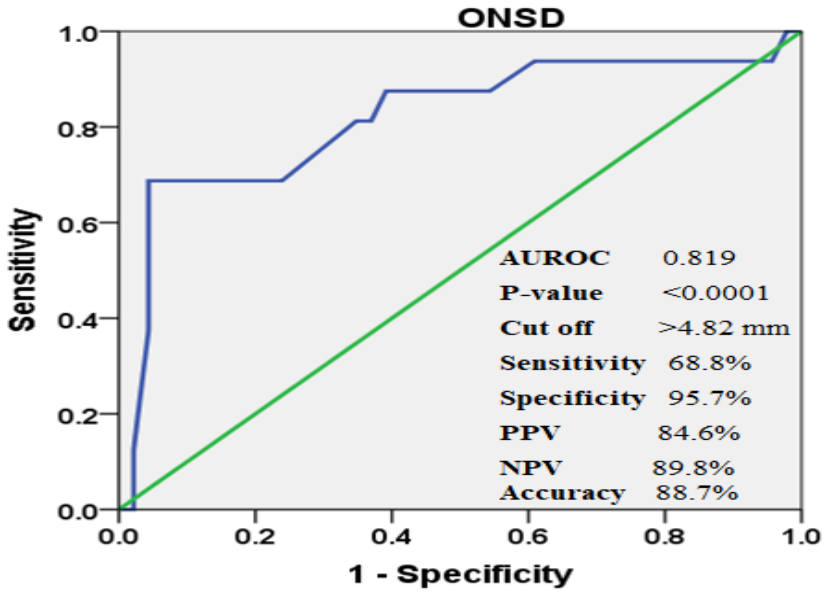

Figure (4): ROC curve for detection of the cut-off value of ONSD with best performance in discriminating resolving and vanishing ALF patients.

DISCUSSION

Paediatric ALF is an uncommon condition that can be brought on by a variety of illnesses, including as ischemia, infections, metabolic and genetic problems, medication overdoses and toxicity, and immune-mediated illnesses. An underlying reason for ALF may never be identified in up to 50% of affected children [(6)]. Hepatitis A was the commonest etiologies for ALF in our cohort followed by indeterminate hepatitis and fulminant Wilson.

Regardless of the cause, all illnesses have similar mechanisms of damage and hepatocellular regeneration. Innate and adaptive immune cells work together to play a key part in these processes. The ratio of continued liver damage to the pace of hepatocyte regeneration determines whether a patient needs a liver transplant or heals on their own [(7)]**.** In the current study, the outcome was favorable without liver transplantation in nearly two thirds of cases, while the remaining passed the way or underwent liver transplantation.

Patients diagnosed with ALF may have nebulous symptoms in the absence of clinical instability or ESLD. Depending on the child's age and baseline developmental capabilities, hepatic encephalopathy in children might be challenging to diagnose. Moderate symptoms might include lethargy, agitation, and disorientation, while severe encephalopathy could quickly advance to seizures, cerebral edoema, stupor, and coma [(8)].

Jaundice was the main presentation of our ALF patients. Constitutional symptoms as fever, nausea and vomiting, abdominal pain, anorexia and diarrhea were present with lower frequencies than jaundice. Bleeding disorders aren't common in ALF patients. Disturbed conscious level was present in one fourth of our patients. Hepatomegaly was a main sign in nearly two thirds of cases while splenomegaly and ascites were seldomly detected in clinical examination. Diagnostic workup of the ALF patients showed disturbed liver functions with shouting of ALT and AST, and prolongation of PT.

On admission, the clinical presentations weren't a prognostic factor for occurrence of mortality except for presence of encephalopathy. Total and direct bilirubin levels were the main critical values on admission. With advancement of the clinical state, bilirubin levels showed progressive elevation and prothrombin time progressively prolonged in died group, which are evidence of worsening hepatic failure.

In ALF, elevated ICP is a significant contributor to both mortality and disability. The accumulation of ammonia in glial cells, which is subsequently converted to glutamine and causes an osmotic gradient and cellular edoema, is thought to be the cause of cerebral edoema. Cerebral hyperperfusion and vasodilatation could possibly be involved. Therapeutic intervention may be possible through ICP monitoring prior to cerebral herniation and catastrophic brain damage [(9)].

Elevated ICP causes the ONS to dilate and is transferred across the subarachnoid space, much like the process that causes papilledema [(10)]. While, distension of the ONS may happen quickly after an ICP increase, papilledema may take hours or days to develop [(10)]. It has been noted that noninvasive ultrasonographic ONSD estimate is a helpful technique for assessing increased ICP [(11)].

Patients with ALF had wider ONSD than age- and sex-matched healthy controls. On admission, the ONSD was comparable in the resolved and died groups, while with follow up of the patients and progression of the condition, the ONSD progressively increased in died group and decreased in living group. Interestingly on admission, the ONSD was found to be higher in ALF patients with disturbed conscious level than that in conscious patients. Besides, there was significant change of ONSD with change of conscious level. The ONSD > 4.82 mm showed a very good accuracy in predicting vanishing ALF patients.

Nevertheless, nothing is known about the ONSD cutoff value for predicting children's increased ICP. The cut-off ultrasonographic value for aberrant ONSD enlargement predictive of higher elevated ICP was found to be above 4 mm in babies, 4.71 mm in children aged 1-10 years, and 5.43 mm in older children, according to **Rehman *et al.*** [(12)]**.** The diagnostic accuracy of ONSD cut-off values for elevated ICP detection was evaluated by **Kerscher *et al.*** [(13)]**.** For infants under one year old, the ONSD measurement was 4.99 mm (SE 50%, SP 58.8%, PPV 22.2%, and NPV 83.3%) to detect ICP ≥ 20 mm Hg; for children over one year old, it was 5.75 mm (SE 91.7%, SP 66.7%, PPV 45.8% and NPV 96.3%).

Concomitant with our results, **Das *et al.*** [(4)]**,** had assessed the ONSD in kids who have ALF. A total of eleven ONSD measures (ALF-74, controls-47) were collected without any issues. The ONSD values for controls, ALF without HE, ALF with HE, and at recovery were 4.2 (3.9-4.3), 4.4 (4.0-4.6), 5.2 (4.8-5.8), and 3.9 (3.3-4.1) mm respectively. Compared to ALF without HE, ALF with HE had a considerably higher ONSD. ALF without HE and with showed comparable ONSD to controls upon recovery. ALF with clinically evident elevated ICP had greater ONSD than those without (5.4 [4.9-5.7] vs 4.6 [4.1-5.3] mm; P =.01). ALF with HE vs non-HE and good vs bad non-transplant outcome were distinguished with an ONSD of 4.6 mm with ≥ 80% sensitivity and specificity. The ONSD showed a positive correlation with both BA (r =.42, P =.002) and INR (r =.53, P <.001).

In the current study, ONSD significantly increased with deterioration of the patients Glasgow coma scale, total bilirubin, direct bilirubin, PT, INR and serum creatinine, which reflect the importance of serial measurements of ONSD for prediction of patient outcome for early stratification of patients in urgent need for liver transplantation.

CONCLUSION

ONSD, a safe bedside technique, can be employed for serial monitoring of children with ALF. It is a good prognostic factor for prediction of patients' outcome.

Conflict of interest: none declared.
Fund: non-fundable.

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