

# The magnetic resonance imaging assessment of optic nerve sheath diameter in pediatric acute liver failure patients

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**Abstract. – OBJECTIVE:** To evaluate the diagnostic value of optic nerve sheath diameter (ONSD) using brain MRI in the pretransplantation period in the pediatric acute liver failure patients, and correlate the ONSD with clinical grade of hepatic encephalopathy (HE) and MRI findings.

**PATIENTS AND METHODS:** Forty acute liver failure patients and 40 control group patients were retrospectively analyzed. The high signal intensities in T2W (T2-weighted image), FLAIR (Fluid Attenuated Inversion Recovery) and DWI (diffusion-weighted imaging) sequences were evaluated and ONSD were measured. The patients were grouped first into 5 according to their West Haven score, and HE grade 0 and grade 1 were accepted as low grade HE, HE grade 2, 3 and 4 were accepted as high grade HE. The patients were grouped to 2 according to the MRI findings as low grade and high grade MRI group.

**RESULTS:** The mean value of ONSD was  $6.0 \pm 1.80$  and  $4.94 \pm 1.27$  in all the patients and in the control group, respectively. There was statistically significant difference between both the ONSD and the low grade-high grade HE groups ( $p=0.01$ ), and between the ONSD and the low grade-high grade MRI groups ( $p<0.001$ ).

**CONCLUSIONS:** Although high ONSD values do not make the diagnosis of cerebral edema, it may cause suspicion in the early period. MRI can be helpful in the diagnoses of increased intracranial pressure like ultrasound. Our study is the first study to compare ONSD and MRI findings in addition to HE grades. The widespread use of MRI in children in recent years may help determine the normal range of ONSD values.

*Key Words:*

Optic nerve, Magnetic resonance imaging, Hepatic encephalopathy, Acute liver failure, Ultrasound.

## Introduction

Acute Liver Failure (ALF) is a serious condition that can result with hepatic encephalopathy

(HE) in the patients, who had not a history of severe liver related dysfunction and chronic liver disease<sup>1</sup>. As a result of the accumulation of ammonia which is toxic in HE, various pathologies have been described in the brain magnetic resonance imaging (MRI) in T2W (T2-weighted image), FLAIR (Fluid Attenuated Inversion Recovery) and DWI (diffusion-weighted imaging) sequences. Symmetrical high signal intensities in insula, thalamus, posterior limbs of internal capsule (PLIC), cingulate gyrus and diffuse cortical edema are these pathologies<sup>2</sup>. The prevalence of these pathologies is related to the clinical severity of the disease<sup>2</sup>.

Increased intracranial pressure (ICP) develops in HE secondary to cerebral edema which is responsible for the mortality and the morbidity of the disease. ICP measurement is done directly with epidural, subdural and intraventricular devices, but these are very invasive methods<sup>3</sup>. Instead, indirect methods have been developed to suspect an increase in ICP. A positive correlation was found between optic nerve sheath diameter (ONSD) value and increased ICP<sup>4</sup>. The optic nerve is associated with the durameter, and is covered by leptomeninges. Any change in ICP is reflected in the potential space below the optic nerve sheath, and this causes enlargement in ONSD<sup>5</sup>. ONSD measurements are done with non-invasive imaging methods, such as ultrasound (US) and MRI in the ALF patients especially in the pretransplantation period<sup>6,7</sup>, but the number of clinical studies in pediatric patients is few<sup>8</sup>.

The aim of this study was to evaluate the diagnostic value of measuring ONSD using MRI in the pretransplantation period in the pediatric ALF patients, and correlation the ONSD with clinical grade of HE, and brain MRI findings.

## Patients and Methods

All procedures followed were in accordance with the Helsinki Declaration, and all of the parents of the patients have been informed and approved to participate in this study. This study was approved by the Inonu University Ethical Committee with the number 2021/2440 in 07-09-2021.

### Patient Selection

The brain MRI findings of 40 patients aged 0-17 years, who had liver transplantation due to ALF in the transplantation institute of our hospital between 2012 and 2019 were retrospectively analyzed *via* Picture Archiving and Communication Systems (PACS). The medical data, HE grades of the patients were examined in detail by the responsible clinician from the patient files. Patients, who did not have brain MRI in the pre-transplant period or who did not have T2-FLAIR and DWI sequences in MRI were excluded from the study. In addition, patients with missing medical data were excluded from the study.

Brain MRIs were obtained within 7 days before transplantation. The mental status of the patient was determined according to the clinically used West Haven scoring<sup>9</sup>. This was obtained through a retrospective review of medical record. West Haven scores were evaluated from the data just before the brain MRI examination time.

The patients were grouped into 5 according to their HE grades. HE grade 0 was named as HE group 1, grade 1 as HE group 2, grade 2 as HE group 3, grade 3 as HE group 4 and grade 4 as HE group 5. Group 1 and 2 were accepted as low grade HE, Groups 3, 4 and 5 were accepted as high grade HE.

### MR Imaging Sequence Parameters

The 1.5 T device (Siemens, Magnetom-Avanto) was used for MRI scans and a single pediatric radiologist (with 5 years of experience) and reported the whole brain MR images in the PACS system. The radiologists were unaware of the clinical information and West Haven scores of the patients. Axial T1WI, T2WI, FLAIR and DWI with Apparent diffusion coefficient (ADC) maps sequences were evaluated in MR images.

The patients were grouped as follows according to the signal intensity features in T2W-FLAIR and DWI sequences.

MRI group 1: there was no pathological signal intensity in T2W-FLAIR or DWI. MRI

group 2: there was a symmetric involvement of the following: thalami, PLIC, dorsal brain stem (DBS), periventricular white matter (PVWM) or cerebellar white matter (Figure 1). MRI group 3: there was diffuse cortical involvement (Figure 2). MRI group 1 and 2 were accepted as low grade MRI, MRI group 3 was accepted as high grade MRI.

Age-matched children, who had brain MRI due to headache and had no pathology on MRI were selected as the control group.

ONSD measurements were made from axial T2W images for both 40 patients and 40 control groups. Measurements were made by a single pediatric radiologist. ONSD was performed in transverse diameter perpendicular to the optic nerve at 3 mm behind the globe. The measure at 3 mm behind the globe was taken in accordance with the findings in the Helmke and Hansen study<sup>10</sup>. ONSD was performed between the inner edges of the dura surrounding the optic nerve (Figure 3).

### Statistical Analysis

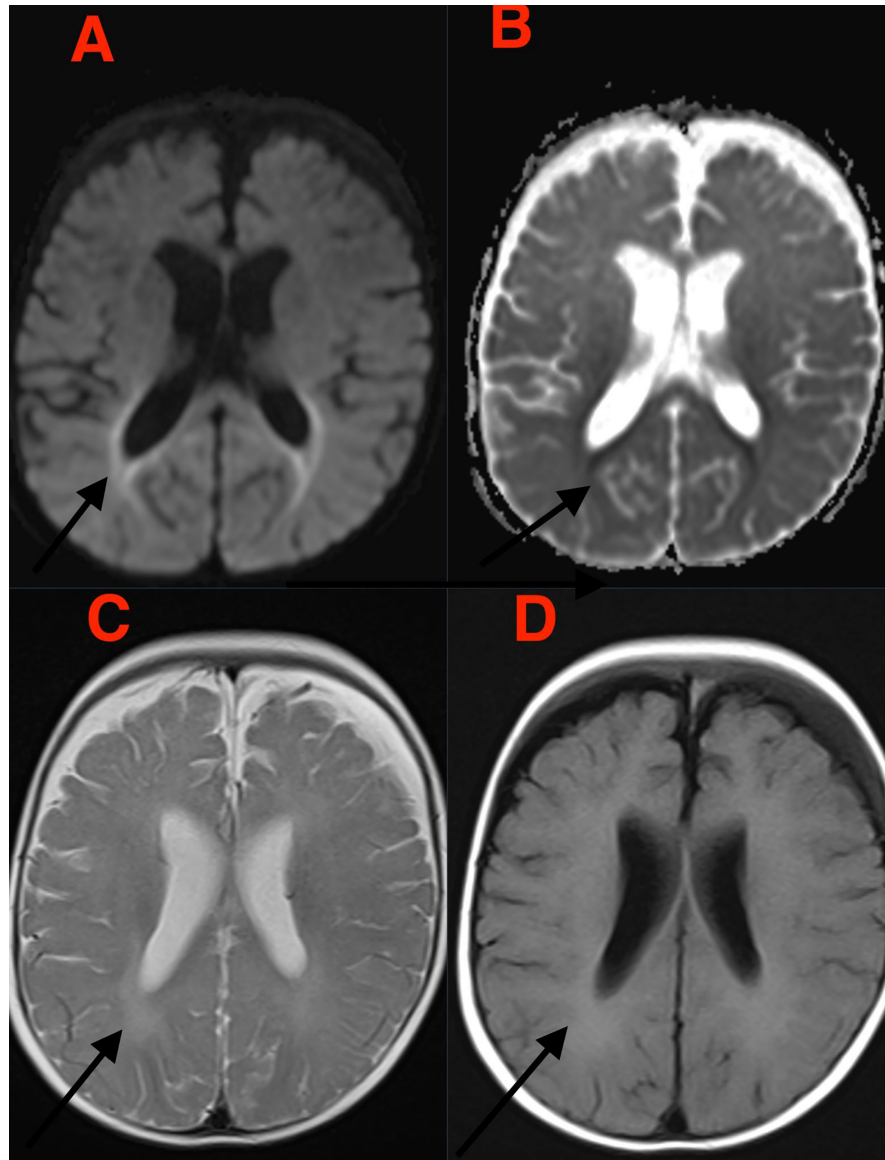
Numerical and categorical variables in the data set were expressed as median (min-max) and frequency (percent), respectively. Kruskal-Wallis H test was used to compare numerical variables in terms of groups. After the Kruskal-Wallis H test, paired group comparisons were performed by the Conover test. Statistical significance level was accepted as  $p < 0.05$ . In the analysis, web-based applications KruskalWallis<sup>11</sup> and IAY: Statistical Analysis Software<sup>12</sup> developed by İnönü University Faculty of Medicine, Department of Biostatistics and Medical Informatics were used.

## Results

In our study, the 23 (57.5%) of the patients were male, and 17 (42.5%) were female. The mean age was found to be  $6.45 \pm 4.03$ . The cause of ALF was cryptogenic in 22 (55%), HAV (hepatitis A virus) in 13 (32.5%) and toxic in 5 (12.5%) of the patients.

Twenty (50%) of the patients had hyperintense signals in the insular cortex, 19 (40%) in the PVWM, 15 (37.5%) in the basal ganglia, 14 (35%) in the DBS, 12 (30%) in the PLIC, 11 (27.5%) in the thalamus, and 15 (37.5%) in diffuse cortical region in T2WI-FLAIR or DWI. Comparison of the pathological signals in T2-FLAIR and DWI is shown in the Table I.

**Figure 1.** A, DWI (Diffusion-weighted imaging). B, ADC (Apparent diffusion coefficient). C, Axial T2W sequence. D, Axial FLAIR sequence. 6-year-old male patient, increased signal intensity on T2-FLAIR and restricted diffusion in the bilateral periventricular white matter.



The mean value of ONSD was  $6.0 \pm 1.80$  in all the patients. The mean value of ONSD was  $4.94 \pm 1.27$  in the control group.

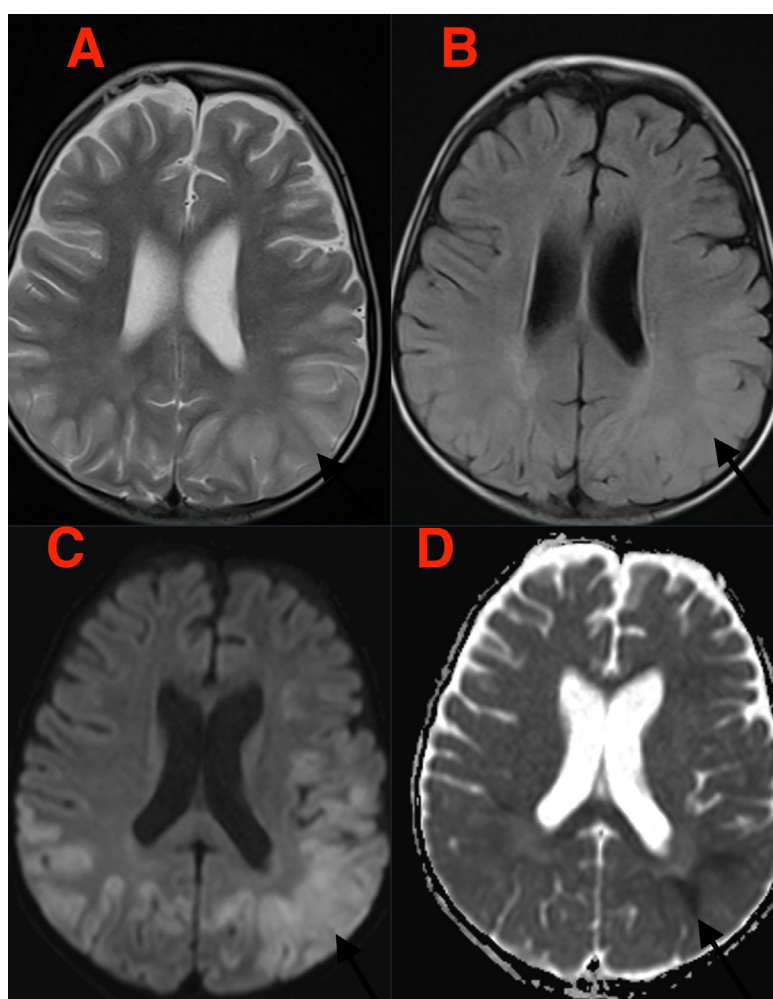
The number of the patients and the mean value of the ONSD in the HE and in the MRI groups were given in the Table II and III.

While there was no statistically significant difference between the ONSD and the HE groups ( $p=0.07$ ), a statistically significant difference was found between the ONSD and the MRI groups ( $p<0.001$ ).

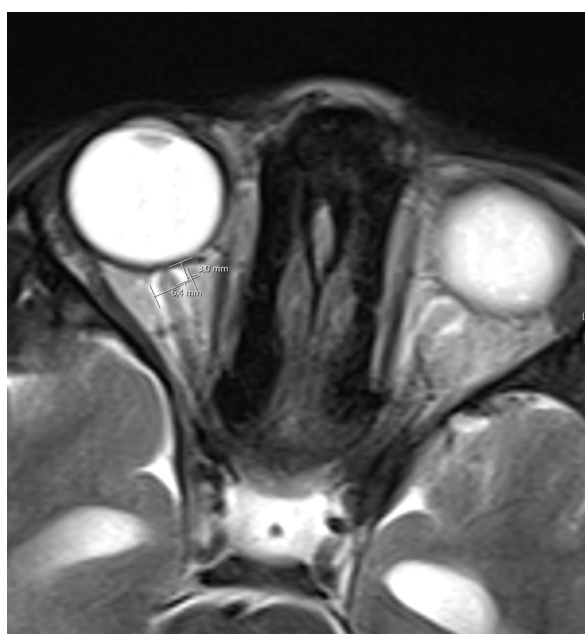
There was statistically significant difference between both the ONSD and the low grade-high grade HE groups ( $p=0.01$ ), and between the ONSD and the low grade-high grade MRI groups ( $p<0.001$ ) (Table IV, V).

## Discussion

In the brain MRI of ALF patients, high signal intensities can be seen in some regions in FLAIR-T2WI, or DWI sequences. These regions are the thalamus, the basal ganglion, the PLIC, the PVWM, and the dorsal brain system<sup>13</sup>. It has been shown that the excess involvement in FLAIR or DWI is strongly correlated with serum ammonia levels and moderately with the severity of the disease<sup>2</sup>. If diffuse cortical involvement is present, the prognosis of the patients is much more serious<sup>14</sup>. According to our results, ONSD values with diffuse cortical involvement were found to be statistically higher than the patients with normal MRI findings or



**Figure 2.** A, Axial T2W sequence. B, Axial FLAIR sequence. C, DWI (Diffusion-weighted imaging). D, ADC (Apparent diffusion coefficient). 10-year-old male patient, increased signal intensity on T2-FLAIR and restricted diffusion in the bilateral parietooccipital cortical region.



**Figure 3.** Axial T2W sequence. The ONSD was measured 3 mm behind the optic disc. Abbreviation: ONSD, optic nerve sheath diameter.

**Table I.** Correlation of the hyperintensities in T2W, FLAIR and DWI abnormalities.

|                                        | FLAIR-T2WI | DWI      |
|----------------------------------------|------------|----------|
| Thalamus                               | 11 (27.5%) | 8 (%)    |
| Basal ganglia                          | 15 (37.5%) | 10 (%)   |
| Posterior limb internal capsule (PLIC) | 12 (30%)   | 12 (%)   |
| Periventricular white matter (PVL)     | 19 (40%)   | 17 (%)   |
| Dorsal brain stem (DBS)                | 14 (35%)   | 7 (%)    |
| Diffuse cortical                       | 15 (37.5%) | 15 (%)   |
| Insular cortex                         | 20 (50%)   | 20 (50%) |

FLAIR: Fluid-attenuated inversion recovery; T2WI: T2 weighted image; DWI: Diffusion-weighted imaging.

**Table II.** Correlation of the mean ONSD value between the HE groups.

| $p = 0.07$ | HE group 1<br>(n = 7) | HE group 2<br>(n = 5) | HE group 3<br>(n = 7) | HE group 4<br>(n = 15) | HE group 5<br>(n = 6) | Healthy group<br>(n = 40) |
|------------|-----------------------|-----------------------|-----------------------|------------------------|-----------------------|---------------------------|
| ONSD       | 5.0 (4.8-6.8)         | 5.3 (4.9-6.9)         | 6.4 (4.7-7.5)         | 6.2 (4.8-7.3)          | 6.8 (6.0-7.1)         | 4.94 (4.2-5.4)            |

ONSD: Optic nerve sheath diameter; HE: Hepatic encephalopathy.

**Table III.** Correlation of the mean ONSD value between the MRI groups.

| $p < 0.001$            | ONSD           |
|------------------------|----------------|
| MRI group 1 (n = 13)   | 5.0 (4.7-5.3)  |
| MRI group 2 (n = 13)   | 6.2 (5.6-6.4)  |
| MRI group 3 (n = 14)   | 6.75 (6.1-7.5) |
| Healthy group (n = 40) | 4.94 (4.2-5.4) |

ONSD: Optic nerve sheath diameter.

**Table IV.** Correlation of the mean ONSD value between low grade HE and high grade HE.

| $p = 0.01$ | Low grade HE | High grade HE |
|------------|--------------|---------------|
| ONSD       | 5.12         | 6.38          |

ONSD: Optic nerve sheath diameter; HE: Hepatic encephalopathy.

**Table V.** Correlation of the mean ONSD value between low- grade MRI score and high grade MRI.

| $p < 0.001$ | Low grade MRI | High grade MRI |
|-------------|---------------|----------------|
| ONSD        | 5.0           | 6.48           |

ONSD: Optic nerve sheath diameter; HE: Hepatic encephalopathy.

with mild involvement. It can be said that, as the ONSD values increase, the prognosis of the disease will be poor.

Our study is the first study to compare ONSD and MRI findings in addition to HE grades. The mean value of ONSD was found to be higher in the high grade HE group compared to the low grade HE group in the present study. In the study of Das et al<sup>8</sup> in 41 pediatric patients with ALF, ONSD values were shown to be correlated with HE grades and BA. They also showed that the ONSD of the control group and the ONSD of patients without HE were similar. Although ONSD values were increased in correlation with HE grades, there was no statistically significant difference between HE groups in our study. The mean ONSD values of the patients without HE group and the low-grade MRI group were similar to the control group in our study too. In another study, the prognosis of the children was worse with higher ONSD values than lower ONSD values<sup>15</sup>. In the study made by Cardoso et al<sup>16</sup> in adults, a higher ONSD value was associated with higher hospital mortality. In all of these studies, ONSD measurement was made with US. US is used more frequently for ONSD measurement, since it is easily accessible, inexpensive, and easy to apply at the bedside in intensive care units. On the other hand, US has some disadvantages. US is a user dependent technique and US beam has

poor penetration and it has low spatial resolution. MRI has a higher spatial resolution and can separately show the optic nerve size and sheath of ONSD.

There are only a few studies, in which ONSD was performed with MRI in healthy children and it is very similar to the ONSD values of our control group<sup>17</sup>. The mean value of ONSD was  $4.94 \pm 1.27$  in the control group in our study. The only study that was an exception was the study by Steinbord et al<sup>18</sup> and the mean ONSD value was 5.96 in normal children aged 5-18 years. This mean value was quite high both compared to the literature and our results. This was shown as thinner slice thickness and the images acquisition plane parallel to the optic nerve in the above-mentioned study<sup>17</sup>.

In a study, in which ONSD was measured in pediatric patients with MRI, ONSD value was found to be significantly high in the patients with idiopathic intracranial hypertension<sup>19</sup>. In this study, the mean ONSD value of the control group was found to be lower than in our study. This was due to the fact that ONSD measurement was made from different places with different technique. We measured ONSD at 3 mm distal to origin of the optic nerve, because this is the most distensible part of optic nerve sheath. In another study<sup>4</sup>, the mean value ONSD of the control group was lower than the patients with intracranial hypertension. Although this study involved adult patients, ONSD values of the control group (4.92) was similar to ONSD of our control group (4.96). The mean age was 6.45 in our study, only 8 (20%) of the patients were <4 years of age. This may explain the similarity of ONSD values. As known, there is a significant increase in the thickness of the myelin sheath in the first 2 years of life, and this thickness reaches the adult level at about 4 years of age<sup>17</sup>. While that study was performed with high-resolution orbital images, whole-brain axial T2W images were used in our study. The various layers of the optic nerve sheath cannot be resolved in whole-brain axial T2W images and measurements are made based on the outer fibrous layer at the junction with the periorbital fat<sup>20</sup>. As a result, the ONSD values are found to be higher like in our study.

In comparison of US and MRI, it was found that both methods showed a very good correlation and both methods detect increased ICP with almost the same sensitivity and specificity<sup>20</sup>. In addition, ONSD values tend to be higher in MRI than in US, in accordance with our study.

Our study included some limitations. It was a retrospective study and MRI measurements were made with low-resolution brain axial T2 images. In addition, true ICP was not measured in our study, and ONSD was compared with clinical and MRI findings.

## Conclusions

Although high ONSD values do not make the diagnosis of cerebral edema, it may cause suspicion in the early period. MRI can be helpful in the diagnoses of increased ICP like US. The widespread use of MRI in children in recent years may help determine the normal range of ONSD values. There is a need for studies to determine cut-off values with larger patient groups in pediatric ALF patients.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

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## Authors' Contribution

TStudy concept and design: G.M.D., G.O., E.Ç.; statistical analysis: A.K.A.; analysis and interpretation of data: G.M.D., E.Ç., G.O.; drafting of the manuscript: G.M.D., A.S., S.Y., S.M.D.; critical revision of the manuscript for important intellectual content: A.S., S.M.D., S.Y. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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