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Original Article

Imaging spectrum of extracorporeal membrane oxygenation related neurologic events in children

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ABSTRACT

Background. Extracorporeal membrane oxygenation (ECMO) can be associated with severe neurological complications increasing morbidity and mortality. We aimed to evaluate imaging findings in patients with neurological complications associated with ECMO.

Methods. Children (<18 years) who had ECMO support and received cross-sectional imaging (cranial CT and/or MRI) were retrospectively evaluated. Age, gender, clinical and imaging findings were documented and the relation to ECMO duration and survival rates with imaging findings and imaging time (during ECMO or after weaning) were examined.

Results. Twenty children who had cranial CT/MRI during (n=6) ECMO and after weaning (n=14) were included in the study. The median duration of ECMO was 12.5 days (IQR=5-25 days) with a survival rate of 65%. Fourteen patients had positive imaging findings including ischemic stroke (n=4), hemorrhagic stroke (n=4), hypoxic-ischemic encephalopathy (n=2), posterior reversible encephalopathy syndrome (PRES) (n=3) and cerebral vein thrombosis (n=1). The duration of ECMO and survival rates did not significantly differ between patients with positive and unremarkable imaging findings. However, the survival rate was significantly higher ($p<0.001$) and the duration of ECMO was significantly lower in patients scanned after weaning compared to patients imaged during ECMO support ($p=0.033$).

Conclusions. Our series revealed PRES in ECMO-related neurologic events in addition to commonly reported thrombotic and hemorrhagic stroke in the literature. Availability of cross-sectional imaging and awareness of radiologists to these complications during ECMO or after weaning help in prompt diagnosis and treatment.

Key words: extracorporeal membrane oxygenation (ECMO), neurologic complications, imaging.

Extracorporeal membrane oxygenation (ECMO) is a set of extracorporeal life support providing cardiopulmonary bypass. Following the initial successful runs of ECMO in a posttraumatic patient in 1972 and then a newborn patient in 1976, it has been increasingly used worldwide in children and infants with severe cardiac or respiratory failure unresponsive to conventional therapies.[1-3]

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ECMO comprises a drainage cannula (either through a large central vein or right atrium) which drains deoxygenated blood from the body and passes it to the ECMO circuit. Deoxygenated blood is pumped into the ECMO circuit, where the O2/CO2 gas exchange takes place, and adjustments are done according to the metabolic needs of the patient. Then, a reinfusion cannula sends oxygenated blood backward to the body through a large central vein (venovenous - VV) or artery (venoarterial - VA) depending on the ECMO mode. Anticoagulation is used to avoid thrombosis in the circuit.[4]

According to a recent report of the Extracorporeal Life Support Organization Registry, the overall

survival of pediatric patients receiving ECMO was 61%.[3] The registry reviewed the most frequent neurologic complications among neonates and non-neonates according to ECMO indications, i.e. respiratory, cardiac and extracorporeal cardiopulmonary resuscitation (ECPR). The incidence of these neurologic complications varied according to age and ECMO indication: seizures 3-6%, central nervous system (CNS) infarction 3-11%, intracranial hemorrhage 6-14% and brain death 0.4-10%. Children with CNS hemorrhage had the lowest survival rates ranging between 21-40%, following brain death. It is reported that intracerebral hemorrhage was more common among neonates (11-14%) compared to non-neonates (5-9%), especially in patients in need of ECMO for cardiac support; but it carried a stronger association with mortality among non-neonates.[3] Additionally, these neurologic injuries during ECMO are related to an increased risk of mortality and neurologic disability among survivors.[5] Risk factors for neurological complications include indication of ECMO as ECPR, VA ECMO, carotid cannulation, younger age, renal failure, sepsis, plasma creatinine >3 mg/dL, lower pH, need for inotropic support and thrombocytopenia in children.[6-13]

Cranial imaging has a significant role in determining the precise and prompt diagnosis of neurologic injury. Most imaging studies of patients with ECMO support focused on stroke, whether hemorrhagic or ischemic and its relation to survival. On the other hand, neuroimaging spectrum of various complications, other than stroke, has not been studied and demonstrated in detail among children, yet. In this research, we aimed to determine the neuroimaging spectrum of complications during ECMO or shortly after weaning in children and its relation to factors including ECMO duration, imaging time-lapse from ECMO initiation and survival.

Material and Methods

This retrospective study was approved by the Hacettepe University institutional review board (IRB) (04.05.2021 - GO21/607), informed consent was waived by the IRB. Pediatric patients who received ECMO support during hospitalization between 01.01.2013 – 31.12.2020 were collected. Inclusion criteria were set as follows: 1) patients <18 years old 2) patients with cross-sectional cranial imaging (computerized tomography -CT- and magnetic resonance -MR-imaging) during ECMO support or within two weeks after weaning. Patients with known intracranial pathology before initiation of ECMO support were excluded from the study.

Ultrasound (US) was not included as a diagnostic imaging modality in our study, because it was not possible to review the US studies retrospectively and the inclusion of US reports would be limited to findings based on the subjective reports.

Age, gender, diagnosis of patients, indications of ECMO, type of ECMO (VA or VV), cannulation site, duration of ECMO were retrieved from the Hospital Information Systems and archives of the Pediatric Intensive Care Unit. The systemic complications that occurred prior to imaging and the time gap between cessation of therapy and cranial imaging were also noted.

Nonenhanced cranial CT (NECT) scans were obtained using 16- and 64-slice multidetector scanners (GE Optima, GE Healthcare, United States and Somatom Definition, Siemens Healthineers, Germany, respectively). All patients had axial sections with 3 mm thickness. MR studies were carried out on 1.5T scanners (Symphony, Siemens Healthineers, Germany and Achieva, Philips, Netherlands) and included axial T2 weighted image (WI), T1WI, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted image (DWI) and susceptibility-weighted image (SWI). Two neuroradiologists with an experience of 5 and 21 years evaluated the cranial imaging studies in consensus.

Following documentation of clinical information and imaging findings, we searched for differences in terms of ECMO duration,

imaging time-lapse from ECMO initiation and survival when the patients were grouped according to neuroimaging findings i.e. patients with clinically important (positive) and normal/unremarkable (negative) findings and according to imaging time i.e.patients initially imaged during ECMO and after weaning. Also, the presence of renal failure, sepsis, inotrope support and thrombocytopenia were compared between patients with positive and negative imaging findings.

Statistical Analysis

Numeric variables were tested with the Kolmogorov-Smirnov test to clarify if normal distribution existed. If normal distribution was present, comparisons were made among groups using student t-test, otherwise, Mann Whitney-U test was used. Categorical variables were compared by chi-square test.

Results

One hundred and thirty-six patients received ECMO during the aforementioned period (seven years) in the pediatric intensive care unit. Cranial imaging was performed in 22 patients (16.2%). One patient had imaging four weeks after weaning and therefore was excluded from the study. Another patient with an underlying intracranial disease was also excluded from the study.

Twenty patients (female/male=5/15, median age 3.5 years with an interquartile range -IQR- 1.25-11.4) met the inclusion criteria. A chart showing the distribution of age among the study group is shown in Fig. 1. Diagnosis of the patients included congenital heart disease (CHD) (n=9), cardiomyopathy (n=5), pulmonary hypertension (n=2), Langerhans cell histiocytosis (n=1), immune deficiency (n=1), congenital diaphragmatic hernia (n=1), multisystem inflammatory syndrome in children (MIS-C) (n=1) (Table I). Indications for ECMO were cardiac support (n=13), ECPR (n=4), respiratory support (n=3) (Table I). Indications for cranial imaging were seizure (n=8), pupillary fixation (n=2), anisocoria (n=2), blurring of vision (n=1) alterations in consciousness (n=5), bradycardia (n=1) and headache (n=1) (Table I). The median duration of ECMO support was 12.5 days (IQR=5-25 days). Five patients could not be weaned from ECMO support (25%) and a total of 7 patients died (35%). Detailed information concerning clinical and imaging features of all patients are given in the Supplementary Table.

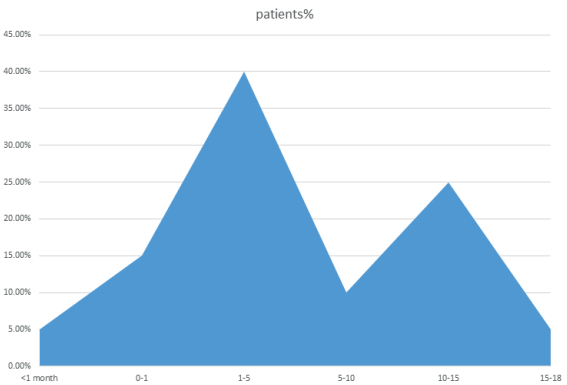

Fig. 1. Age distribution of patients.

Table I. Clinical features of patients.

Gender (M/F)	15/5
Age, years, Median (IQR)	3.5 (1.25-11.4)
Diagnosis	
Congenital heart disease	9
Cardiomyopathy	5
Pulmonary hypertension	2
Langerhans cell histiocytosis	1
Immune deficiency	1
Congenital diaphragmatic hernia	1
Multisystemic inflammatory syndrome in children	1
ECMO indications	
Cardiovascular failure	13
Respiratory failure	3
ECPR*	4
ECMO type	
Venoarterial	15
Venovenous	3
LVAD**	2

*ECPR: Extracorporeal cardiopulmonary resuscitation
**LVAD: Left ventricle assist device

Three patients were managed with VV ECMO, two patients with left ventricle assist device (LVAD) and the remaining patients had VA ECMO (Table I). The cannulation site of VA ECMO was the right atrium-aorta in all patients. Double-lumen jugular catheterization was used in 2 patients with VV ECMO, and right-left jugular vein catheterization was used for one patient with VV-ECMO.

Six patients had cranial imaging during ECMO support and all of them died (100%). The median duration of ECMO support before imaging and the total median duration of ECMO support was 5 days (IQR=3.5-17.5 days) and 19 days (IQR=13-28 days), respectively. Fourteen patients were imaged after weaning and one of them died (7.1%), and the median duration of ECMO support for these patients was 6 days (IQR=4-16 days). The survival rate was significantly higher in patients who had imaging after weaning compared to patients imaged during ECMO support ($p<0.001$). The total duration of ECMO was significantly higher in patients who were imaged during ECMO compared to those who had imaging after weaning ($p=0.033$).

Sixteen patients had CT and 8 patients had MRI scans, and 4 patients had both. To enhance understanding of neurologic events in the patients, findings were grouped as stroke (hemorrhagic/ischemic), hypoxic-ischemic encephalopathy (HIE), venous thrombosis and posterior reversible encephalopathy syndrome (PRES) following re-evaluation of the imaging studies. Ischemic stroke was grouped as a large vessel occlusion and embolic ischemia in different arterial territories. Hemorrhagic stroke was grouped as lobar parenchymal hematomas extending into the ventricles with >3cm transverse diameter and hematomas <3 cm in transverse diameter. Hemorrhagic transformation of ischemic stroke was also noted according to the Heidelberg classification.[14] The presence of microhemorrhages was also noted using SWI.

Four patients had an ischemic stroke (2.9%), one large vessel occlusion (0.7%), three embolic strokes (2.2%). The patient with a large vessel occlusion (middle cerebral artery) (Fig. 2, A) had an LVAD for cardiac support and was lost. He was imaged during ECMO and had been on ECMO support for 28 days before imaging. Two patients had embolic ischemic infarcts without hemorrhagic transformation (Fig. 2, B-C), both had VA ECMO for cardiac support, imaged after weaning and survived. One patient had a hemorrhagic transformation of embolic ischemic stroke with Type 1 a-b hemorrhage (scattered small or confluent petechial, no mass effect) according to Heidelberg classification (Fig. 2, D). The patient was on VA ECMO for

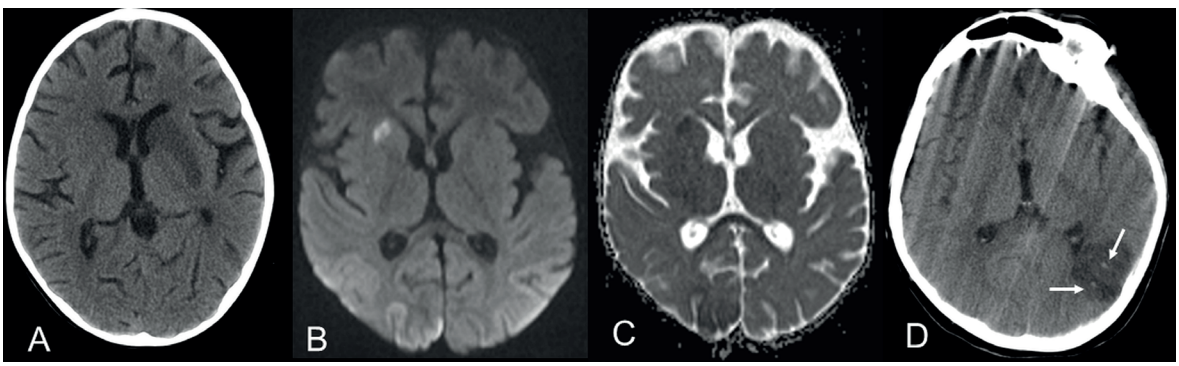

Fig. 2. (A) An acute striatal infarction with left middle cerebral artery occlusion as seen on axial non-enhanced CT (NECT) image in a 6-year-old male patient with ECMO support. Trace image (B) and ADC maps (C) of diffusion weighted imaging (DWI) detect embolic acute infarctions in the right striatum and ipsilateral occipital lobe, without hemorrhagic transformation in a 15-year-old patient after weaning. (D) Left parietooccipital acute infarction with scattered small petechial hemorrhage (Heidelberg classification type 1a) (arrows), on axial NECT image in an 11-year-old male with ECMO support.

ECPR, imaged during ECMO and was lost. Four patients had hemorrhagic stroke (2.9 %), three patients with lobar parenchymal hematomas extending to ventricles (2.2%) (Fig. 3, A), and one patient with a small hematoma (0.7%) (Fig. 3, B). Two of the patients with ventricular hemorrhage were lost (VA/VV=1/1), the others survived (VA/VV=1/1). Two patients (10%) had imaging findings consistent with HIE (1.4%), both had VA ECMO and were imaged after weaning (Fig. 4, A-B). The survival rate was 100%. Three patients had PRES (2.2%) (Fig. 4, C-D), all had VA ECMO, the patient imaged during ECMO was lost (survival rate 66.7%). Records of the patients with PRES revealed that all patients had hypertension prior to imaging, one was receiving cyclosporine and another one was receiving anakinra for their underlying diseases which were discontinued after diagnosis. One patient (0.7%) had a diffuse dural venous sinus thrombosis (Fig. 5). He had VV ECMO with right-left jugular vein catheterization and was lost. Scattered microhemorrhages were present in all MRIs on SWI. Six patients had unremarkable/normal findings on imaging. Imaging diagnosis and patients' progress are summarized in Table II. The distribution of imaging findings among different age groups is shown in Table III.

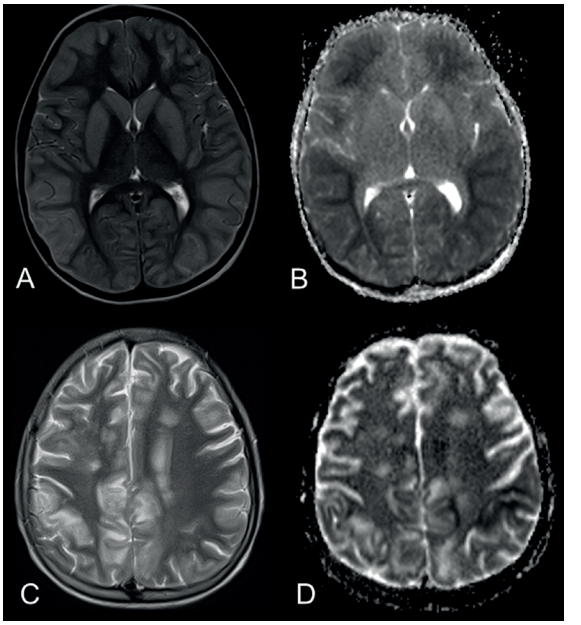

Fig. 4. MRI of a 5-year-old male patient after weaning showing diffuse cortical hyperintensity on T2-weighted MR image (A) and restricted diffusion with prominent signal loss in cortex on ADC map of diffusion weighted image (B) consistent with hypoxic ischemic encephalopathy. (C) Axial T2W MR image of a 13-year-old female after weaning demonstrating patchy hyperintense lesions in cortex and (D) subcortical white matter in both frontal and parietal lobes with heterogenous signal on ADC maps of diffusion weighted image, consistent with PRES.

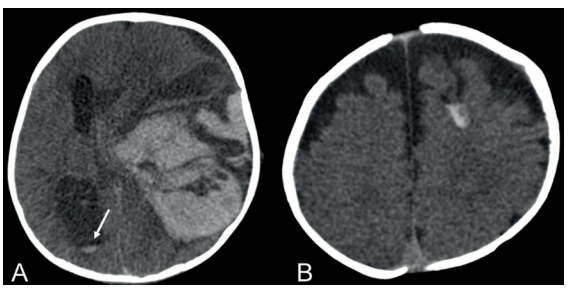

Fig. 3. (A) Axial NECT image of a 5-months-old male (A) with ECMO support, demonstrating a left parietal parenchymal hematoma (>3 cm transverse diameter) extending into ventricles resulting with a midline shift. (B) Axial NECT image of a two month-old male patient after weaning, showing a left frontal parenchymal hematoma with a transverse diameter <3 cm (B).

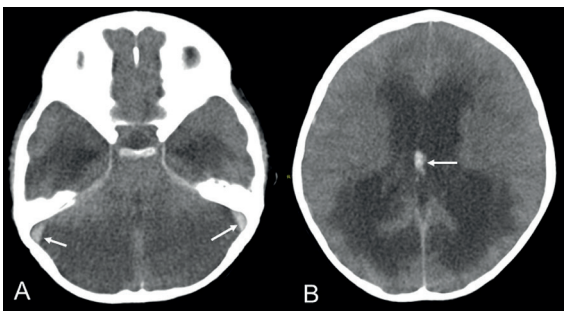

Fig. 5. (A) Diffuse cerebellar edema with hyperdensity in both sigmoid sinuses on axial NECT image of a four-year-old male patient who is on ECMO. The patient also has hydrocephalus with periventricular hypodensity and internal cerebral veins are hyperdense. Findings were suggestive of extensive cerebral venous thrombosis.

Table II. Imaging features and progress of patients.

	Numbers of patients	ECMO type (VA/VV)	Imaging time (during/ after weaning)	CT/MRI	Patient progress (survived/exitus)
Hypoxic ischemic encephalopathy	2	2/0	0/2	0/2	2/0
Posterior reversible encephalopathy syndrome	3	3/0	1/2	2/2	2/1
Venous thrombosis	1	0/1	0/1	1/0	0/1
Ischemic Stroke					
- Large vessel occlusion	1	LVAD	1/0	1/0	0/1
- Embolic infarcts	2	2/0	3/2	1/2	2/0
- Infarcts with hemorrhagic transformation	1	1/0	1/0	1/0	0/1
Hemorrhagic Stroke					
- Large	3	2/1	2/1	3/1	1/2
- Small	1	0/1	0/1	1/1	1/0
Unremarkable/Normal imaging findings	6	6/0	1/5	6/0	5/1

MRI: Magnetic resonance imaging, LVAD: Left ventricle assist device,
ECMO: extracorporeal membrane oxygenation, VA: venoarterial, VV: venovenous,
CT: computerized tomography

Table III. Distribution of imaging findings among ages.

	<1 year old	1-5 years old	>5 years old
Ischemic stroke (±hemorrhagic transformation)	-	1	3
Hemorrhagic stroke	2	2	-
Hypoxic ischemic encephalopathy	-	2	-
Posterior reversible encephalopathy syndrome	-	1	3
Cerebral venous thrombosis	-	1	-
Unremarkable imaging findings	1	2	3

The median duration for ECMO support of patients with unremarkable/normal imaging findings was 8.5 days (IQR 4.25-16.75 days). Of these patients, only one patient (16.7%) was lost due to systemic complications, i.e. lactic acidosis. Fourteen patients had positive neuroimaging findings, the median duration of ECMO was 13 days (IQR 5.5-26.5 days) and 6 patients died eventually (42.9 %). Despite the higher rate of exitus in patients with positive neuroimaging findings, the survival rate and duration of ECMO did not show a statistically significant difference among patients with unremarkable/normal and positive neuroimaging findings ($p>0.05$). Besides, renal failure, sepsis, inotrope support and thrombocytopenia were present in 3/1, 3/0, 11/4 and 9/1 patients with positive and normal/ unremarkable imaging findings, respectively. These features did not significantly differ between patients with positive and normal/ unremarkable imaging findings ($p>0.05$).

Discussion

Patients with ECMO are at risk of severe neurological injury, which in turn increases mortality and morbidity.[5] In our study, we aimed to document the imaging spectrum of ECMO related neurological injuries. In this cohort, the most common neurologic event was hemorrhagic and ischemic stroke (each 2.9%). Our results showed that PRES also occurs in

the setting of ECMO support (2.2%) besides the well-known hemorrhagic /thrombotic stroke and HIE. The major risk factor for ischemic stroke during ECMO is circuit thrombosis with a distant embolus, which might be aggravated by activating pro-thrombotic response due to exposure to foreign surfaces of ECMO and underlying severe systemic diseases.[15-18] Internal carotid artery cannulation is considered another risk factor, yet, not present in our study.[7] The latest Complication Trend Report revealed the survival rate after CNS infarction was 50% for pediatric respiratory, 45% for pediatric cardiac and 20% for pediatric ECPR in 2019.[19] However, it did not include data about hemorrhagic transformation of ischemic strokes. The survival rate of ischemic stroke was 50% in our study. Not surprisingly, occlusion of a large vessel and hemorrhagic transformation of ischemic infarct was related to poor outcome in the patients, as those who did not survive had large vessel occlusion and hemorrhagic transformation of ischemic embolic stroke.

Major risk factors for intracerebral hemorrhages in adults were shown by studies that revealed pre-ECMO cardiac arrest, sepsis, renal replacement therapy, thrombocytopenia, hemolysis, inotropic support, acute rapid increase in PaO2, and decrease in PaCO2 with the initiation of ECMO as the risk factors.[20-22] On the other hand, pediatric risk factors for hemorrhage have not been extensively studied. In our cohort, there were three patients with lobar hemorrhages extending into ventricles and only one survived. The survival rate was the lowest (33.3%) in this group in our cohort. The hematoma size, mass effect and presence of extension into ventricles in 3 of 4 patients with hematoma can explain poor survival rates herein this cohort.

The incidence of hemorrhagic and ischemic stroke (2.9%) was lower in our cohort compared to the ELSO Report which reported CNS infarction as 3-11%, and intracranial hemorrhage as 6-14%.[3] This might be due to the exclusion of US as a diagnostic tool in this study. On the other hand, the ELSO registry did not report stroke patterns in detail (i.e. ischemic vs HIE, hemorrhagic transformation of ischemia vs hematoma). While the detailed classification of neuroimaging patterns in our study fills in the lacking information, it also leads to lower rates.

Cerebral diffuse ischemia (HIE), one of the associated neurological complications of ECMO, was not listed as a discrete complication until 2016. In the pre-ECMO period, the underlying severe diseases leading to severe cardiogenic shock or hypoxia may end up with decreased cerebral blood flow or oxygen delivery, therefore it may not be directly related to ECMO. On the other hand, the pericannulation period is a risk factor for HIE.[4] Although both patients with HIE in our study survived, the survival rate from HIE was reported as 6-50 % for 2019 in the latest Complication Trend Report.[19] As HIE has been reported in Complication Trend Reports since 2016, the incidence and risk factors for HIE associated with ECMO remain to be unclear.

Impairment of cerebral autoregulation can be considered as increased vulnerability of our patients' brains to any kind of insult in the presence of ECMO as cerebral autoregulation impairment was previously shown to be correlated with the presence of abnormal and severe neuroimaging findings.[23] Animal studies showed that exposure to hypoxia affected cerebral autoregulation, which also remained impaired during the recovery phase.[24,25] Especially low flow rates (<150ml/kg/min) and loss of pulsatile flow in ECMO were shown to alter cerebral autoregulation.[26-29] Several studies in pediatric patients with ECMO supported these findings with noninvasive monitoring.[30-32] In the literature, there are only two adult case reports defining PRES in patients with ECMO.[33,34] However, in the present cohort, there were 3 patients with PRES (2.2%), who were imaged during or post-ECMO. Medical records of these patients revealed a slight increase in systemic blood pressure during ECMO and two of them were receiving medications (anakinra, cyclosporine) which were potential risk factors for PRES. Although the classical risk factors for PRES were present, impaired cerebral

autoregulation in these patients might have caused the brain microcirculation to become vulnerable to slight changes in these patients.

The studies in the literature do not differentiate ECMO related venous complications in the CNS. However, central vein catheterization is a known risk factor for jugular vein and/or cerebral sinus venous thrombosis. In a study of CT imaging after VV ECMO, 63.1% of patients with femoro-jugular catheterization demonstrated deep venous thrombosis.[35] The only patient with cerebral sinus venous thrombosis in our cohort had jugulo-jugular catheterization which might have induced and aggravated the formation of venous thrombosis and extension cranially.

The imaging findings demonstrated slight differences between different age groups as shown in Table III. Ischemic stroke and PRES tend to be seen in elder children, however, hemorrhagic stroke is more common in younger children. Due to the limited number of patients, these findings should be investigated further in larger cohorts.

The limitations of our study include retrospective design and the limited number of patients, especially infants. The transportation of patients with ECMO to imaging units is problematic. With the advances and access to portable CTs, patients can be imaged more easily which will help with the understanding of neurological complications in these patients. The limited number of infants in the present study is a consequence of our exclusion criteria. We excluded the patients having only US, which is the situation for most infants due to its bedside availability. Because of the retrospective design, it was not possible to review the US studies. We avoided including findings based on the subjective reports limited by the user's experience. As a result of the exclusion of US, the study population mostly consisted of elder children. So, we can say that our findings might not represent infants. The absence of cranial imaging prior to ECMO is another limitation, however imaging for all ECMO candidates is not practical in clinical routine especially given the current status of these patients.

Neurological complications during or after ECMO are potential risk factors for increased morbidity and mortality. Besides the commonly encountered intracranial thrombotic and hemorrhagic complications, PRES can also be seen. The patients with ECMO should receive appropriate radiological evaluation regarding the spectrum of neuroimaging abnormalities.

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Ethical approval

This retrospective study was approved by the Hacettepe University institutional review Board (04.05.2021 - GO21/607).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: EG, BK, ŞP, SK, BB, KKO; data collection: EG, BK; ŞP; analysis and interpretation of results: EG; SK; BB, KKO; draft manuscript preparation: EG, SK, BB, KKO. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

Supplementary information is available at: http://www.turkishjournalpediatrics.org/uploads/turkjped.2022.323.S1.pdf

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