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Original article

Cytotoxic lesions of the corpus callosum in children: Etiology, clinical and radiological features, and prognosis

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Abstract

Objectives: Cytotoxic lesions of the corpus callosum (CLOCCs) are secondary lesions associated with entities like infection manifested by restricted diffusion on diffusion-weighted cranial magnetic resonance imaging. Our objectives are to evaluate the clinic-radiological spectrum of pediatric patients with cytotoxic lesions of the corpus callosum (CC).

Methods: Children (0–18 years) admitted between February 2017 and May 2020 with splenial lesions showing diffusion restriction on MRI, either isolated or within involvement of other parts of the brain, were included retrospectively. The primary lesions of the CC (e.g. acute disseminated encephalomyelitis, acute ischemic infarction, and glioblastoma multiforme) were excluded. CLOCCs were divided into infection-associated, metabolic disorder–associated, and trauma-associated lesions, as well as CLOCCs involving other entities. Data were collected from the medical databases.

Results: Forty-one patients were determined to have CLOCCs. Twenty-five (61%) were infection-associated, nine (22%) were trauma-associated, and three (7%) were metabolic disorder–associated cases, including 2 inherited disorders of metabolism. There were four (10%) patients with other entities, three with epilepsy, and one had an apparent life-threatening event. Six patients had a known etiology among the infection-associated group; one had multisystem inflammatory syndrome caused by COVID-19 and one had been infected by COVID-19 without any complications. All the infection-associated patients with isolated splenial lesions recovered totally, although six patients required intensive care hospitalization. Four trauma-associated patients had sequela lesions.

Conclusions: CLOCCs are associated with a spectrum of diseases, including the new coronavirus, COVID-19 infection. Infection-associated CLOCCs has the best prognosis, although severe cases may occur. Sequelae are possible based on the etiology.

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1. Introduction

The corpus callosum (CC), consisting of white matter tracts responsible for interhemispheric communication and coordination, is the primary telencephalic commissure. It comprises the rostrum, the genu, the body, and the splenium [1]. Transient ovoid lesions in the splenium with diffusion restriction were first reported in epileptic patients in the late 1990s and early 2000s [2-4]. Later, infectious causes, such as influenza and rotavirus, were identified in patients with splenial lesions, and these findings were published as case reports [5,6]. In 2004, Tada et al. described mild encephalitis/encephalopathy with reversible splenial lesion (MERS) as a new clinico-radiological syndrome in 15 patients. In their description, the hallmarks of this disease were initial infectious signs with mild encephalopathy, splenial diffusion restriction on magnetic resonance imaging (MRI; either ovoid or extending laterally), and total recovery of the patients and the lesions in at most 2 months [7]. Later, in addition to the infection-related entity called MERS, a general term called reversible splenial lesion syndrome (RESLES) was proposed for diverse etiologies, such as antiepileptic drug withdrawal, high-altitude cerebral edema, and metabolic disorders (e.g., hypoglycemia and hypernatremia) [8]. Recently, a new, more extensive term—cytotoxic lesions of the CC (CLOCCs)—has been used as a general description for all conditions, including MERS, RESLES, reversible splenial lesions, and transient splenial lesions. CLOCCs are secondary lesions of the CC that are usually reversible; they tend to differ from primary lesions of the CC, such as acute disseminated encephalomyelitis (ADEM), glioblastoma multiforme, and acute arterial ischemia. Infection- and trauma-associated causes are the most common etiologies of CLOCCs [9].

Although many case reports and a small series of patients have been presented since the first description of CLOCCs, these sources mainly focus on infection-associated patient series with a reversible outcome or isolated case reports of rare presentations [10-14]. While most patients with CLOCCs have only splenial CC involvement, such etiologies as metachromatic leukodystrophy, urea cycle defects (by causing hyperammonemia), and diffuse axonal injury (DAI) may all cause lesions in different parts of the brain with splenium involvement, potentially resulting in irreversible damage [15,16]. To our knowledge, there are no pediatric case series of CLOCCs with a wide spectrum of etiologies involving irreversible causes. Furthermore, the clinical course of infection-associated CLOCCs is not always mild as reported at first; some patients show a complete recovery in a few days [7], whereas in others, recovery is much longer and the course is more severe, necessitating pediatric intensive care unit (PICU) admission [17]; still, many studies do not present intensive care unit hospitalization rates [12,18]. Our aim is to present a large series of pediatric patients with CLOCCs that involve both reversible and irreversible etiologies. We also describe rare entities, including inborn errors of metabolism, emphasizing the clinical course with impairment of consciousness classification, PICU hospitalization rates, and detailed radiological features.

2. Materials and methods

Children aged 0–18 years who were treated at five different pediatric neurology/radiology centers between February 2017 and May 2020 were included in the study. Patients had splenial lesions showing diffusion restriction on MRI, either isolated or with the involvement of other parts of the brain. The radiology database was searched in the centers using the terms "diffusion restriction" and "splenium" to identify patients. All imaging was performed using 1.5 Tesla MRI scanners. At a minimum, beyond diffusion-weighted imaging (DWI), the sequences obtained included T1- and T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR), and the apparent diffusion coefficient. DWI was performed in axial planes according to the standard protocol. A gadolinium-based contrast agent was used when necessary. A pediatric radiologist reviewed each image for suitability for the study and imaging characteristics. A follow-up MRI was obtained in the first 30 days after the first MRI to see if the lesions were resolved. Each patient with an isolated splenial lesion except two patients had a follow-up MRI performed. The radiological features associated with CLOCCs were as follows: (a) a small round or oval lesion located in the center of the splenium and (b) a lesion centered in the splenium but extending laterally through the callosal fibers into the adjacent white matter [9]. Patients who had involvement in other parts of the brain were included in the study when at least one of the above criteria was present. Primary lesions of the CC (e.g., ADEM, acute ischemic infarction, and glioblastoma multiforme) were excluded.

CLOCCs were divided etiologically into infection-associated, metabolic disorder-associated, and trauma-associated lesions, as well as CLOCCs involving other entities [9]. We also divided CLOCC patients into two categories radiologically, with one group including those with isolated splenial lesions and the other including those with splenium and other brain parts involvement. The following data were retrospectively reviewed and recorded for each patient with isolated splenial lesions: demographics; prodromal and initial neurological symptoms; neurological examination results; medical history; electroencephalography (EEG) findings; relevant laboratory findings, such as C-reactive protein (CRP) and cerebrospinal fluid (CSF) results; infection etiology; the presence of seizures; treatments; follow-up MRI; hospitalization days, including intensive care unit (ICU) stay; and final etiology of CLOCCs. To group patients, impairment of consciousness was divided into two categories—reduced mental state and activated state. Drowsiness, stupor, obtundation, and coma were all reduced states, while hallucinations and delirium were activated states of impaired consciousness [19]. Hyperactive delirium is characterized by agitation, restlessness, hypervigilance, irritability, delusions, and hallucinations, and mixed delirium is a combined form of hypoactive (mainly slowed speech, mental retardation, and somnolence) and hyperactive delirium [20]. For patients with splenial lesions with other brain parts involved, demographics, prodromal and initial neurologic symptoms, neurologic examination results, significant laboratory investigations, cranial MRI findings, follow-up MRI findings when available, sequela rates, and final diagnoses of patients were recorded. Ethical committee approval was obtained for this retrospective study. Frequency distribution (number, percentage) for categorical variables and descriptive statistics (mean, standard deviation) for numerical variables were described using SPSS 21.0.

3. Results

Forty-one patients were determined to have CLOCCs. The patients' mean age was 7.82 ± 4.84 years, with a median of 7 years (range: 0.25–17). Nineteen (46%) patients were girls, and 22 (54%) were boys. Twenty-five (61%) patients had infection-associated CLOCCs. There were nine (22%) trauma-associated cases and three (7%) metabolic disorder–associated cases, including two inherited disorders of metabolism (saposin B deficiency and argininosuccinic aciduria). There were four (10%) patients with other entities. A detailed etiological summary is presented in Table 1.

Table 1
Etiological summary of all patients with CLOCCs.

Etiologies	Number of patients (%)
Infection-associated	**25 (61%)**
COVID 19 PCR positive	1
COVID 19 Ig M positive IgG positive	1
Influenza A H1N1 positive	1
Influenza A positive	1
Meningococcemia	1
Stool amoeba cysts	1
Unknown	19 (76%)
Trauma-associated	**9 (22%)**
Diffuse axonal injury	9
Metabolic disorders-associated	**3 (7%)**
Hypoglycemia	1
Saposin B deficiency	1
Argininosuccinic aciduria	1
Other	**4 (10%)**
Epilepsy	3
ALTE	1

3.1. Infection-associated patients

Twenty-five patients had infection-associated CLOCCs. The average age of the infection-associated patients was 8.8 ± 4.15 years (median: 8 years, range: 3–17 years). Twelve (48%) patients were girls, and 13 (52%) were boys. Details of 23 infection-associated patients with isolated splenial lesions, excluding the two infection-associated patients with meningococcemia and encephalitis with splenium and other brain parts involvement, are given in Table 2. Fever was the most common complaint in the infection-associated group of patients, and 21 (84%) patients had this symptom. Vomiting was present in 13 (52%) and diarrhea in 5 (2%) patients in the infection-associated group. Neurological signs were present in 22 (88%) patients. The most common neurological symptoms/findings were impairment of consciousness with reduced mental state in seven (28%) patients and seizure in seven (28%) patients (five had isolated seizure; two had seizures with impairment of consciousness, one with a reduced and one with an activated mental state; Table 3). CRP levels of infection-associated patients were available in 22 patients, with a median of 15.5 (range: 0.4–392 mg/L; normal levels < 5 mg/L). Serum sodium levels are also described in Table 2. Fifteen patients underwent lumbar puncture, and CSF glucose and protein levels were normal in all of them; only three patients had mild pleocytosis of 10, 50, and 64/mm^3. The most common pattern of splenial diffusion restriction was ovoid (Fig. 1). EEG was also conducted in 15 patients; normal results were observed in 11 (73%) patients, encephalopathic changes in 3 (20%) patients, and epileptic activity in 1 (7%) patient.

The median total hospitalization length was 10 days (range: 2–21 days). Patients were mostly treated with ceftriaxone and acyclovir. Six patients were treated in the ICU, with a median stay of 5 days (range: 3–11 days). All patients with isolated splenial lesions had a normal follow-up MRI. The patient described as having encephalitis in Table 4 had multiple lesions, including

Table 2
Detailed features of CLOCCs patients with isolated corpus callosum splenium involvement.

Case no	Age yrs	Sex	Complaints	Neurological exam	History	Serum Sodium, CRP	CSF analysis	Infectious Etiology	EEG	Seizure	Treatment	ICU stay (days)	Hospital Stay (days)	Follow-up MRI	Final diagnosis
1	6	F	Fever, vomiting, sleepiness	Stupor	Febrile seizures	134 mEq/L 107 mg/L	CSF glu, prot N Leu70/mm^3 Eryt 176/mm^3	Unknown	Backgro-und slowing	No	Ceftriaxone Acyclovir Oseltamivir Levetiracetam	6	14	Normal	Infection-associated
2	10	F	Fever, vomiting, abdominal pain, seizure	Lethargy	ADHD	135 mEq/L 13 mg/L	NA	Stool Amoeba cyst	NA	Yes	Ceftriaxone	None	7	Normal	Infection-associated
3	12	M	Fever, sleepiness, nonsense talk	Confusion, lethargy	None	135 mEq/L 42 mg/L	NA	Influenza A	NA	No	Ceftriaxone Oseltamivir	None	7	Normal	Infection-associated
4	7	F	Fever, vomiting, seizure	Lethargy	None	133 mEq/L 99 mg/L	NA	Unknown	NA	Yes	Vancomycin Ceftriaxone Acyclovir	None	NA	Normal	Infection-associated
5	4	M	Fever, ataxia	Ataxia	Adenoidec-tomy	137 mEq/L 72 mg/L	NA	Unknown	Normal	No	Ceftriaxone Acyclovir	None	13	Normal	Infection-associated
6	14	F	Fever, vomiting, diarrhea, malaise	Obesity Conjunctival hyperemia Fundus GII papilla edema	None	NA 370 mg/L	NA	Unknown	NA	No	Ceftriaxone Vancomycin Meropenem Steroids oral Acetazolamide	None	14	Normal	Infection-associated
7	8	M	Fever, 4 GTC seizures	Postictal	None	140 mEq/L NA	CSF glu, prot N, Leu 3/mm^3	Unknown	Normal	Yes	Ceftriaxone Levetiracetam	NA	NA	Normal	Infection-associated
8	3	M	Fever, seizure, diarrehea, confusion	Postictal	None	128 mEq/L 25 mg/L	CSF glu, prot N, No cells CSF viral PCR neg	Unknown	Normal	Yes	Ceftriaxone Acyclovir Levetiracetam	3	10	Normal	Infection-associated
9	17	M	Nausea, vomiting, paresthesia on the face	Normal other than sensory symptoms	None	137 mEq/L 4,6 mg/L	Not performed	Unknown	NA	No	None	None	2	Normal	Infection-associated
10	11	F	Fever, headache, hallucinations	Confusion, lethargy, mixed delirium	None	131 mEq/L 12,7 mg/L	CSF glu, prot N, Leu 4/mm^3 viral CSF PCR neg	InfluenzaA (H1N1)	Normal	No	Ceftriaxone Acyclovir	None	7	Normal	Infection-associated
11	5	M	Fever, seizure, vomiting, diarrhea	Normal	Eight febrile seizures	130 mEq/L 4,4 mg/L	CSF glu, prot N	Unknown	Tempo-ral epilepticactivity	Yes	Ceftriaxone Acyclovir Valproic acid	None	10	Normal	Infection-associated
12	14	F	Cough, seizure	Normal	None	137 mEq/L 1,3 mg/L	CSF glu, prot N, Leu 5/mm^3 viral CSF PCR neg	Unknown	Normal	Yes	Ceftriaxone Acyclovir	None	10	Normal	Infection-associated
13	11	F	Fever, vomiting, sleepiness	Lethargy	Premature birth	137 mEq/L 0,4 mg/L	CSF glu 49, prot 54 mg/dl 64 cells	Unknown	Normal	No	Ceftriaxone Acyclovir Vancomycin	11	14	Normal	Infection-associated
14	8	M	Fever, sleepiness, seizure	Lethargy	Myasthenia gravis, using pyridostig-mine	134 mEq/L 16 mg/L	CSF glu, prot N, No cells CSF	Unknown	Normal	No	Ceftriaxone Acyclovir	3	7	Normal	Infection-associated
15	5	F	Fever, vomiting, diarrhea, seizure, agitation	Lethargy	None	133 mEq/L 1,3 mg/L	CSF glu, prot N, No cells CSF viral PCR neg	Unknown	Normal	Yes	Ceftriaxone Acyclovir	4	7	Normal	Infection-associated

16	6	M	Cough, vomiting, confusion	Normal other than confusion	None	134 mEq/L 5,8 mg/L	CSF glu, prot N, No cells CSF CSF viral PCR neg	Unknown	Normal	No	Ceftriaxone Acyclovir	None	11	Normal	Infection-associated
17	7	M	Fever, vomiting, headache	Normal	None	134 mEq/L 6,2 mg/L	NA	Unknown	NA	No	NA	NA	NA	Normal	Infection-associated
18	14	M	Fever, vomiting, con-fusion, ataxia	Lethargy	None	130 mEq/L 15,1 mg/L	CSF glu, prot N, Leu 10/mm^3 viral CSF PCR neg	Unknown	NA	No	Ceftriaxone Acyclovir	None	21	Normal	Infection-associated
19	12	F	Fever, vomiting	Nuchal rigidity	None	131 mEq/L 33,7 mg/L	CSF glu, prot N, Leu 1/mm^3 viral CSF PCR neg	Unknown	NA	No	Ceftriaxone Acyclovir Oseltamivir	None	10	Normal	Infection-associated
20	3	M	Nausea, fever, vomiting, malaise, vision loss for 1 h	Normal	None	133 mEq/L 13 mg/L	CSF glu, prot N, no cells	Unknown	Normal		Levetiracetam Ceftriaxone Acyclovir	None	7	Normal	Infection-associated
21	7	F	Abdominal pain, fever, vomiting, diarrhea, headache, double vision	Normal	Oligohydram-nios, emergent C/S NICU hospitaliza-tion due to respiratory distress	NA, 159 mg/L	NA	Unknown	NA	No	Ceftriaxone	None	7	Normal	Infection-associated
22	10	M	Fever, skin eruptions (trunk, hand, and feet), diarrhea, hallucinations, disorientation	Skin eruptions, CNS dysfunction, Hyperactive delirium	None	133 mEq/L 392 mg/L	CSF glu, prot N, no cells	COVID Ig M and Ig G positive, PCR negative	Back-ground slowing	No	Ceftriaxone Vancomycin Azithromycin Prednisolon IVIG LMWH	11	11	Normal	Infection-associated (COVID – multisystem inflammatory syndrome)
23	16 years1 mo	M	Headache, fever	Normal	None	138 mEq/L 45 mg/L	CSF prot: 17,9 glu: 62 mg/dl, no cells. Culture: sterile. Viral and bacterial panel negative	Covid-19 PCR +	NA	No	Hydroxychloro-quine	None	10	Normal	Infection-associated (COVID)
24	4	F	Vomiting, diarrhea	Lethargic Tachycardic Hypotensive	None	24,5 mg/L	NA	Unknown	NA	Yes	Cefotaxime Gentamycin Plasmapheresis	12	22	NA	Metabolic-associated (Hypoglycemia)
25	13	M	Seizure	Postictal	Epilepsy After normal 24 h EEG antiepileptic drug withdrawal	NA	Not performed	No infection	Normal	Yes	None	None	1	Normal	Other (Epilepsy)
26	3 days	F	Seizure	Normal	Term, no known HİE	NA	NA	No infection	NA	Yes	Antiepileptics	45	45	Normal	Other (Epilepsy)
27	8	F	Seizure	Normal	Epilepsy 2 months ago another seizure	2 mg/L	NA	No infection	Normal	Yes	Oxcarbazepine Levetiracetam	None	1	Normal	Other (Epilepsy)
28	5 mos	M	Found in bed pale and not moving	Normal	None	11 mg/L	NA	Unknown	NA	?	Ceftriaxone	None	9	NA	Other (ALTE)

Table 3
Neurological signs and symptoms of infection-associated patients with CLOCCs.

Neurological signs and symptoms	Number of patients (%)
Impairment of consciousness with a reduced mental state	**7 (28%)**
Stupor	4
Confusion	1
Confusion and stupor	1
Stupor and ataxia	1
Impairment of consciousness with an activated mental state	**2 (8%)**
Headache and mixed delirium	1
Hyperactive delirium	1
Seizure	**7 (28%)**
Isolated	5
Seizure and impairment of consciousness with an activated mental state (agitation)	1
Seizure and impairment of consciousness with a reduced mental state (confusion)	1
Others	**6 (24%)**
Ataxia	2
Paresthesia on face and hands	1
Headache	1
Vision loss	1
Headache and double vision	1
None	**3 (12%)**

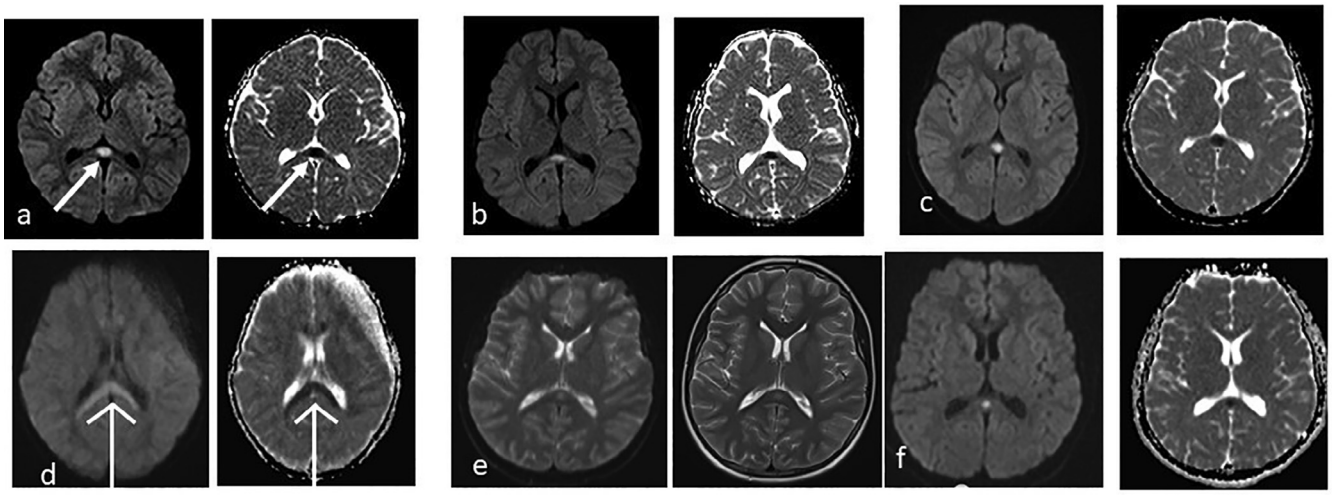

Fig. 1. Examples of infection-associated CLOCCs on diffusion and apparent diffusion coefficient weighted cranial MRIs, ovoid-shaped (a,b,c) is more common although lesions extending through the callosal fibers laterally into the adjacent white matter (d) can be encountered. Only lesions in figures (a) and (d) are represented with arrows to orient readers. Diffusion and T2 weighted MRI of patient 22 in Table 2 with COVID- 19 associated multisystem inflammatory syndrome (e). Diffusion weighted MRI of patient 23 in Table 2 with COVID-19 is shown (f).

diffusion restriction in the CC genu, splenium, bilateral dentate nucleus, and left parietal cortical-subcortical T2 hyperintensity. Her follow-up MRI was normal, and the patient with meningococcemia in Table 4 had a sequela of gliosis in the right periventricular white matter.

To give examples of how the clinical course of the disease differed, two patients are described. Patient 1 (aged 6 years and female) in Table 2 was admitted with fever, vomiting, and sleepiness; she stayed in the ICU for 6 days and was hospitalized for 14 days. Following her 6 days in the ICU, she did not have excessive sleepiness but could not sit without support. A few days later, she could sit without support, and later, she could stand independently. Before discharge, she could walk and speak two- to three-word sentences. In her follow-up examination after a month, the patient's muscle strength and coordination were normal. Although she had become more fluent, her speech was slower than usual. Two months after the disease onset, the patient's speech returned to normal. Patient 21 in Table 2, a 7-year-old girl, had only headache and double vision lasting a few seconds as neurological signs, without any impairment of consciousness; her first diffusion-weighted

Table 4
Details CLOCCs patients with splenial diffusion restriction with other brain parts involvement with/without sequela lesions.

Features of patients	Number of patient (%)
Etiology	
Trauma-associated	9
Diffuse axonal injury	9
Infection-associated	2
Encephalitis	1
Meningococcemia	1
Metabolic disorders-associated	2
Argininosuccinic aciduria	1
Saposin B deficiency	1
Radiological features of patients	
Only splenium involvement in CC	9 (69%)
Involvement of other CC parts than splenium	4(27%)
Brain involvement other than CC	12 (92%)
Contrast enhancement	1 (7%)
T2/FLAIR hyperintense cortical lesions	5 (39%)
T2/FLAIR hyperintense subcortical lesions	9 (69%)
Additional intraparenchymal hemorrhage/microhemorrhage	5 (39%)
Mass effect	0
Patients with a follow-up MRI	
Diffuse axonal injury	6 (67%)
Encephalitis	1
Meningococcemia	1
Argininosuccinic aciduria	0
Saposin B deficiency	0
Sequela lesions on follow-up MRIs	
Diffuse axonal injury	
Cystic	1
Gliotic	2
Cystic-Gliotic	1
None	2
Meningococcemia	
Gliotic-hemorrhage	1
Encephalitis	
None	1

MRI (performed 2 days after symptom onset) was normal, although slight diffusion restriction could be detected retrospectively; her second MRI, performed 5 days after the first one, revealed obvious diffusion restriction (Fig. 2). The patient's neurological signs had resolved by about 7 days. Two patients with coronavirus disease 2019 (COVID-19) were also represented in the present study; details are given in Table 2 (patients 22, 23). A case study on one of these patients, who had multisystem inflammatory syndrome, has been previously published [21].

3.2. Trauma-associated patients

Out of nine trauma-associated patients, three children had traffic accidents as pedestrians and two as passengers in a motor vehicle. Two had fallen from heights, and two had a television fall on them. Beyond the splenial lesions, five patients had both T2/FLAIR hyperintense cortical and subcortical lesions (Fig. 3), while four had only subcortical lesions. Five patients had intraparenchymal hemorrhage/microhemorrhage. Six patients had a follow-up MRI performed, and four had sequelae lesions. Although this patient group had multiple lesions, a patient with a history of a traffic accident as a passenger had only splenial diffusion restriction mimicking infection-associated CLOCCs (Fig. 4). A neuroradiological summary of 13 patients (age: 5.94 $\pm$ 5.45 years; six girls, seven boys) with multiple lesions, including trauma-associated CLOCCs, is given in Table 4.

3.3. Metabolic disorder–associated patients

Three patients exhibited CLOCCs associated with metabolic disorders. The first had argininosuccinic aciduria, the second had saposin B deficiency, and the third had hypoglycemia. The patient with argininosuccinic aciduria had hyperammonemia (2,500 μg/dl) and was treated with plasmapheresis as a newborn, but she died at 3 months of age. The patient with saposin B deficiency had spastic tetraparesis. The patient with hypo-

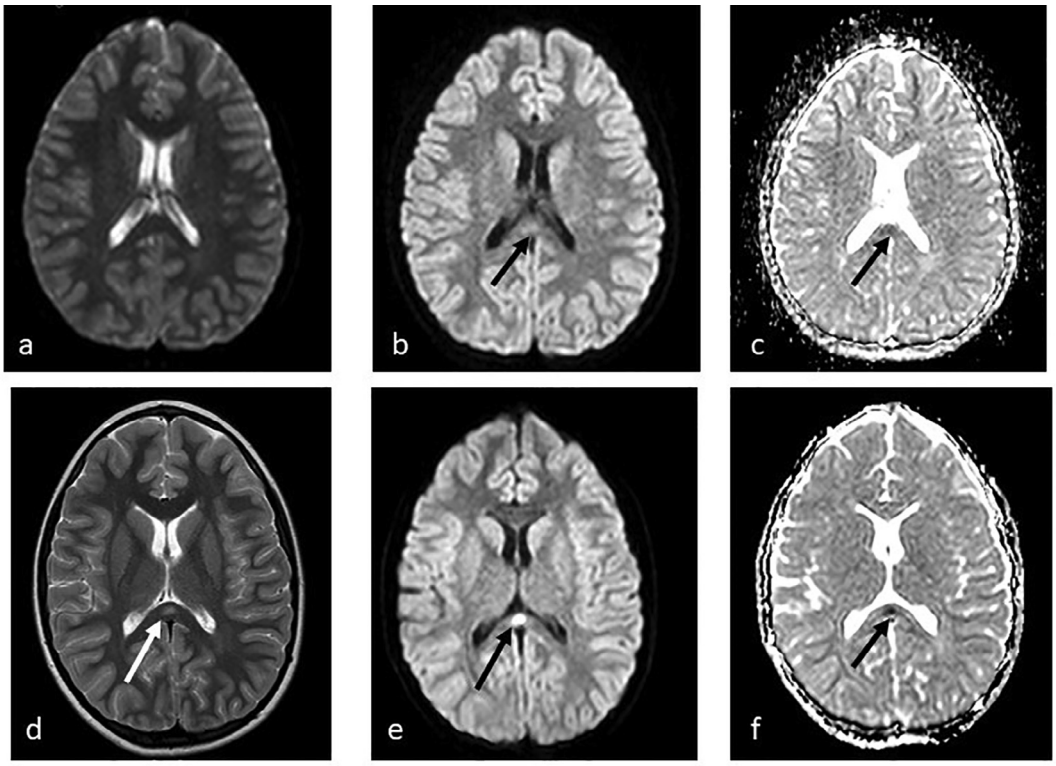

Fig. 2. Patient 21′s (Table 2) first T2 (a) and diffusion weighted MRI (b,c) reported to be normal although very slight diffusion restriction with normal T2 intensity in the splenium could be identified retrospectively. Her follow-up MRI (d,e,f) 5 days later reveals splenial ovoid diffusion restriction with T2 hyperintensity.

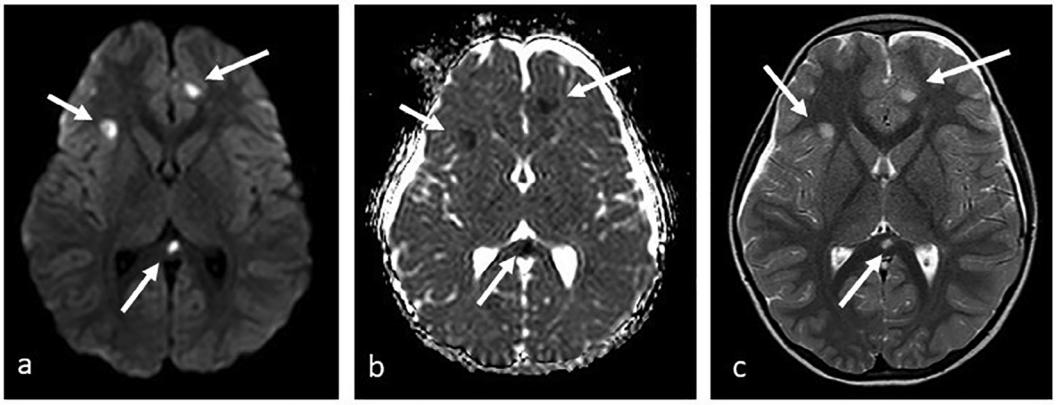

Fig. 3. Diffuse axonal injury of another patient caused by trauma due to in-car traffic accident, splenial, frontal cortical and, subcortical splenial diffusion restriction (a,b) and, T2 hyperintensity in the same areas of involvement(c).

glycemia, who had an isolated splenial lesion (patient 24 in Table 2), was normal neurologically at her follow-up examination. None of these patients had follow-up MRIs. Fig. 5 shows the MRIs of patients with inborn metabolism errors.

3.4. Other entities

Four patients were categorized into the group of other entities with CLOCCs. Three patients had epilepsy, whereas one had an apparent life-threatening event (ALTE; Fig. 5). Details of these four patients are presented in Table 2 because they had isolated splenial lesions. Patient 25 (13-year-old boy) in Table 2 with epilepsy using antiepileptic drugs had stopped medications because he had a normal 24-hour EEG, but a few days later, he was admitted to hospital because of a seizure, and CLOCCs were detected in his MRI. Two other female patients (patients 26 and 27 in Table 2) had refractory epilepsy despite antiepileptic therapy; one

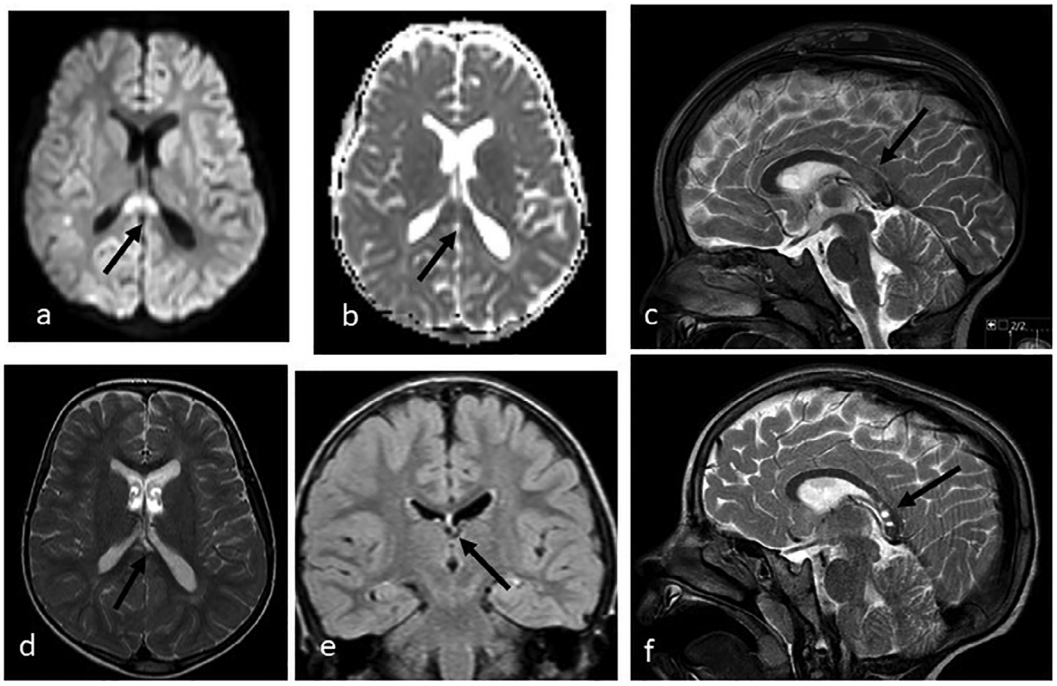

Fig. 4. Diffuse axonal injury due to television fall over in a 3-year-old child showing splenial diffusion restriction irregularly shaped (a,b,c), 2 months later cystic sequela changes is evident in the same area on T2 and FLAIR weighted MRI (d,e,f).

had seizures starting as a newborn, and the other had seizures since 5 years old, both with unknown etiology. A 7-month-old patient was found pale, not breathing, and not moving in bed (patient 28 in Table 2). He was not resuscitated by mouth, but he was given a tactile stimulus. At the emergency department, his blood gas analysis results were pH 7.35, HCO_3^- 15 mEq/L, and lactate 4.1 mmol/L. The patient was hospitalized, and his follow-up blood gas analysis was normal. His status was accepted as an ALTE. He had severe vitamin B12 deficiency (68 pg/ml), and treatment with intramuscular hydroxocobalamin was started. The patient's later vitamin B12 level was 309 pg/ml. He did not have any further events in the hospital and was discharged home after 5 days. He did not have a follow-up MRI.

4. Discussion

The present work is the only CLOCC series of pediatric patients with multiple etiologies in the literature, involving not only infection-associated patients but also patients with trauma, epilepsy, neurometabolic disease, hypoglycemia, and ALTE. Fang et al. [11] described 29 children with MERS, 19 of which were enrolled by reviewing the available literature. Twenty-three episodes of reversible splenial lesions during febrile illness have been reported by Kashiwagi et al [22], with six episodes associated with MERS. Chen et al. presented 16 RESLES episodes, with 13 involving MERS [12]. We presented clinico-radiological data on 41 patients, with 25 associated with infection. Although transient splenial lesions seem uncommon in children, there may be more than are detected because such lesions may go unrecognized in many cases [15]; in our series, one patient's first diffusion-weighted MRI report was normal, but it was retrospectively found to have slight diffusion restriction; a second MRI performed 5 days later showed ovoid diffusion restriction compatible with infection-associated CLOCCs. Many children exhibit malaise and headache during infectious illnesses, which is supposed to be due to high fever, and they do not have neuroimaging performed. The favorable clinical outcome without any specific therapy contributes to the phenomenon whereby the cases remain unnoticed [8].

Other than infection, trauma, metabolic diseases, and epilepsy are the most common etiologies of CLOCCs [8]. To our knowledge, no previous case of ALTE has been reported to have splenial lesions. One case report identified cranial MRI lesions associated with hypoxia without any splenium involvement [23]. ALTE was once referred to as *near-miss* sudden infant death syndrome, and this phenomenon has multiple causes, including gastroesophageal reflux, seizures, acute respiratory infection, arrhythmia, and non-accidental trauma [24]. Hypoxia, circulation failure, and perhaps metabolic alteration caused by ALTE may all contribute to CLOCCs. Unfortunately, the exact cause of our patient's ALTE is unknown, although severe vitamin B12 deficiency was discovered.

Various infectious agents have been reported to be linked with infection-associated CLOCCs in children, and viruses are the most common of these [12]. We

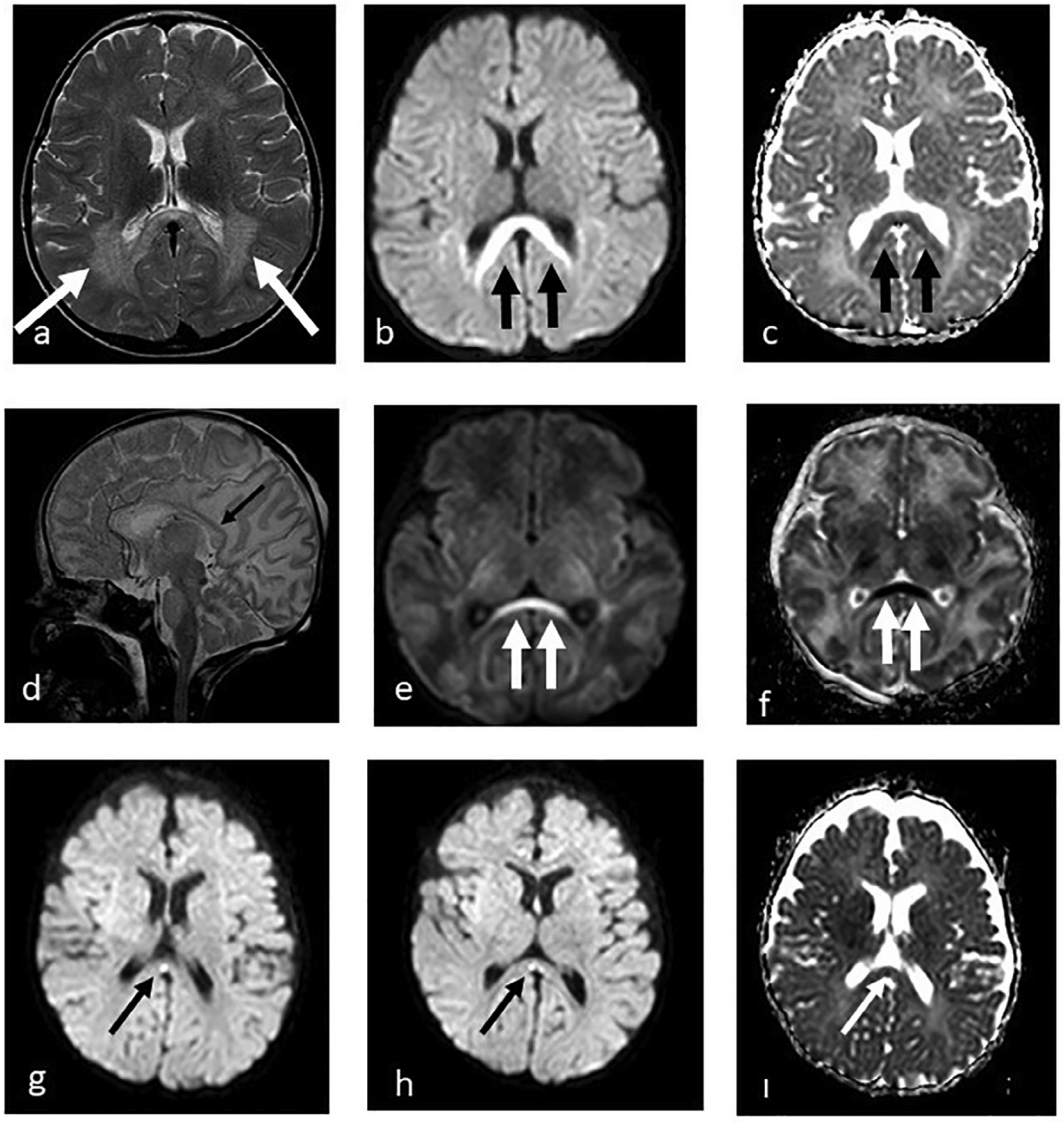

Fig. 5. Periventricular white matter involvement more significant in the posterior, revealing as T2 hyperintensity (a) of the patient with saposin B deficiency showing also splenial diffusion restriction extending laterally (b,c). Patient with argininosuccinic aciduria with T2 hyperintensity of splenium (d) with similar diffusion restriction pattern (e,f) and Patient with appearing life threatening event showing millimetric diffusion restriction (g,h,ı).

could only identify an etiology in 24% of our infection-associated cases, which was lower than the reported rate [12,22]. We found that fever was the most prevalent symptom in infection-associated patients, and this was evident in 84% of cases; vomiting was the second most prevalent symptom. Fever has been reported to be exhibited in 57.1%–100% [7,12,22] of evaluated patients, similar to our results. Lymph node enlargement and joint effusion are rare manifestations in the literature [12], whereas vision loss, paresthesia on the face and hands, and papilledema were infrequent and striking presentations in our study.

PICU unit hospitalizations occurred in six (26%) patients with infection-associated CLOCCs in our study, although all had a complete recovery. Infection-associated CLOCCs are generally known to have a benign clinical course [11], but there are still reports describing patients who have had a severe clinical course, and some have even found sequelae in children and adults [12,17,18]. Regarding severity, Chen et al. [12] classified patients into two groups, severe and non-severe, according to the clinical global impression scale. They found that the non-severe group had statistically significantly lower rates of altered consciousness, motor deterioration, abnormalities of initial EEG, or extra-splenial lesions; however, only days of hospitalization were reported, whereas PICU admissions were not mentioned. There are no clear reasons why our patients

seem to be admitted to the PICU more. We think that PICU hospitalization rates have not been reported frequently in the existing literature, whether the patients had PICU stays or not, but we would like to highlight that some patients may necessitate PICU hospitalizations and have a slower recovery than usually expected.

The present series includes two patients with COVID-19-associated illness grouped with infection-associated CLOCCs. COVID-19 is the new coronavirus that emerged in 2019 from Wuhan, China, resulting in a pandemic [25]. One of the cases had a newly defined multisystem inflammatory syndrome and responded well to oral steroids. In the literature, 4 children out of 27 pediatric patients with multisystem inflammatory syndrome have been reported as presenting with neurological symptoms. All four had splenial lesions showing diffusion restriction. They all needed ICU administration and were treated with immune-modulating agents; only two recovered fully [25]. Both of our COVID-19 patients, one with multisystem inflammatory syndrome, had complete recovery.

Two patients with inborn errors of metabolism were identified in the study, one with argininosuccinic aciduria who had hyperammonemia and the other with saposin B deficiency. To our knowledge, no reports of an argininosuccinic aciduria patient with splenium involvement, such as ours, have been presented, although hyperammonemia has been identified as one of the causes of CLOCCs [9].

Saposin B deficiency, also known as metachromatic leukodystrophy due to saposin B deficiency (phenotype MIM number: 249900), is characterized by a very similar clinical and radiological picture with metachromatic leukodystrophy but with normal levels of arylsulfatase A. Diffusion restriction in metachromatic leukodystrophy has been reported [26], and the researchers argued that the disintegration of the white matter and mobility of the water molecules within the myelin sheath resulted in this diffusion MRI pattern. Many causes, such as trauma, infection, and inflammation, bring about the release of inflammatory cytokines and increased amounts of glutamate in the extracellular space; glutamate leads to an influx of water into both astrocytes and neurons, causing excitotoxic edema [9,14]. We suggest that high glutamate levels caused by axonal disruption contribute to changes in metachromatic leukodystrophy/saposin B deficiency.

In the present study, six patients out of nine with trauma-associated CLOCCs had follow-up MRI, and four had cystic, gliotic changes. Although reversibility is almost a rule in infection-associated CLOCCs, the trauma-associated lesions may evolve into cystic and gliotic changes. Chung et al. [27] presented the follow-up MRI of 14 patients with 24 lesions that they called *nonhemorrhagic lesions*; among these cases, 13 lesions resolved, 5 showed cystic changes, and 6 showed atrophic changes [27]. In trauma-associated CLOCCs, subsequent tissue injury is characterized by axonal stretching, disruption, and eventual separation of nerve fibers [27]. The lesions caused by DAI may involve the body of the CC or the genu other than the splenium, and lesions of the fornices, internal capsules, superior cerebellar peduncles, midbrain, and white matter may accompany the callosal lesions in a random fashion according to the impact and severity of the traumatic injury [9], as we presented. However, radiologically, infection-associated CLOCCs specifically affect the CC splenium with smooth borders, generally in an ovoid pattern. The higher density of cytokine and glutamate receptors in CC is postulated to lead to a tendency for cytotoxic edema when cytokinopathy occurs in infection-associated cases [9,28]. Metabolic disorder-associated CLOCCs, such as the CLOCCs with saposin B deficiency presented in our study, primarily affect white matter tracts [29], and the CC is the largest commissural white matter bundle in the brain; thus, it is substantially affected during the disease process [1]. A single disease may present with different patterns of injury, and multiple diseases may present with similar imaging findings [15]. CLOCCs are an example of multiple diseases causing similar images on MRI that eventually originate from cytokinopathy and excitotoxicity.

Epilepsy was detected in three patients as the etiology of CLOCCs in the present investigation. One study evaluated the pre-surgical tests of 891 drug-resistant epilepsy patients [30] and found CLOCCs on MRI in 6 patients (0.7%), 4 of which later had a normal follow-up MRI. A rapid dose reduction of antiepileptics to provoke seizures in epilepsy surgery centers and frequent seizures may be reasons for CLOCCs, as was found in the patients with epilepsy in our study [3,30]. Some authors have suggested that a transient disturbance of energy metabolism and ionic transport occurring from repeated excessive activity of commissural projections from temporal structures results in reversible myelin vacuolization or intramyelinic edema [3]. Pathophysiology could be identified better in the future with more advanced research in the area.

5. Conclusion

CLOCCs have a diverse spectrum of etiologies, as presented in our study. Beyond the most common infection-associated CLOCCs, including the pandemic-causing agent COVID-19, less frequently identified etiologies, such as neurometabolic diseases, are encountered. Excitotoxic edema triggered by cytokinopathy and consequent extracellular glutamate elevation is postulated in the CLOCCs pathophysiology. Some etiologies of CLOCCs can be irreversible due to the nature of the diseases, such as in trauma-associated patients. The clinical course of infection-associated CLOCCs

can vary, although a total recovery is ultimately anticipated. Early recognition of infection-associated CLOCCs will prevent unnecessary treatment and provide reassurance because this disorder has an excellent clinical and radiological prognosis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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