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# Etiologic factors and imaging features of cytotoxic lesions of the corps callosum (CLOCCS): A series of 5 patients

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**ABSTRACT**

Cytotoxic Lesions of the Corpus Callosum (CLOCCS) are secondary lesions associated with various etiologies, including trauma, infection, and metabolic disorders. Recognizing these lesions is crucial as they can mimic primary callosal lesions such as ischemia. This retrospective study presents a series of five patients with CLOCCS, evaluating their clinical and radiological characteristics over a 1-year period. Imaging, particularly MRI, plays a pivotal role in diagnosis, with diffusion-weighted sequences revealing characteristic features of cytotoxic edema. Clinical context, additional imaging findings, and patient history aid in distinguishing CLOCCS from other pathologies. The study highlights diverse etiologies contributing to CLOCCS, including trauma, infection (e.g., Malaria and COVID-19), and metabolic disorders. Treatment strategies depend on addressing the underlying cause. Understanding the spectrum of etiologies and imaging features of CLOCCS is vital for accurate diagnosis and appropriate management.

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**KEYWORDS**

CLOCCS; MRI; trauma; infection

## Introduction

Cytotoxic lesions of the corpus callosum (CLOCCS) also known as secondary lesions of the corpus callosum are lesions that are associated with multiple conditions, including trauma, infection, and metabolic diseases. These lesions are mainly due to cytotoxic edema and lead to dysfunction of the callosal neurons and microglia [1,2]. Features on MRI and especially diffusion-weighted images suggest the diagnosis. As they manifest as areas of low apparent diffusion coefficient ADC value [1]. Sometimes the radiological appearance is not specific and other factors such as clinical findings and additional imaging features are necessary to make the diagnosis. Radiologists and clinicians should be familiar with the imaging features of CLOCCS and their etiologic factors to differentiate this entity from other primary callosal lesions such as callosal ischemia which is the primary differential diagnosis. Treatment relies on addressing the underlying cause.

## Materials and Methods

This study took place in the radiology department of 20 Aout 1983 Hospital, Casablanca, Morocco. A total of 5 cases of CLOCCS with clinical data and MRI images were enrolled in this work; in a 1 year period from December 2022 to December 2023. Their radiological and clinical findings were evaluated retrospectively through the image archive system and the hospital database records. Patients with suggestive lesions and clinical evidence or history of a differential diagnosis were not included such as demyelinating disease and ischemia. The main information that we were able to evaluate is sex, age, initial complaint, clinical signs, history, and initial MRI findings. MRI examinations of these patients were performed with a 1.5 Tesla (T) device. MRI protocol included T1 and T2 weighted images, fluid-attenuated inversion-recovery (FLAIR), diffusion, and contrast was administrated for 3 of our patients. We were able to evaluate the shape, localization, diffusion restriction, contrast enhancement as well as extra callosal lesions.

## Results

### *Cases presentation*

#### *First case*

18-year-old male, a victim of polytraumatic shock with a Glasgow score of 6/15. MRI

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findings included a corpus callosum splenium lesion with high signal intensity on T2/FLAIR weighted images and diffusion restriction, suggestive of cytotoxic edema (Fig. 1). We also noted hypointense punctiform lesions of the corpus callosum on T2* weighted images, suggestive of hemorrhage. Extra callosal lesions included, a right temporal hemorrhagic contusion, right frontal and temporal epidural hematomas, fronto-temporal right subdural hematoma, and a fronto-parietal right subgaleal hematoma.

***Second case***

A 26-year-old male presenting to the ER for severe traumatic brain injury. Admitted to the intensive care unit due to a deterioration of neurological status where he was intubated and sedated. MRI demonstrated a corpus callosum splenium lesion with high signal intensity on T2/FLAIR weighted images and diffusion restriction. No abnormality was detected on T2* weighted images on the corpus callosum. Other lesions included a temporo-occipital hemorrhagic contusion,

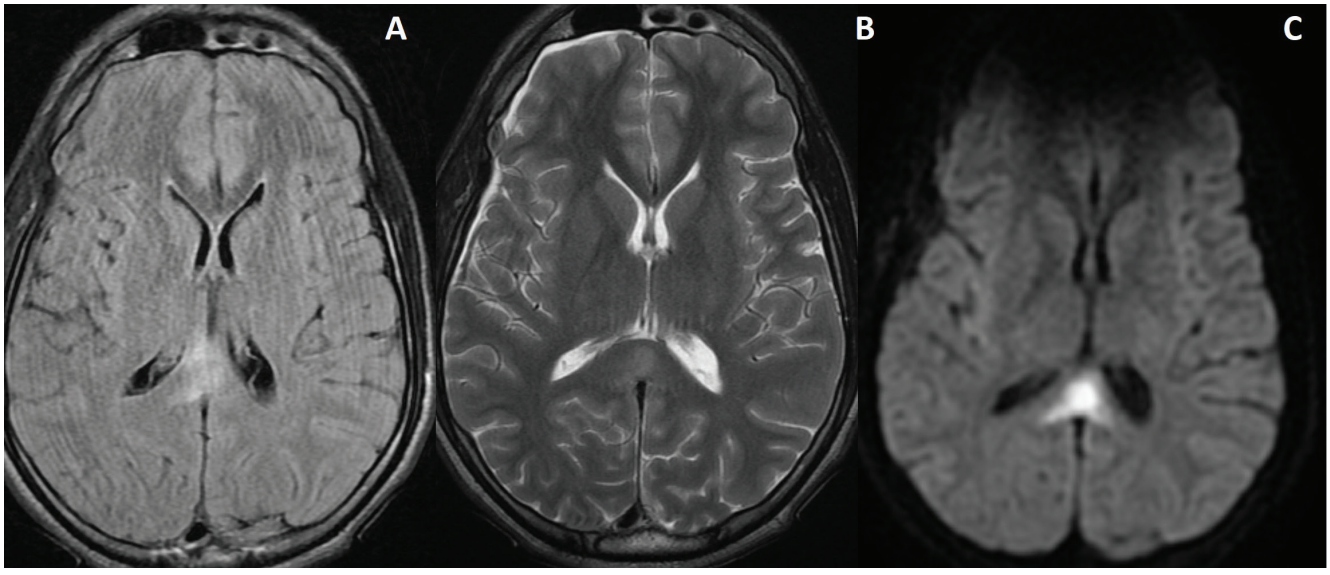



**Figure 1.** (first case) A and B: FLAIR and T2 weighted images demonstrating a corpus callosum splenium lesion with high signal intensity. C: signal hyperintensity of the same lesion on the diffusion-weighted image.

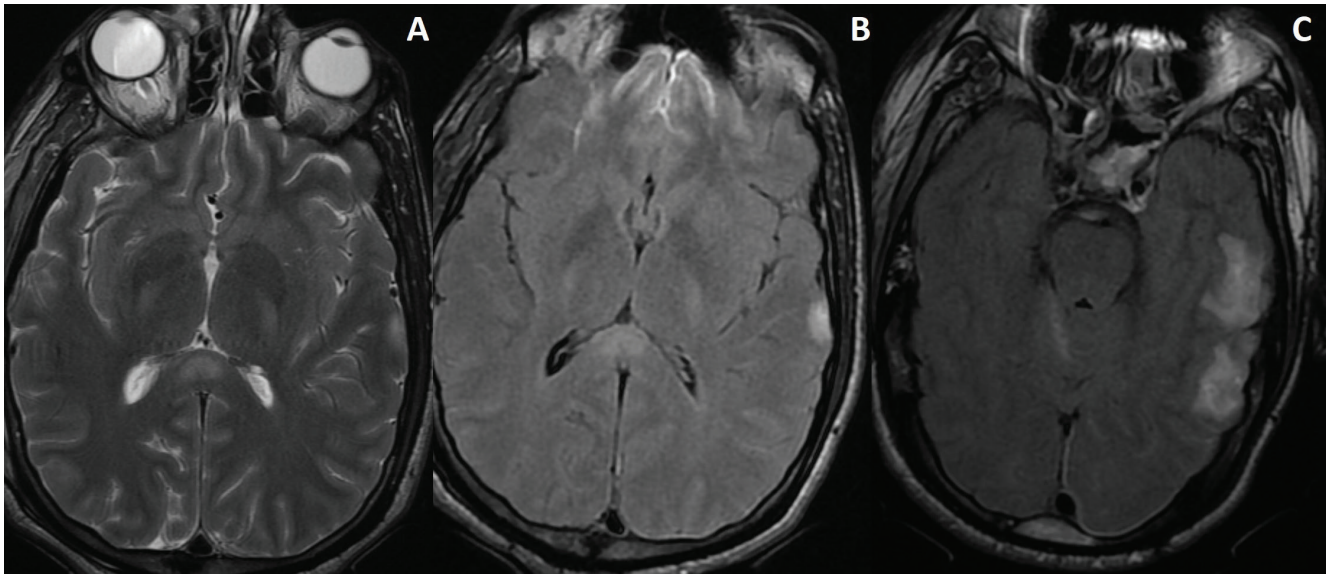



**Figure 2.** (second case) A and B: FLAIR and T2 weighted images demonstrating a corpus callosum splenium lesion with high signal intensity. C: temporo-occipital contusion and subarachnoid hemorrhage.

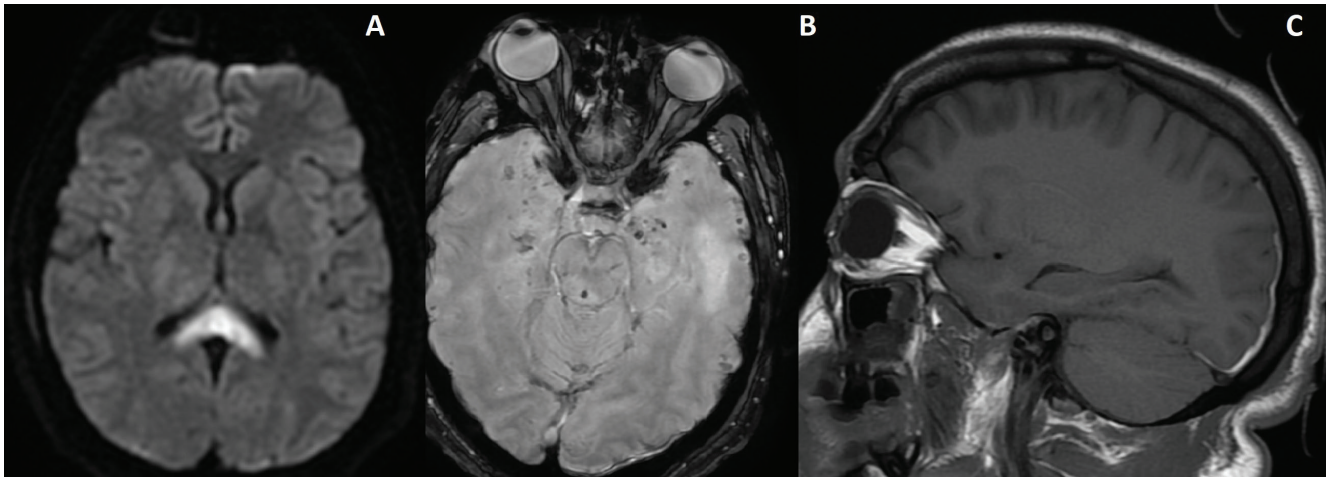



**Figure 3.** (third case) A: Corpus callosum splenium lesion demonstrating hyper signal intensity on diffusion sequence with "boomerang sign" aspect. B: T2* sequence showing diffuse bilateral temporal axonal injury. C: T1WI demonstrating an occipital subdural hematoma.

subarachnoid hemorrhaging (Fig. 2), and left occipital subdural hematoma.

***Third case***

22-year-old male, a victim of polytraumatic shock with an initial Glasgow score of 4/15. He was admitted in the intensive care unit. MRI evaluation showed corpus callosum splenium lesion with the low signal intensity of T1 weighted images, high signal intensity on T2/FLAIR weighted images, and diffusion restriction, and the overall aspect was suggestive of the "boomerang sign". Extra callosal lesions included diffuse axonal injury, subarachnoid hemorrhaging, left occipital subdural hematoma (Fig. 3), and bilateral temporal hemorrhagic contusion.

***Forth case***

A previously healthy 30-year-old male, with no significant past medical history presented to the emergency room, he was lethargic and in respiratory distress. The family reported the onset of gastrointestinal symptoms following his return from a Malaria endemic region. He was diagnosed of severe Malaria and admitted in the intensive care unit. MRI demonstrated a corpus callosum splenium lesion with high signal intensity on T2/FLAIR weighted images, diffusion restriction (Fig. 4), and no enhancement after administration of contrast. We also noted signs of intracranial hypertension.

***Fifth case***

A 64-year-old female with a history of arterial hypertension, coronary artery disease, and multiple ischemic strokes episodes in the past. The family reported probable recent COVID-19 infection (not confirmed). MRI showed a corpus callosum splenium well-defined lesion with diffusion restriction (Fig. 5) and no other abnormality on the other sequences. Other MRI abnormalities included hypertensive-related microbleeds, a chronic ischemic lesion of the right cerebellar hemisphere, lacunar infarct of the left cerebellar hemisphere as well as leukoaraiosis. The 3D TOF sequence was unremarkable.

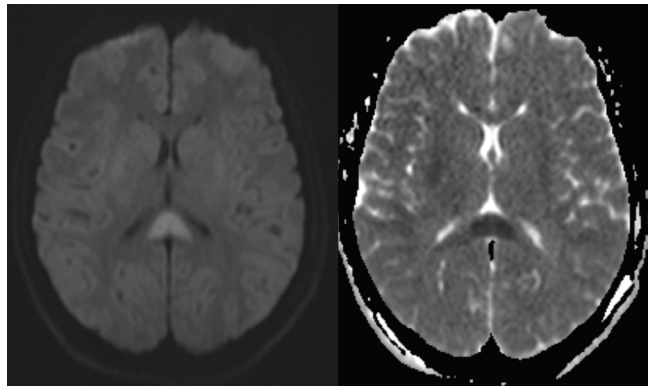


**Figure 4.** (fourth case) A corpus callosum splenium lesion with hyper signal intensity on diffusion sequence and Low ADC value.

Our study included 4 male patients and 1 female patient. Ages ranging from 18 to 64. Imaging features as well as clinical presentation and context were suggestive of CLOCCS for all of our patients: 2 patients presented for polytraumatic shock, 1 patient for severe brain injury, and 2 patients for post-infectious episodes (Malaria and COVID-19).

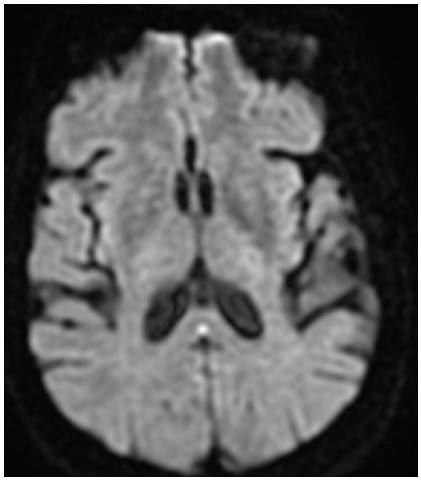


**Figure 5.** (fifth case) A corpus callosum splenium well-defined lesion with hyper signal intensity on diffusion.

## Discussion

CLOCCS are also known as secondary lesions of the corpus callosum and multiple other names throughout history. They were also previously referred to as transient or reversible splenial lesions [3]. Currently, the term CLOCCS is the most accurate and used. On a cellular level, the cytotoxic edema that we observe is mainly due to the action of glutamate on N-methyl-D-aspartate receptors, sodium–potassium pumps, α-amino- 3 - hydroxy-5-methyl-4-isoxazole propionic acid receptors and also aquaporins, as it results in an influx of water into astrocytes and neurons. The excessive trapped water within the cells is responsible of intra-cellular edema, causing reduced diffusion of water molecules [1,4]. The corpus callosum seems to be more susceptible to these lesions compared to other areas because its neurons, astrocytes, and oligodendrocytes have more excitatory receptors. The splenium is usually most vulnerable to cytokinopathy [5]. Clinically, patients may present impaired consciousness, ataxia, seizures, paresthesia, headache, vision loss, and diplopia [6].

Imaging techniques and specifically MRI is very contributive in the diagnosis of CLOCCS. They typical aspect on MRI is corpus callosum lesions with low signal intensity on T1 weighted images, and increased signal intensity on FLAIR-weighted images. Diffusion restriction, meaning increased signal intensity on diffusion sequence with low ADC value (mean ADC value, $0.31 \times 10^{-3}mm^2/sec$; range, $0.13 \times 10^{-3}/sec$ to $0.48 \times 10^{-3}mm^2$ /sec). These lesions do not demonstrate any enhancement after administration of contrast and are usually midline and symmetric [7]. Three patterns of lesion have been described [1]:

- ✓ Small round/ oval lesion in the center of the splenium
- ✓ A splenium-centered lesion extending laterally into the adjacent white matter
- ✓ A posteriorly centered lesion extending to the anterior part of the corpus callosum

CLOCCS can be identified in MRI as an incidental finding in patients performing this examination for encephalopathy, seizures, encephalitis, or other complaints. These lesions have been associated with a wide range of diseases.

- ✓ Malignancy: cases of CLOCCS were reported in patients treated with chemotherapy but also in patients with primary central nervous system malignancies, even before treatment. It was suggested that malignant cells infiltrate meningeal cells and release cytokines into the cerebrospinal fluid [1,7].
- ✓ Infection: Many cases of infection-associated CLOCCS were reported in the literature. Leukocytes produce pro-inflammatory cytokines that can increase the permeability of the blood-brain barrier, leading cytokines and inflammatory cells to enter the CNS. This inflammatory process activates glial cells causing cytotoxic edema. Among the infectious causing agents that were cited in literature: Adenovirus, Epstein-Barr virus, *Escherichia coli*, herpes, influenza virus A (H1N1), influenza, *Legionella*, malaria, measles, Mycoplasma, rotavirus, *Salmonella*, *Staphylococcus*, *Streptococcus*, varicella-zoster virus [1,3].
- ✓ Trauma: Usually located in the splenium. The lesions can be symmetric or asymmetric, single or multiple. Cases have been reported with the association of diffuse axonal injuries but also other brain injuries [1].
- ✓ Drug toxicity: It was first suggested that antiseizure drug therapy such as carbamazepine induces CLOCCS. Other types of therapy have also been implicated from chemotherapy to steroid therapy [1,8, 9].

Other entities were also incriminated, including: metabolic disorders, sub arachnoid hemorrhage, and high altitude.

In a series of pediatric patients led by Aksu Uzunhan et al. [10] of 41 patients, there were 25 cases related to infectious processes, 9 associated with trauma, 3 with metabolic disorders and 4 patients had other entities. MRI demonstrated splenium involvement with diffusion restriction in all patients, which was either isolated or in association with other brain lesions [10].

According to a PRISMA-conform systematic review (with a total of 441 references and 1353 patients included), CLOCCS can be associated with a broad panel of disease entities among them toxic/drug-treatment-associated, infectious, traumatic, vascular, metabolic, and neoplastic. This comprehensive literature search confirms that CLOCC shows typical high T2 signal, low T1 signal, and restricted diffusion with a lack of contrast enhancement. And that the majority of the lesions were reversible within the follow-up period [11].

Differential diagnoses include ischemic infarction due to occlusion of the distal branches of the anterior cerebral artery. Also, ADEM lesions (Acute disseminated encephalomyelitis) may involve the corpus callosum. However, in these conditions, lesions tend to be asymmetric. Multiple sclerosis can also be confused with CLOCCS, but the association with other typical matter lesions can diverge the diagnosis. Other entities such as lymphoma or glioblastoma appear more aggressive. MRI findings can be very contribute to differentiation, using MR angiographic images and contrast administration [1,12].

If isolated the prognosis of this entity can be benign, as the lesions are usually reversible. Treatment schemes are related to the causing factor (infection, trauma, drug usage). Immunomodulatory treatment was also suggested in some cases [6].

## Conclusion

CLOCCS can be associated with a variety of entities. These entities and MRI features should be very well known by radiologists and clinicians to avoid any misdiagnosis.

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