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Case Report

Cytotoxic Lesions of the Corpus Callosum (CLOCCs)

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Abstract

Background: Cytotoxic lesions of the corpus callosum (CLOCCs) are rare but increasingly recognized radiological entities, often secondary to various infectious, metabolic, or drug-related etiologies. They primarily involve the splenium of the corpus callosum and are characterized by cytotoxic edema visible on MRI.

Case Presentation: We report the case of a 9-year-old child admitted with persistent febrile rash and altered consciousness. Initial investigations, including CT and lumbar puncture, were inconclusive. Brain MRI revealed a well-defined lesion in the splenium of the corpus callosum, showing restricted diffusion without enhancement, consistent with a cytotoxic lesion of the corpus callosum (CLOCC).

Conclusion: This case highlights the importance of considering CLOCCs in the differential diagnosis of pediatric febrile encephalopathy. MRI remains the key diagnostic modality, allowing early identification and guiding appropriate management of the underlying cause.

Keywords: *Corpus Callosum; Splenium; Cytotoxic Edema; MRI*

Introduction

The corpus callosum, the largest commissural bundle in the brain, plays a crucial role in interhemispheric communication. Its posterior segment, the splenium, exhibits particular vulnerability due to its high density of glutamate-sensitive oligodendrocytes [1].

Cytotoxic lesions of the corpus callosum (CLOCCs) are transient radiological abnormalities often secondary to a broad spectrum of infectious, metabolic, drug-related, or inflammatory conditions. Previously described under the terms MERS (Mild Encephalitis/ Encephalopathy with a Reversible Splenial Lesion) or RESLES (Reversible Splenial Lesion Syndrome), these findings are now collectively referred to as CLOCCs, reflecting their shared pathophysiological mechanism: cytotoxic edema resulting from a neuroinflammatory cascade [1,2].

Magnetic resonance imaging (MRI) plays a pivotal role in their diagnosis, with diffusion-weighted imaging providing characteristic features.

We present here a pediatric case of CLOCC in the setting of unexplained fever, emphasizing the importance of recognizing this diagnostic entity in pediatric neurology.

Case Report

A 9-year-old child with no notable medical history and an up-to-date vaccination record was admitted for a febrile rash persisting for seven days.

On clinical examination, the patient exhibited an altered level of consciousness with a Glasgow Coma Scale (GCS) score of 13, accompanied by a high fever of 41°C and a widespread cutaneous rash affecting the entire body. The remainder of the physical examination was unremarkable.

A brain computed tomography (CT) scan was performed and returned normal. A lumbar puncture was also carried out, with negative results. Given the persistence of symptoms and the undetermined etiology, a brain magnetic resonance imaging (MRI) scan was requested (Figure 1A-1E).

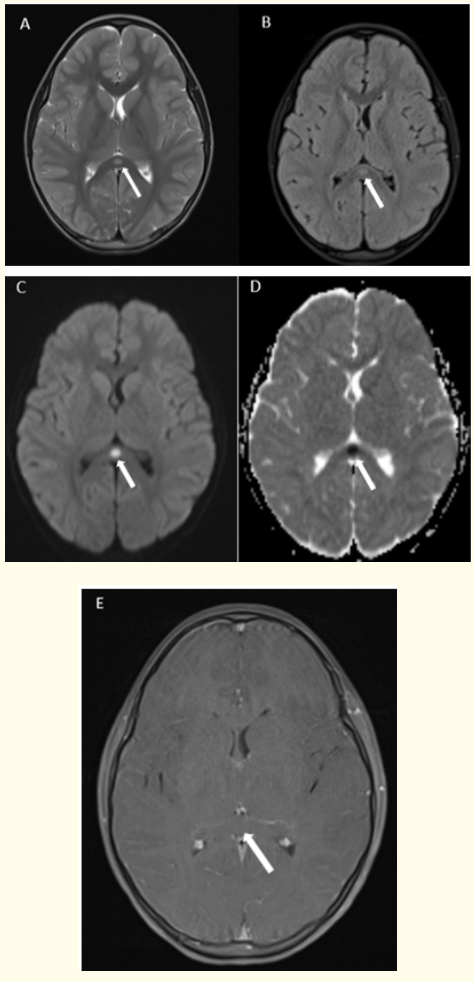

Figure 1A-1E: *Axial brain MRI showing a well-defined, rounded cytotoxic lesion of the splenium of the corpus callosum, appearing hyperintense on T2-weighted (1A) and T2 FLAIR (1B) sequences, with diffusion restriction on DWI (1C) and corresponding low signal on the ADC map (1D). No enhancement is observed after contrast administration on post-contrast T1-weighted imaging (1E) (white arrows).*

Discussion

The corpus callosum is the largest commissural white matter tract in the brain, containing between 200 and 250 million interhemispheric fibers. Most of the corpus callosum receives its arterial supply from the carotid system, except for the splenium, which is vascularized by the vertebrobasilar system [1].

Cytotoxic lesions of the corpus callosum (CLOCCs) are secondary radiological abnormalities caused by various conditions that produce signal changes within the corpus callosum, most frequently involving the splenium [1,2].

The term "cytotoxic lesions of the corpus callosum" has been proposed as a more accurate descriptor for this phenomenon, which was previously known under several other names, such as MERS (Mild Encephalitis/Encephalopathy with a Reversible isolated Splenial lesion) and RESLES (Reversible Splenial Lesion Syndrome) [1,2].

Although numerous underlying causes have been described, these lesions appear to result from a stereotyped cascade of cytokine and cellular activation. An initial insult leads to the release of pro-inflammatory cytokines, such as interleukin-1 (IL-1) and interleukin-6 (IL-6), by macrophages. This, in turn, initiates a series of events, including T-cell recruitment, disruption of the blood-brain barrier, tumor necrosis factor-alpha (TNF-α) production, and astrocyte activation. The final result is a massive increase in extracellular glutamate, which, through interactions with various cell membrane receptors, induces water influx into astrocytes and neurons, manifesting macroscopically as cytotoxic edema [2].

The preferential involvement of the splenium is thought to be due to its high density of oligodendrocytes, which express a large number of glutamate-sensitive receptors [2].

This phenomenon was first described by Chason., *et al.* [1]. CLOCCs have been identified as secondary lesions in a wide range of clinical contexts [1,2]. Common causes include [1-3]:

- Seizures, particularly in the context of antiepileptic drug withdrawal.
- Drug-related toxicity, including metronidazole and chemotherapeutic agents.
- Metabolic disorders, such as hypoglycemia, hypernatremia, hemolytic-uremic syndrome, hepatic encephalopathy, Marchiafava-Bignami disease, osmotic demyelination, Wernicke encephalopathy, and Wilson's disease.
- Infectious causes, including cerebral infections such as abscesses, encephalitis, and meningitis:
- Viral infections: Influenza, measles, herpes simplex virus, mumps, adenovirus, varicella-zoster virus, rotavirus, SARS-CoV-2 (COVID-19).
- Bacterial infections: *Salmonella, Legionella*.
- Mycobacterial infections: Tuberculous meningitis.
- Subarachnoid hemorrhage has also been implicated.

Clinical presentation is generally related to the underlying disease rather than to the callosal lesion itself [1,2].

The differential diagnosis of splenial lesions includes ischemia, posterior reversible encephalopathy syndrome (PRES), diffuse axonal injury, multiple sclerosis, Marchiafava-Bignami disease, lymphoma, and diffuse glioma [1,2].

Key features helping to distinguish CLOCCs from other pathologies include the absence of disconnection syndromes (e.g. left-hand apraxia, neglect, alien hand syndrome, agraphia, alexia, visual apraxia's) and complete reversibility following treatment of the underlying condition [1,2].

CLOCCs are best detected using magnetic resonance imaging (MRI) and typically present in one of three forms [1,2]:

- Small, well-defined midline oval lesions in the splenium (most common form).
- Larger, poorly defined boomerang-shaped lesions involving the entire splenium.
- Lesions extending anteriorly into the body of the corpus callosum.

These lesions appear hypointense on T1-weighted images, hyperintense on T2-weighted images, and restrict diffusion, with low ADC values (generally 300 - 500 × 10^{-6} mm^2/s). They do not enhance after gadolinium administration [1,2] (Figure 1). These imaging features reflect cytotoxic edema, thereby justifying the term cytotoxic lesions of the corpus callosum (CLOCCs) [1,2].

CLOCCs are often-but not always-reversible. When identified, it is crucial to investigate and treat the underlying cause [1-3].

Conclusion

Cytotoxic lesions of the corpus callosum represent a critical radiological diagnosis, particularly in the context of febrile neurological presentations in children. Early detection via MRI allows for prompt etiological orientation and helps avoid unnecessary invasive investigations.

The frequently reversible nature of these lesions further underscores the importance of accurate diagnosis and rapid management of the underlying cause.

This case highlights the pivotal role of brain MRI in identifying CLOCCs and emphasizes their broad etiological spectrum, predominantly involving viral infections in the pediatric population.

Declaration of Conflicting Interests

The authors declare that they have no conflicts of interest.

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