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# **Radiologic and clinical features of infection related cytotoxic lesions of corpus callosum splenium in adults**

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#### Ethics Committee Approval

Ethical Committee of SANKO University, Gaziantep, approved this study (Date: 21.11.2018, Decision Number: 03). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest No conflict of interest was declared by the authors.

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**Background/Aim:** The cytotoxic lesion of corpus callosum splenium (CLCCS) is a clinical-radiologic syndrome that typically manifests in children. It is characterized by restricted diffusion in the splenium of the corpus callosum on magnetic resonance imaging, and accompanying symptoms of encephalopathy. There are a few case reports regarding the adult population in the literature, and only a couple of these are related to febrile illness in adults. We aimed to evaluate the clinical and the radiologic characteristics of infections related to CLCCS in adults.

# **Methods:** For this case series study, we reviewed the MRI examinations that were performed in our hospital between 2014 and 2019 to identify cases with corpus callosum splenium lesions related with febrile diseases in adults. We excluded the cases with demyelinating diseases, trauma, arterial or venous occlusive diseases, metabolic-toxic diseases, and posterior reversible encephalopathy syndrome (PRES), patients who had alcohol or drug abuse, or known malignancies. The admission dates, symptoms within the prodromal period, physical and laboratory findings, electroencephalograms, MRI features, medications and patient outcomes were recorded. Corpus callosum involvement on MRI was classified as Type 1 if lesions were limited to splenium, and Type 2 if pericallosal white matter extension was present.

**Results:** Seven patients (four males, three females, and ages ranging from 18 to 33 years with a mean of 26.4 years) were included in the study. All patients experienced prodromal symptoms such as fever (n=7), nausea (n=5), vomiting (n=4), diarrhea (n=4) and abdominal discomfort (n=3). Neurological symptoms included drowsiness (n=4), speech disorder (n=2), impairment of consciousness (n=4), lower extremity weakness (n=2), and seizures (n=1). Neurological examination revealed confusion (n=4), nuchal rigidity (n=2), and ataxia (n=2). In one patient, the blood culture was positive for *Staphylococcus epidermidis*, and the stool culture was positive for *Enterococcus species*. MRI findings of all patients revealed Type 1 oval (n=4) or round (n=3) shaped corpus callosum splenium lesions that appeared hyperintense on T2 and FLAIR images with diffusion restriction. None of our patients had band-like Type 1 or Type 2 lesions. Clinical relief was observed in 2 days in six patients, however, rapid clinical deterioration resulting in death occurred in one patient.

**Conclusion:** The leading symptoms in adults are fever and gastrointestinal disturbances including, nausea, vomiting, and diarrhea, while neurological examinations mostly reveal confusion, nuchal rigidity, and ataxia. In adult patients, restricted diffusion on MRI is usually limited to splenium, and pericallosal white matter is usually not involved. Mostly encountered in autumn and winter, encephalitis/encephalopathy with diffusion restriction in the splenium of corpus callosum in an adult febrile patient usually has a good prognosis, although it may lead to severe outcomes, and even result with death. Clinicians should be aware that, if even Type 1, isolated corpus callosum diffusion restriction on MRI may has catastrophic results in a febrile patient. Further studies may be useful to delineate the mechanism and its relationship with higher bilirubin levels in patients with CLCCS.

Keywords: Corpus callosum, Infection, MRI

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# Introduction

Cytotoxic lesion of corpus callosum splenium (CLCCS) is a clinical-radiologic syndrome that typically manifests in children. It is characterized by restricted diffusion in the splenium of the corpus callosum on magnetic resonance imaging (MRI), and accompanying symptoms of encephalopathy, ranging from headache to seizures. There is a wide spectrum of disorders responsible of CLCCS, including bacterial or viral infections, malignancies, drugs, and trauma, toxic or metabolic diseases. Though most of these conditions have favorable outcomes, some may have severe prognosis [1, 2].

Prior work in the literature consists of case studies for radiologic and clinical features of CLCCS in the adult population. Only a few of these are related to febrile illness in adults, as most focus on children. In this work, we aim to close this gap by evaluating the clinical and the radiologic characteristics of infections related to CLCCS in adults. We present our findings for adult febrile patients characterized by restricted diffusion in the splenium of the corpus callosum.

#### Materials and methods

We reviewed the brain MRI studies in our radiology database system to identify the cases with lesions of the corpus callosum from 2014 to 2019. The Ethics Committee of SANKO University, Gaziantep, approved this study (Date: 21.11.2018, Decision Number: 03).

We obtained patient demographics and clinical and laboratory data from the institutional database. We excluded the cases with known or new onset demyelinating diseases such as multiple sclerosis, patients with trauma, arterial or venous occlusive diseases, metabolic-toxic diseases, and posterior reversible encephalopathy syndrome (PRES), patients who had alcohol or drug abuse, or known malignancies. The admission dates, symptoms within the prodromal period, physical and laboratory findings including cerebrospinal fluid analysis if exists, electroencephalograms, MRI features, medications and patient outcomes were recorded.

All MRI studies were performed with a Siemens Magnetom Avanto, a 1.5 Tesla device, including vendor's preset T1 and T2 weighted sequences, fluid attenuated inversion recovery (FLAIR), and diffusion weighed imaging (DWI), apparent diffusion coefficient (ADC) map and post contrast T1 studies. All patients were given Dotarem (gadoterate meglumine, Guerbet) as a paramagnetic intravenous contrast agent. Radiological images were evaluated by two radiologists who were experienced in MRI for at least 15 years. The shape of the splenial lesion, other involved parts of the corpus callosum, pericallosal white matter, and additional findings on MRI were noted. Callosal lesions were classified as Type 1 if the lesion was limited to the splenium, including round, oval or band-like signal changes, and Type 2 if pericallosal white matter was involved.

# Statistical analysis

The findings in the patient population were given in numbers and percentages.

## Results

Seven patients were included in the study (four males (57%), three females (42%), and ages ranging from 18 to 33 years with a mean of 26.4 years). There were no notable diseases in any of the cases except for one. That patient was under treatment for hypothyroidism. Table 1 presents our findings.

All patients experienced prodromal symptoms. All had fever (axillary temperature >38°C) within a week of hospital admission and their final diagnosis were acute encephalitis/encephalopathy. Prodromal symptoms were nausea (n=5, 71%), vomiting (n=4, 57%), diarrhea (n=3, 42%), abdominal discomfort (n=3, 42%), sore throat (n=2, 28%), muscle weakness (n=2, 28%), headache (n=2, 28%), and arthralgia (n=1, 14%). Neurological symptoms included drowsiness (n=4, 57%), speech disorder (n=2, 28%), impairment of consciousness (n=4, 57%), lower extremity weakness (n=2, 28%), and seizures (n=1, 14%). Neurological examination revealed confusion (n=5, 71%), nuchal rigidity (n=2, 28%), and ataxia (n=2, 28%). Laboratory findings revealed elevation in white blood cell count (n=6, 85%), C-reactive protein (n=4, 57%), erythrocyte sedimentation rate (n=3, 42%), liver function tests (n=5, 71%), fibrinogen (n=2, 28%), procalcitonin (n=1, 14%), and bilirubin (n=3, 42%). Electroencephalography was performed on four patients, and all were normal. Lumbar puncture and cerebrospinal fluid (CSF) analysis was performed on three patients. Two had slightly and the other had significantly elevated protein levels. Glucose levels and cell counts of cerebrospinal fluid were normal, and cultures were sterile.

One patient died (number 6). She was the only patient who had seizures on admission day and during hospitalization. Rapid clinical deterioration, status epilepticus, sepsis, acidosis, and respiratory failure occurred; she died on the fifth day of hospitalization following intubation. Her blood culture was positive for *Staphylococcus epidermidis*, and her stool culture was positive for *Enterococcus species*. No responsible pathogens were identified in the other patients. The patients were admitted to the hospital in September (n=2), November (n=1), December (n=2), June (n=1) and July (n=1). All initial MRI examinations were performed within the first two days of hospital admission, and the follow-up MRI exams were done after 19-38 days, except for the patient who died.

Corpus callosum involvement was limited to the splenium in all patients. All patients had Type 1 oval (n=4, 57%) or round (n=3, 42%) shaped corpus callosum splenium lesions that appeared hyperintense on T2 and FLAIR images with diffusion restriction (Figures 1 and 2). None of our patients had a band like Type 1 or Type 2 lesion. All patients underwent postcontrast T1 studies, but there was no contrast enhancement in any of the lesions. Lesions were completely resolved in six patients (85%) at control MRI studies.

All patients were treated with antibiotics and supportive care. Five patients received ceftriaxone, one received ampicillin/sulbactam. Patient 6 was treated with ceftriaxone, vancomycin, antiepileptic medication, and prednisolone. Acyclovir was also added to the therapy for patient 6 because she did not respond to antibiotics. Clinical relief was observed in two days in six patients, and full recovery was achieved. JOSAM

Table 1: Demographics, clinical, radiologic and laboratory findings of patients with CLCC

	Age and Gender	Admission Month	Complaints	Neurological manifestations	Physical examination	Time of MRI (days)	Lesion Type	Laboratory	EEG	CSF Findings	Follow up MRI (days)	Outcome
1	28,M	November	Fever, nausea, vomiting,	Speech disorder, drowsiness	Confusion	1	1 round	Elevated WBC, CRP, Fibrinogen,	N	Slightly high protein	38	Complete Recovery
2	33,M	September	Fever, nausea, vomiting, diarrhea, abdominal pain	Drowsiness	Ataxia	2	1 oval	Elevated WBC, CRP, ALT, AST, Bilirubin	N	-	33	Complete Recovery
3	18,F	September	Fever, abdominal pain, nausea, diarrhea,	Impairment of consciousness, drowsiness, lower extremity weakness	Confusion, nuchal rigidity	1	1 round	Elevated WBC, CRP, ESR, ALT	Ν	Markedly high protein	19	Complete Recovery
4	27,F	December	Fever, sore throat, muscle weakness	Speech disorder	Ataxia	1	1 oval	Elevated ESR, LDH, Bilirubin	N	-	30	Complete Recovery
5	25,M	December	Fever, nausea, vomiting, arthralgia	Impairment of consciousness, lower extremity weakness	Confusion	1	1 round	Elevated WBC, ALT, AST, GGT, LDH, Bilirubin	-	-	27	Complete Recovery
6	33,F	July	Fever, abdominal pain, diarrhea, nausea, vomiting	Headache, impairment of consciousness, drowsiness, seizures	Confusion, nuchal rigidity + Extensor plantar reflex	1	1 oval	Elevated WBC, CRP, ESR, ALT, AST, Fibrinogen, Procalcitonin	-	Slightly high protein	-	Died
7	21,M	June	Fever, muscle weakness, sore throat	Headache, impairment of consciousness	Confusion	1	1 oval	Elevated WBC	-	-	33	Complete Recovery

CLCC: Cytotoxic lesion of corpus callosum, EEG: Electroencephalography, CSF: Cerebrospinal fluid, WBC: White blood cell count, CRP: C-reactive protein, ALT: Alanine transaminase, AST: aspartate transaminase, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, GGT: Gamma-glutamyl transferase

Figure 1: Initial Diffusion MRI (a) and corresponding ADC map (b) of Patient 1. There is a round Type 1 splenial lesion in the center of corpus callosum splenium that shows diffusion restriction. Control Diffusion MRI (c) and ADC map (d) show normal signal



Figure 2: Diffusion weighted MRI and ADC maps of initial MRI examinations of Patient 2 (a, and b), Patient 3 (c and d), Patient 4 (e and f), Patient 5 (g and h), Patient 6 (i and j), and Patient 7 (k and l), respectively, that show diffusion restriction characterized by a high signal in DWI, and a low signal in ADC maps



#### Discussion

Reversible splenial lesions were first described in patients under antiepileptic therapy. Then, an association with encephalitis/encephalopathy that were caused by a few pathogens, including rotavirus, influenza and E. Coli were reported [3-10]. In their study including 15 patients, most of which consisted of children, Tada et al. [11] reported that reversible splenial diffusion restriction might be observed together with mild encephalitis/encephalopathy, following an infection. The involvement of corpus callosum splenium and the presence of diffusion restriction was named as mild encephalitis/encephalopathy with reversible splenial lesion (MERS), reversible splenial lesion syndrome (RESLES) or reversible splenial lesion during febrile illness (RESLEF). Recently, it has been depicted that diffusion restriction in the splenium may be due to numerous bacterial or viral infections, malignancies, drugs, trauma, toxic or metabolic diseases, and it was proposed to name this entity as cytotoxic lesions of corpus callosum (CLCC), because not all these conditions have full clinical recovery [12-18]. Though the mechanism is not precisely depicted, cell-cytokine interactions leading to high extracellular glutamate, trapped water in the cells, and cytotoxic edema are held responsible [18].

In our study, fever and gastrointestinal symptoms were leading in the prodromal period, including nausea and vomiting, diarrhea, and abdominal discomfort. Prodromal symptoms, neurological evaluation and clinical outcomes in our patients did not differ from the previous studies at large [2, 10]. When compared with the children, these findings also show similarity, except for seizures, which is the most frequent admission reason in children [1]. Only one of our patients had seizures, and other initial clinical, laboratory and MRI findings were similar. Seizure is related to poor prognosis [2]. This finding correlates with our study, as the only patient presenting with seizure died. Also, none of our adult patients showed visual disturbances, although it is relatively common in children [1]. In a previous study, impairment of consciousness was correlated with poor prognosis [2]. Among four of our cases who had that symptom, three fully recovered and one died.

It is reported that nearly half of the patients showed diffuse slow waves on EEG studies and that this finding was correlated with poor prognosis [2]. In our study, four patients underwent EEG (all fully recovered cases) and all were reported as normal. This may be related with the spared pericallosal white matter in our patients.

Analysis of CSF was available in three patients, two had slightly and one had significantly elevated protein levels. One of the patients with slightly elevated protein levels died, the others survived without any sequelae. It is reported that CSF studies are nonspecific in this patient population, however, one study depicted high interleukin 6 levels and suggested that immunological response may be related with pathogenesis [19, 20].

Three of our patients had elevated serum bilirubin levels and one died. Apart from bilirubin encephalopathy that is encountered in the neonatal period, we have not been able to find any data about high serum bilirubin levels and encephalitis/encephalopathy. This subject may be delineated with further studies.

Previous studies reveal that Type 1 splenium lesions have favorable prognosis when compared with Type 2 lesions. In our study, all our patients had type 1 lesions, although one had a catastrophic outcome resulting with death. This finding suggests that not all Type 1 splenium lesions will recover completely, and clinicians should be aware of this entity. In their study consisting of three patients with reversible splenial lesions caused by antiepileptic treatment, da Rocha et al. [21] reported that one of the lesions showed contrast enhancement, and according to our knowledge, this is the only case in the literature that showed contrast enhancement. None of our patients had contrast enhancement in post-contrast studies. Previous studies reveal that normalization of pathologic signal changes in isolated splenial lesions occur within 1 week [10, 11]. The earliest control MRI in our group was on the 19th day, all surviving patients had normal signal intensity in the splenium in their control MRI examinations.

Patient 6 was a 33-year-old female, with the only one admitted with seizure. She was under treatment for hypothyroid for 3 years. She did not have any history of substance or alcohol use. Before the admission, she experienced stomachache, diarrhea, and fever for 3 days. She was brought to ER with confusion and developed seizures. After hospitalization, rapid clinical deterioration resulting with coma, acidosis, and sepsis occurred, leading to intubation, and a few days later, death. According to the clinical course, the findings could suggest acute disseminated encephalomyelitis (ADEM) or Marchiafava-Bignami disease (MBD), but MRI findings were unlikely, because MBD typically starts from the body of corpus callosum and extends towards genu and splenium, callosal necrosis is usually seen, and contrast enhancement occurs in acute presentations [22]. Also, our patient did not have alcohol use or malnutrition, and she had normal serum B<sub>12</sub> levels. In ADEM, corpus callosum is usually involved by the extension of neighboring white matter lesions. Though corpus callosum involvement may be up to 15%, isolated splenial lesion in ADEM has not been reported before [23].

Most our patients were admitted to the hospital in autumn and winter. These are the seasons which most viral diseases are encountered, and MERS with seasonal influenza infection was previously reported [7, 24, 25]. We have been able to identify a responsible pathogen in only 1 of 7 patients.

This is the largest case series including the adult population with infection-related corpus callosum splenium lesions from Turkey. In their study that focused on the etiology of splenial lesions, Balcik et al. [26] reported 5 infection-related cases (3 tuberculosis meningitis and 2 viral encephalitis), where the outcomes of the patients were not stated. There are also a few case reports from our country on the adult population [27-29].

Also, according to our knowledge, this is the first study that involves a case who died with an isolated splenial lesion.

#### Limitations

Small sample size is the major limitation of the present study. Also, a responsible pathogen was identified in only one of the 7 patients. The study was undertaken in a local tertiary center, and the results may not represent the entire condition in other districts of Turkey.

#### Conclusions

Mostly autumn encountered in winter. and encephalitis/encephalopathy with diffusion restriction in the splenium of corpus callosum in an adult febrile patient usually has a good prognosis, though it may lead to severe outcomes, even death. The leading symptoms are fever and gastrointestinal disturbances including, nausea, vomiting, and diarrhea, while neurological examinations mostly reveal confusion, nuchal rigidity, and ataxia. In adult patients, restricted diffusion is usually limited to splenium, and pericallosal white matter is usually not involved. Clinicians should be aware that, if even Type 1, isolated corpus callosum diffusion restriction on MRI may have catastrophic results in a febrile patient. Further studies may be useful to delineate the mechanism and relationship of higher bilirubin levels in patients with CLCCS.

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