

A Reversible Isolated Lesion in the Splenium of Corpus Callosum in a Patient with Probable Neuroleptic Malignant Syndrome -- Case Report

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Abstract-

Purpose: A reversible isolated lesion in the splenium of the corpus callosum (SCC) is rare. We present such a case in a young female patient with neuroleptic malignant syndrome (NMS) and elaborate on its proposed pathophysiology and the possible differential diagnoses.

Case Report: A 28-year-old female was on neuropsychiatric treatment (clozapine) for schizoaffective disorder. NMS was diagnosed based on the clinical presentation of fever, mental status change (with disorientation and visual hallucination), generalized muscular rigidity (catatonic signs), tremor, and markedly increased creatine phosphokinase (1824 U/l) after 10-day administration of clozapine. The SCC lesion had a "boomerang" appearance and high signal intensity on the initial T2-weighted, T2 fluid attenuated inversion recovery, and diffusion-weighted magnetic resonance images, and decreased apparent diffusion coefficient values. The follow-up magnetic resonance imaging 12 weeks later showed complete resolution of the SCC lesion.

Conclusion: A reversible isolated SCC lesion is a distinct clinicoradiological syndrome of varied etiology. The changes may occur in certain psychiatric patients with NMS and most patients with epilepsy and encephalitis. The etiological mechanism remains uncertain and enigmatic, but the neurological course and outcome are good.

Key Words: splenium of corpus callosum, neuroleptic malignant syndrome, magnetic resonance images, neuropsychiatry

Acta Neurol Taiwan 2015;24:87-91

INTRODUCTION

A reversible isolated lesion in the splenium of the corpus callosum (SCC) or so-called reversible splenial lesion syndrome⁽¹⁾ is rare, and little is known about its pathophysiology. It has been reported to occur in a

number of clinical paradigms, such as encephalitis and encephalopathy caused by various infective agents^(2,3), and in patients with or without epilepsy receiving antiepileptic drugs⁽³⁻⁶⁾. We report a case of this rare entity in a young female patient with neuroleptic malignant syndrome (NMS) who was undergoing neuropsychiatric treatment

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Received January 12, 2015. Revised May 25, 2015.
Accepted June 11, 2015.

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for schizoaffective disorder, and we elaborate on possible differential diagnoses and its proposed pathophysiology.

CASE REPORT

A 28-year-old female presented with depressive mood and insomnia for about 2 weeks because of disappointment in a love affair. Then she developed abnormal behaviours, mental status changes, and refused to eat and talk. Initially, she was brought to our neurological department where brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and laboratory investigations failed to show any specific abnormalities. Under the impression of schizoaffective disorder, she was placed on neuropsychiatric treatment (clozapine 12.5 mg daily and titrated to 25 mg daily one week later). No previous seizures, anticonvulsant therapy, other systemic diseases, or history of smoking, drinking, or drug addiction were noted.

About 10 days after clozapine therapy, she developed a low grade fever (around 37.4 ~ 38.2°C), mental status change with disorientation, visual hallucinations, mutism, and occasionally psychomotor agitation, tachycardia, and diaphoresis. Under the impression of encephalitis, she was referred to our neurological department again. On examination, she was drowsy, able to open her eyes spontaneously, but without verbal expression. Her pupils were equally reactive. There was mild neck stiffness. Motor examination showed the same muscle power (about 4/5) in all four limbs, brisk deep tendon reflexes, and no plantar reflexes bilaterally. Generalized muscular rigidity (catatonic signs) was superimposed on occasional tremors.

The complete blood count, erythrocyte sedimentation rate (5 mm/h), C-reactive protein concentration (0.05 mg/dl), and renal profile were normal. Her liver profile (aspartate aminotransferase 33 IU/L, alanine aminotransferase 42 IU/L) was mildly increased and creatine phosphokinase (CPK) was markedly increased (1824 U/l). A repeat lumbar puncture showed a slightly elevated opening pressure (20 cm H₂O), absence of white cells in the CSF (WBC count 5 /μl), and normal levels of CSF glucose (63 mg/dl) and CSF total protein (32.2 mg/dl). Gram stain, India ink stain, and bacterial culture were all negative.

Brain MRI showed a swollen splenium of corpus

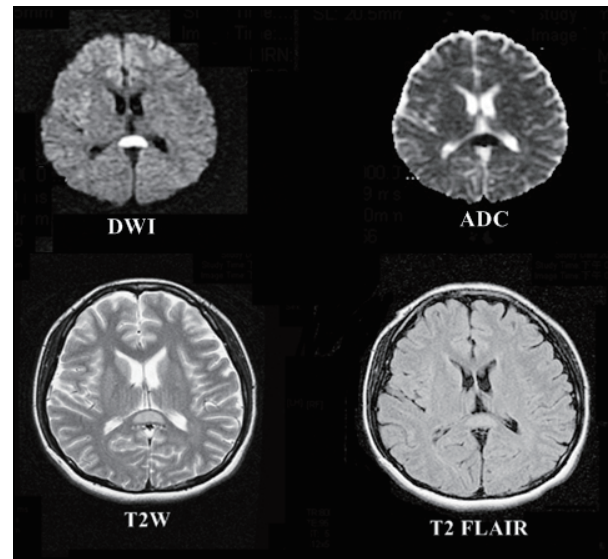


Figure 1. High signal intensity of splenium of corpus callosum on the T2-weighted (T2W), T2 fluid attenuated inversion recovery (FLAIR) and diffusion-weighted images (DWI), decreased apparent diffusion coefficient (ADC) values with "boomerang" appearance is noted.

callosum, which appeared hyperintense on T2-weighted and T2 fluid attenuated inversion recovery (FLAIR) images. Restriction in diffusion was observed in the diffusion-weighted images (DWI) with decreased apparent diffusion coefficient (ADC) values (Figure 1) and no enhancement was noted in a subsequent gadolinium study. Electroencephalography (EEG) revealed diffuse slow waves.

Ceftriaxone 1 g twice daily was empirically prescribed for possible meningoencephalitis until the CSF bacterial culture became negative one week later. Valproic acid 500 mg twice daily was given for abnormal EEG findings and possible seizure disorder, but discontinued one week later because of no improvement in follow-up EEG studies and clinical manifestations. To relieve her clinical symptoms, clozapine was first stopped, and adequate hydration, a minor tranquilizer (Lorazepam), and anticholinergic agent (Trihexyphenidyl) were provided.

Her temperature returned to normal and CPK levels decreased to 361 U/l 3 weeks later. She was discharged with only minimal cogwheel rigidity and mildly mental retardation but was otherwise well, without fever, and

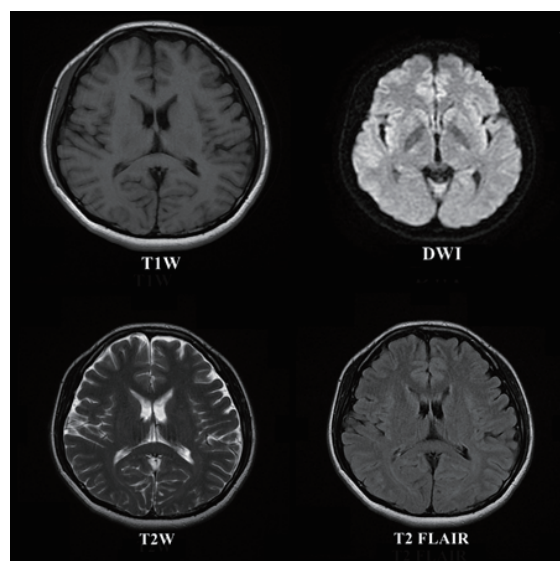


Figure 2. No remarkable finding is seen at the corpus callosum on the T1-weighted (T1W), T2-weighted (T2W), T2 fluid attenuated inversion recovery (FLAIR) and diffusion-weighted images (DWI).

able to talk and eat as usual. A follow-up MRI done 12 weeks after discharge showed complete resolution of the splenial lesion (Figure 2). EEG showed no particular abnormalities, too. Her neurological deficits have improved nearly completely. In view of the whole clinical history and typical presentation as well as the laboratory findings, NMS was highly suspected and associated with a reversible isolated lesion in the SCC.

DISCUSSION

In the present case, a seizure disorder was excluded based on EEG findings and clinical manifestations. This patient also had no exposure to antiepileptic drugs previously, and anticonvulsant toxicity was unlikely. Thorough blood and CSF examinations were all negative for encephalitis or encephalopathy. The likelihood of acute disseminated encephalomyelitis (ADEM) was low because patients frequently have multiple lesions in the white matter in T2-weighted and T2 FLAIR sequences, and analysis of their CSF reveals mild pleocytosis. NMS was diagnosed based on the patient's history of neuropsychiatric treatment as well as her typical clinical

presentation and raised CPK levels.

In the largest case series to date, the most common presentation of NMS was prodromal fever followed by neurological symptoms of delirious behavior, altered consciousness, and seizures (in 33%). The incidence of NMS ranges between 0.02% and 3.23% of psychiatric patients receiving neuropsychiatric treatment. Clinically, it is characterized by an abnormal mental status (Mental status change is the initial symptom in 82% of patients.), hyperthermia (Temperatures of more than 38°C are typical, but even higher temperatures, greater than 40°C are common in 40% of patients.), 'lead-pipe' rigidity, akinesia or dystonia, autonomic instability (Tachycardia is found in 88% of patients.), rhabdomyolysis, myoclonus, coarse tremors, and cogwheeling^(7,8). Common laboratory findings of NMS include increased CPK due to rhabdomyolysis.

The cause of NMS is unknown. Current theories are limited in their ability to explain all clinical manifestations and in supporting data. Because of the class of agents with which NMS is associated, dopamine receptor blockade is central to most theories of its pathogenesis. Central dopamine receptor blockade in the hypothalamus may cause hyperthermia and other signs of dysautonomia. Interference with nigrostriatal dopamine pathways may lead to Parkinsonian type symptoms such as rigidity and tremor. An alternative theory is that rigidity and muscle damage represent a primary effect on the peripheral muscle system, perhaps from direct changes in muscle mitochondrial function. This in itself may represent a primary skeletal muscle defect or a direct toxic effect by neuroleptics on skeletal muscle⁽⁹⁻¹¹⁾.

NMS is not associated with specific neuroimaging features. Brain CT and MRI scans are usually done in patients with NMS to exclude other structural lesions or infections that may give rise to similar clinical presentations. In isolated cases diffuse cerebral edema has been reported in the setting of severe metabolic derangements, as well as signal abnormalities in the cerebellum and basal ganglia that are similar to those seen in malignant hyperthermia⁽¹²⁾. Abnormalities in the corpus callosum have been reported in patients with neuropsychiatric lupus with psychosis⁽¹³⁾, but are rare in NMS cases⁽⁹⁾. The isolated lesion in the SCC associated with pure psychotic disorders raises the possibility that such a lesion may be sufficient to produce acute behavioral

changes and psychotic features in certain patients⁽¹⁴⁾.

Establishing a hypothesis for the precise etiology of the SCC lesion in this NMS patient is difficult. A transient lesion in the splenium of the corpus callosum seems to be a nonspecific end point of different disease processes leading to transient white-matter oedema with or without demyelination⁽⁴⁾, intramyelinic cytotoxic oedema⁽¹⁵⁾, and inflammatory cell infiltration with secretion of proinflammatory cytokines (especially interleukin-6)⁽²⁾. The possible differential diagnoses include epilepsy, antiepileptic drugs toxicity, encephalitis, encephalopathy, cerebrovascular disease, Marchiafava-Bignami disease, alcoholism, and malnutrition, ADEM, reversible posterior leukoencephalopathy syndrome, diffuse axonal injury, multiple sclerosis, lymphoma, and extrapontine myelinolysis. Clinical outcomes are excellent. The majority of patients have complete resolution of brain MRI lesions and clinical symptoms within weeks with no long-term neurological sequelae, as occurred in our patient. No specific treatment is required, particularly steroids or other immunotherapy.

CONCLUSION

A reversible isolated SCC lesion is a distinct clinicoradiological syndrome of varied etiology. The features might be found in certain psychiatric patients with NMS, and most cases occur in patients with epilepsy and encephalitis. The etiological mechanism remains uncertain and enigmatic, but neurological courses and outcomes are good. Knowledge of brain MRI findings and the spectrum of diseases might prevent unnecessary invasive examinations and treatments in clinical practice.

ACKNOWLEDGEMENTS

This paper was not supported by any grants or projects. The authors declare that they have no competing interests.

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