CASE REPORT

Transient Splenial Lesion of the Corpus Callosum after Acute Withdrawal of Antiepileptic Drug: A Case Report

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(Received October 11, 2006; Accepted December 13, 2006)

Transient lesions at the splenium of the corpus callosum (SCC) have been reported after withdrawal of specific antiepileptic drugs (AED), though the pathophysiology of the lesions remains unclear. We examined and treated a schizophrenic patient who developed a transient SCC lesion after withdrawal of the AED, carbamazepine. Interestingly, the SCC lesion was accompanied by the onset of diabetes insipidus, a state of arginine-vasopressin (AVP) insufficiency. Because carbamazepine is shown to potentiate the effect of AVP, our case suggests that an insufficiency of AVP followed by withdrawal of AED could contribute to the pathogenesis of a transient SCC lesion.

Keywords: *splenium, corpus callosum, diffusion-weighted image, carbamazepine, diabetes insipidus*

Introduction

Transient localized lesions of the splenium of the corpus callosum (SCC) are described in various clinical conditions,^{1–3} and some are attributed to the withdrawal of antiepileptic drugs (AED).^{2,4} Although isotropic diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping based on magnetic resonance imaging (MRI) disclosed homogenous reduced diffusion at the lesions that suggested cytotoxic edema,⁵ the lesions were reported reversible.^{1–5} The pathophysiological mechanisms of reversible SCC lesions, however, remain unclear.

Antiepileptic drugs are known to influence the fluid-balance system, i.e., arginine-vasopressin (AVP),⁶ whereas the antiepileptic drug, carbamazepine, is shown to potentiate the antidiuretic effect of AVP.⁷ We present a case of a transient SCC lesion occurring after withdrawal of carbamazepine. Notably, the condition was accompanied by diabetes insipidus, which suggested an imbalance of AVP.

Presentation of Case

A 46-year-old man diagnosed with and treated for schizophrenia for 20 years was seen in our hospital for catatonic symptoms of a month's duration. He had no history of drinking or smoking, and his familial medical history was remarkable only for depression in his mother. After stable psychiatric symptoms for 10 years, his behavior slowed. He kept mute and stood in his room for long periods and occasionally sat motionless in the bath. His family took him to the psychiatric clinic in our hospital at the end of the month. He was hospitalized the same day after being diagnosed with catatonia due to schizophrenia.

Prior to hospitalization, his daily dose of medication was: lithium carbonate 800 mg, carbamazepine 600 mg, promethazine hydrochloride 50 mg, flunitrazepam 2 mg, bulotizolam 10 mg, nimetazepam 5 mg, and oxatomide 60 mg. Carbamazepine has been prescribed for excited mental state from schizophrenia.

On admission, the man was afebrile. His blood pressure was 130/75 mmHg with pulse of 85 and no arrhythmia. During his psychiatric examination, he failed to respond when his name was called. His interaction with others improved immediately after an injection of diazepam, compatible with the

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Fig. 1. Magnetic resonance imaging of the brain 3 days after withdrawal of the antiepileptic drug, carbamazepine. Arrows indicate lesion at the splenium of the corpus callosum.

Fig. 2. Magnetic resonance imaging of the brain 5 days after withdrawal of carbamazepine. Arrows indicate expansion of the splenial lesion.

diagnosis of catatonia from schizophrenia.⁸

Laboratory data for hematology and chemistry were unremarkable except for a mild elevation in creatine kinase. Serum concentrations of lithium carbonate, thyroid-stimulating hormone, and serum ammonia were normal. Urinalysis disclosed specific gravity of 1.016. Electroencephalographic findings were unremarkable.

On hospitalization, all the patient's medications were halted, and flunitrazepam and lisperidone were administered. To rule out intracranial lesion, MRI of the brain was performed on the third day after admission (3 days after cessation of carbamazepine). MRI revealed an isolated oval-shaped abnormal signal on a mid-portion of the SCC that showed low intensity on T₁-weighted imaging (T₁WI) (not shown) and high intensity on

T₂-weighted imaging (T₂WI), fluid-attenuated inversion recovery (FLAIR), and isotropic DWI (Fig. 1). The ADC was reduced on the lesion (Fig. 1). However, neither physical nor neurological abnormalities, including callosal disconnection syndrome, were observed on examination. An electroencephalogram (EEG) proved unremarkable. Another MRI of the brain 2 days after initial study showed enlargement of the abnormal signal (Fig. 2), with no abnormal finding elsewhere. The patient showed no change clinically and remained catatonic. Serum sodium level gradually increased to 155 mEq/L and returned to a near normal 148 mEq/L 2 days later, though his urine excretion remained at about 3000 mL or more each day. We diagnosed diabetes insipidus. Follow-up MRI of the brain 5 days after the previous study (10 days

Fig. 3. Magnetic resonance imaging of the brain 53 days after withdrawal of carbamazepine. Arrows indicate the disappearance of the splenial lesion.

Fig. 4. Magnetic resonance imaging of the splenial lesion and the clinical course. Top: number of days from withdrawal of the antiepileptic drug; second row: change in size of the splenial lesion; third row: clinical course of stupor; bottom: excretion of urine after withdrawal of carbamazepine.

after withdrawal of carbamazepine) disclosed no remarkable change (not shown). Cerebrospinal fluid collected on the twelfth day after initial presentation of the splenial lesion only showed mild elevation of protein to 58 mg/dL. The IgG index was 0.44, and oligoclonal band was not detected.

The patient's stupor improved in a step-wise manner with sequential application of modified electroconvulsive therapy (m-ECT)⁹ and disappeared after 6 treatments. This effectiveness was consistent with the diagnosis of stupor related to schizophrenia. Diabetes insipidus disappeared on the 29th day from initial abnormal finding on MRI brain scan. Final MR imaging immediately before

discharge, 50 days from the initial study (53 days after withdrawal of carbamazepine), revealed complete resolution of the SCC lesion (Fig. 3). The patient was discharged without neurological sequelae. The MR image of the splenial lesion and the clinical course are shown in Fig. 4.

Discussion

MR brain imaging of our patient, diagnosed with schizophrenia, showed an isolated ovoid lesion at the SCC after administration of the AED drug, carbamazepine, was discontinued. The SCC lesion showed low intensity on T₁WI and high intensity on

both T₂WI and FLAIR. Diffusion-weighted imaging demonstrated high intensity, but ADC was decreased. Interestingly, the SCC lesion appeared in conjunction with the cessation of AED and onset of diabetes insipidus. Fifty days from the initial abnormal MR finding, the SCC lesion had disappeared completely, and the patient was discharged without neurological sequelae. We cannot thoroughly rule out the relationship between stupor and the SCC lesion, but the stupor's clear response to mECT strongly supports its relationship to schizophrenia.

Reversible isolated SCC lesions have been associated with administration or withdrawal of AED,^{2,4,5} and the clinical course of our case suggests that abrupt cessation of AED could have induced the SCC lesion observed on MR imaging. Polster and associates reported 3 cases of patients with intractable epilepsy who had reversible SCC lesions.² The authors noted similar lesions on MRI during the tapering of AED to perform noninvasive EEG monitoring for surgery. Because two of the 3 cases showed an isolated ovoid lesion on SCC after cessation of AED without documentation of seizure, the authors hypothesized that the AED cessation itself could have caused the SCC lesion. Recent reports also support an association between withdrawal of AED and appearance of SCC lesions.⁴ These reports compare a group of patients who showed SCC lesions after presurgical long-term EEG monitoring (LTM) with another group who did not. There was a significant difference between these 2 groups concerning the reduction of the AED prior to MRI. However, they could not point to any difference in frequency of seizures between the 2 groups. They concluded that the main factor contributing to a reversible lesion of the SCC in patients with epilepsy is the rapid reduction and duration of complete withdrawal of AED. The rapid cessation and duration of complete withdrawal of AED (median 3.5 days in case of a subgroup having SCC lesions in Gürter's report) is consistent with our case, although our patient was not epileptic. Because there was neither medical history of epilepsy nor documentation of convulsive seizure after hospitalization, our case suggests that patients without epilepsy may develop a transient SCC lesion associated with complete withdrawal of AED and strongly supports the role of AED withdrawal for the induction of an SCC lesion.

The pathogenesis of transient SCC lesions is unknown. Tada and colleagues reported that reversible SCC lesions disclosed homogeneously reduced diffusion in all 7 cases they examined.³ Because the

SCC lesions are reversible, they postulated that intramyelinic edema from the separation of myelin layers and inflammatory infiltrate could be the mechanism responsible for the transiently decreased ADC of the lesion. They considered that ADC may return to normal if the causes for its decrease are resolved quickly. We agree. Unlike vasogenic edema, local fluid retention in a restricted intercellular compartment following the separation of myelin layers could reduce ADC at this location.

How were changes induced in association with the withdrawal of the AED? Polster's team postulated that the AED's effect on fluid-balance systems, namely that of arginine-vasopressin (AVP), is pivotal in the pathogenesis of transient SCC lesions.² Carbamazepine has been shown to enhance the antidiuretic effect of AVP.⁷ The reduction of serum AVP concentration after several weeks of administration of carbamazepine had been reported and interpreted as an adaptive response of the fluid balance system to the influence of carbamazepine.¹⁰ In our case, we found diabetes insipidus after abrupt cessation of carbamazepine, a finding consistent with these reports in that the abrupt disappearance of the effect of carbamazepine could reduce the antidiuretic effect of AVP, which could then induce diabetes insipidus. Our finding is basically consistent with the hypothesis postulated by Polster and associates that suggests an involvement of disequilibrium of AVP with the appearance of transient SCC lesions after withdrawal of carbamazepine.² Although the authors emphasize the role of elevated carbamazepine concentration in causing an inappropriate antidiuresis that could contribute to brain edema in a site of predilection, our case pointed to the possibility that the effect of a shortage of AVP manifested as diabetes insipidus also causes transient SCC lesions. This finding suggests that the mechanism responsible for transient SCC lesions after cessation of AED may be more complex than thus far postulated. A recent study shows that serum AVP measurements revealed altered secretion during the acute phase of the appearance of SCC lesions on presurgical LTM.¹¹ Another possibility is the involvement of hypernatremia, also suggested in previous reports.¹² However, because of the normal serum sodium value (145 mEq/L) at the appearance of the SCC lesion, we could rule out involvement of hypernatremia in the emerging SCC lesion in our case.

Of course, SCC lesions have been reported with many other pathophysiological conditions, including presence of alcohol, trauma, acute dis-

seminated encephalomyelitis, seizure, neoplasia, chemotherapy, electrolyte imbalance, and viral encephalitis.¹²⁻¹⁴ However, we could exclude encephalitis because the EEG finding was normal. Although there is no other report to our knowledge, we cannot completely exclude the possibility that withdrawal of other drugs or administration of flunitrazepam and lisperidone could cause the transient SCC lesions. Further investigation is required to elucidate the pathogenesis of transient SCC lesions.

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