

Transient Lesion in the Splenium of the Corpus Callosum Due to Carbamazepine

Karbamazepin Kullanımına Bağlı Geçici Korpus Kallozum Splenium Lezyonu

ABSTRACT

Keeping in mind that lesions located in the splenium of the corpus callosum can sometimes be temporary may help us avoid invasive diagnostic and therapeutic methods. Transient lesion in the splenium of the corpus related to using or withdrawal of antiepileptic drugs are rarely encountered. In this article, we present a non-epileptic patient found to have a centrally located isolated lesion in the splenium of the corpus callosum on the tenth day following the sudden withdrawal of carbamazepine after two weeks of use. The lesion was observed to disappear two months later and the carbamazepine treatment or sudden withdrawal of the drug was thought to be responsible for this reversible splenial lesion.

KEY WORDS: Antiepileptic drugs, Carbamazepine, Corpus callosum, Transient splenium lesion

ÖZ

Korpus kallozum lokalizasyonlu geçici lezyonlar oluşabileceğini bilmek invaziv tanı ve tedavi yöntemlerinden kaçınmamızı sağlayabilir. Karbamazepinin kullanımına veya kesilmesine bağlı oluşan geçici korpus kallozum splenium lezyonları nadir olarak bildirilmiştir. Burada epileptik olmayan bir hastada iki haftalık karbamazepin kullanımının ardından ilacın kesilmesini takip eden onuncu günde korpus kallozum spleniumda santral yerleşimli lezyon tespit edilen bir hasta sunulmaktadır. İki ay sonra kontrolde lezyonun kaybolduğu görüldü ve bu lezyona karbamazepin kullanılmasının veya kullanımı sırasında aniden kesilmesinin yol açtığı düşünüldü.

ANAHTAR SÖZCÜKLER: Antiepileptik ilaçlar, Karbamazepin, Korpus kallozum, Geçici splenium lezyonu

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INTRODUCTION

Lesions with an unknown origin are sometimes detected during cerebral imaging studies. In such cases of diagnostic difficulty, invasive diagnosis methods such as stereotactic biopsy might be used which can be risky, especially when the lesions are deeply located. However, these lesions can be temporary. Splenium of the corpus callosum (SCC) is a location where transient lesions can rarely be observed. Some of these lesions are associated with epileptic seizures, antiepileptic drug (AED) usage and sudden withdrawal of the AEDs (5,7,9, 10,12-15, 18-24,26-28). The reason for the temporary involvement of the splenium and the pathophysiology of the lesions are still controversial. Factors such as the spread of the epileptic seizure by means of colossal fibers (7, 26), focal demyelination due to the toxicity of the AEDs (9,18), and the effects of the AEDs on the arginine-vasopressin (AVP) and fluid-electrolyte equilibrium (13,15,21,23,27-28) have been held responsible.

We present a non-epileptic patient who was found to have an isolated, reversible lesion in the SCC thought to be associated with the use or sudden withdrawal of carbamazepine.

CASE REPORT

A 19-year-old female was prescribed carbamazepine with a starting dose of 200 mg/day and subsequent doses of 400 mg/day at the hospital where she had presented with complaints of headache, fainting, waking up frightened from her sleep and crying that had started 2.5 months ago. It was decided at the next follow-up to gradually reduce and finally stop the carbamazepine since it was thought that her fainting complaints seemed to fit in with psychogenic seizure during the observation period. Slight paroxysmal abnormalities in bilateral temporal areas were detected in the electroencephalography (EEG) of the patient during this period. Her computer-assisted brain tomography (CT) and cranial magnetic resonance imaging (MRI) of brain were found to be normal (Figure 1). MR venography did not show any pathology except for a hypoplastic appearance of the left transverse and sigmoid sinus. Carbamazepine was suddenly stopped by the patient after using it 2 weeks at a dose of 400 mg/day. The patient presented at our hospital with visual hallucinations starting a few days after stopping the drug in

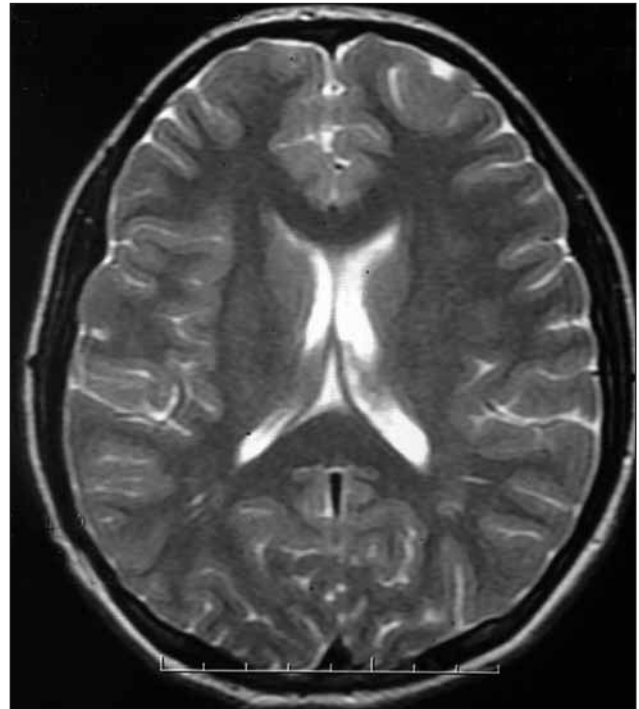


Figure 1: No lesion was seen on the axial image of T2-weighted MRI performed before carbamazepine therapy.

addition to her other symptoms. Her history was unexceptional except for one febrile convulsion in the past. She did not describe any nutritional disorder or alcohol usage. There was nothing of note in the family history. She did not have high fever and other vital findings were stable. The physical and neurological examination findings were normal. The patient described visual hallucinations and had persecution delusions in the thought content. Cranial MRI performed a month after the first MRI, and 10 days after withdrawal of carbamazepine showed a 17x10 mm oval lesion with slightly hypointense signal characteristics in the T1-weighted sections and hyperintense signal characteristics in the T2 and FLAIR sections in the central region of the SCC. (Figure 2,3) The lesion did not display edema effect or contrast enhancement. The lesion showed no findings indicating neuroaxonal damage or demyelination on MR spectroscopy. A slight slow wave paroxysm in the temporal areas was observed in the repeated EEG. The patient had mild anemia but biochemical tests, examinations for coagulopathy and vasculitis, thyroid function tests, vitamin B12 and folate levels, and tumor markers were found to be normal. The hepatitis markers and anti-HIV were negative. CSF

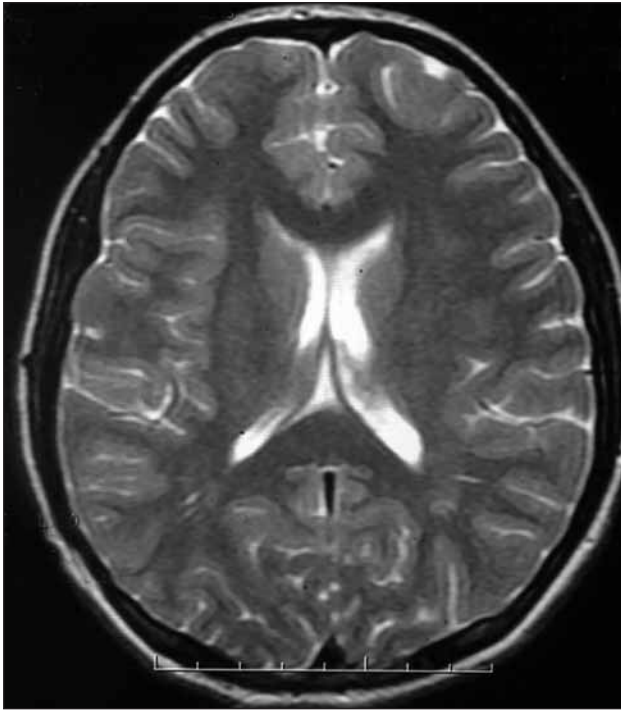


Figure 2: Hyperintense lesion in the SCC on axial image of T2-weighted MRI performed 10 days after carbamazepine withdrawal.

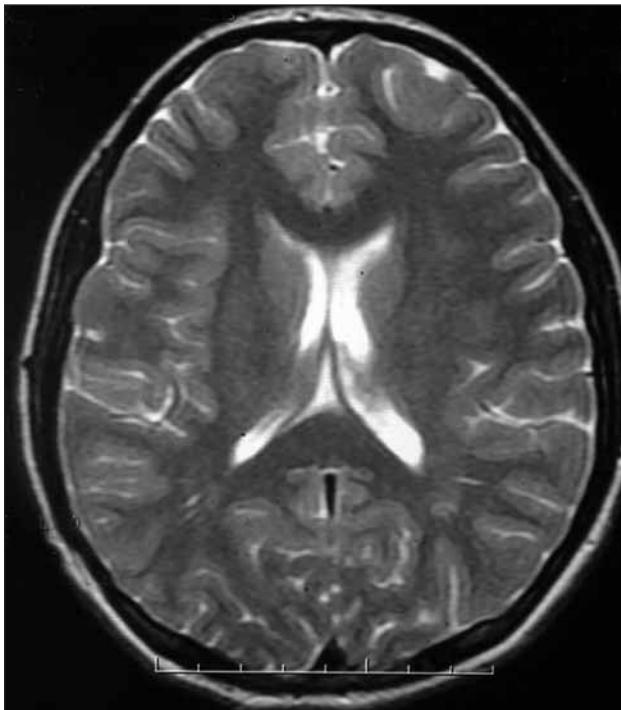


Figure 3: Hyperintense lesion in the SCC on sagittal image of T2-weighted MRI performed 12 days after carbamazepine withdrawal.

examination showed normal pressure with no cells. The CSF biochemistry and the ACE level were normal, while TORCH, tuberculosis, PCR, VDRL, Lyme, and brucella agglutination tests were found to be negative. An oligoclonal IgG band was not observed. The pathergy test was negative. Risperidone 2 mg/day was started for the patient following a diagnosis of schizoaffective disorder by the psychiatry department. MRI taken 2 months later showed that the SCC lesion had disappeared and no other pathological findings had developed. (Figure 4) The hallucinations disappeared, but the persecution delusions continued.

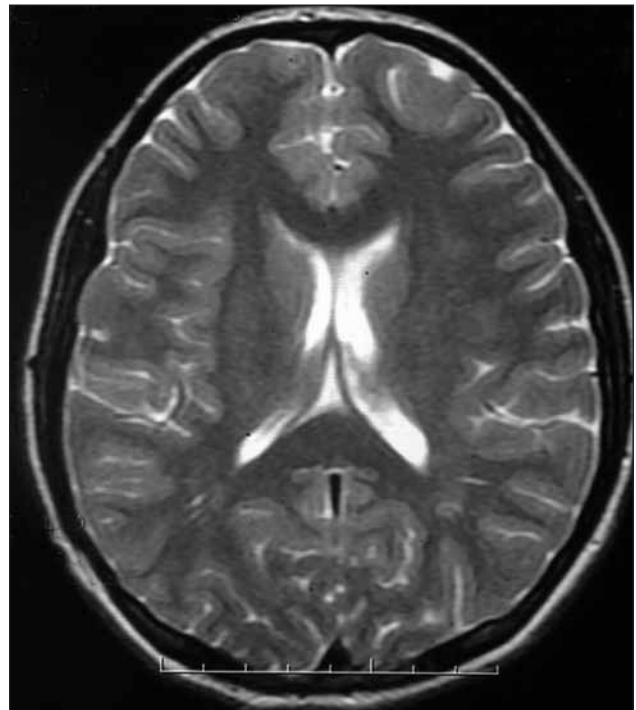


Figure 4: No lesion was seen on the axial image of T2-weighted MRI performed after 2 months after the second MRI.

DISCUSSION

Cerebral morphologic changes caused by antiepileptics have not attracted much attention except for the cerebellar atrophy developing due to phenytoin (22). Transient and isolated SCC lesions thought to develop due to AED usage (9, 12, 14, 18-20) or sudden withdrawal of AEDs (5, 10, 13, 15, 21-24, 27-28) have been reported in both epileptic and non-epileptic patients in recent years. SCC lesions were detected with MRI in epileptic patients after sudden reduction or withdrawal of AEDs before preoperative long term video-EEG monitoring (5,7,

10,13,21,23,26-28). While sudden reduction of AEDs was held responsible for the lesions in some studies (10,13,23,27-28), it was suggested that the lesions were caused by the frequent seizures and could be interpreted as a periictal phenomenon since some patients also had epileptic seizures in this period (7, 26). It was thought that the epileptic seizures or withdrawal of the AEDs, or both could be responsible in some studies (5,21).

Reversible SCC lesions were also reported in non-epileptic patients using AEDs (9,14-15,19,22, 24). Narita et al. reported a well-defined lesion in the MRI taken on the 11th day following the sudden withdrawal of carbamazepine after 21 days of use in a patient with obsessive-compulsive disease who displayed sporadic spike waves in bilateral temporal areas in the EEG. The neurological examination was normal and the lesion mostly resolved 24 days after its first appearance and disappeared 6 months later. They believed that using or withdrawal of the carbamazepine was responsible for the SCC lesion (22). Nifle et al. detected a lesion in the SCC as well as a state of confusion and EEG abnormality in a patient with bipolar affective disorder who stopped the drug suddenly while using oxcarbazepine, and reported that the lesion had disappeared 5 weeks later. They thought that the lesion was caused by the sudden withdrawal of oxcarbazepine (24). Honda et al. presented a schizophrenic patient who developed a temporary SCC lesion after stopping carbamazepine. They reported diabetes insipidus development in this period in the patient whose neurological examination was normal and held the sudden withdrawal of carbamazepine responsible for the lesion (15). In addition, transient SCC lesions have also been reported in non-epileptic patients using AEDs without stopping the drug (9,14,19).

In our patient, an isolated SCC lesion was detected in the cranial MRI taken 10 days after sudden withdrawal of the drug following carbamazepine usage for 2 weeks. This lesion, not present in the MRI taken a month ago, was also not observed in the MRI taken 2 months later. It could not be detected whether the lesion had appeared due to the carbamazepine treatment or to the sudden withdrawal of the drug. However, sudden withdrawal of carbamazepine was thought to be a more probable reason.

The pathophysiology of temporary SCC lesions is not definitely known. It has been suggested that

temporary physiological changes may occur in the callosal fibers due to the interhemispheric spread of the seizure activity via the splenial callosal fibers, and this can result in focal white matter edema (7,10, 26). Kim et al. held the demyelination caused by the toxic effect of the AEDs responsible for the SCC lesions (18). Polster et al. suggested that the fluid-balance disorder developing due to the sudden withdrawal of the AEDs caused vasogenic edema and created the SCC lesions (27). Carbamazepine increases the diuretic effect of AVP. A reduction in the AVP level has been reported a few weeks after carbamazepine treatment and this situation interpreted as an adaptive response to the effects of carbamazepine. The fluid balance system gets adapted to the effects of the AEDs as the treatment goes on. The sudden withdrawal of carbamazepine decreases the antidiuretic effect of AVP and the fluid balance system is impaired (13,15,21,23,27). In a study, AVP measurements were performed during the acute phase of the transient SCC lesion and fluctuations were detected in the AVP level (28). The patient reported by Honda et al. also had diabetes insipidus, which is a state of AVP deficiency, in the period when the SCC lesion appeared (15). It was stated that the osmotic myelinolysis developing due to the quick normalization of the hyponatremia caused by the AEDs after stopping the drug (13) or hypernatremia (15) might also be responsible for the lesion; however, no abnormality was detected in the sodium levels (15). Polster et al. interpreted the transient SCC lesions to be a result of the vasogenic edema caused by many different pathological events and diseases (27). Diffusion-weighted imaging studies have shown diffusion restriction and low ADC values in the lesions (9,10,13,15,17,19-21,23,26, 28-29,31-33) and these were thought to indicate cytotoxic edema (19,21,23,28-29). It was suggested that the temporary focal ischemia appearing due to cytotoxic edema might be responsible since the lesions were reversible (21). It was also thought that the temporary reduction in the ADC values of the lesions might originate from the intramyelinic (intercellular) edema (4,11,15,31,33). Sodium values were found to be normal during both the presentation and the observation period in our patient. There were no findings indicating neuroaxonal damage or demyelization in MR spectroscopy. Another study with MR spectroscopy reported normal spectroscopy findings in a patient

with a SCC lesion with no definite etiology but accompanied by high fever (30).

The neurological examination of our patient was normal and she did not have any interhemispheric disconnection findings. It is worth noting that no disconnection findings were detected in the reported subjects despite the presence of a corpus callosum lesion (10). Alteration of consciousness is the most frequent neurological finding in patients with transient SCC lesions, especially those related to encephalitis-encephalopathy (4, 10, 30-34). However, consciousness alteration is not generally observed in cases related to epilepsy and AEDs and the neurological examinations of these cases were found to be normal (7,15,18,21-22,27). In our patient, the appearance of visual hallucinations almost concurrently with the SCC lesion made us think that this symptom could be related to the splenial lesion. Some studies have also reported that hallucinations were observed with the reversible SCC lesions (10, 30-31). Another feature of the corpus callosum is its relation with schizophrenia. It has been reported that the dimensions of the corpus callosum are smaller in certain areas including the splenium (11, 16) and there are common differences in the microstructure of the corpus callosum including the splenium (3,6) in schizophrenic patients and that these findings indicate interhemispheric disconnection in schizophrenia pathogenesis. Another study reported a lipoma in the SCC of a patient with a schizophrenia-like disorder (2). Our patient had a diagnosis of schizoaffective disorder but its relation with the lesion was not made clear.

Splenial lesions have common imaging characteristics in cases associated with epilepsy and AEDs. Isolated, well-defined, nonhemorrhagic oval or round shaped lesions with isointense or slightly hypointense signal characteristics in T1 weighted images and hyperintense signal characteristics in T2 weighted and FLAIR images with no contrast enhancement located in the central region of the splenium have been reported on cranial MRI (7,10, 12,15,18-24,26-27). These lesions have been found to be temporary and to display total resolution in subsequent MRIs. The lesion detected in our patient also had these common characteristics. Most of the lesions in cases associated with encephalitis-encephalopathy have been reported to display irregular asymmetric extension from the central to the lateral areas while some of the lesions were

isolated, had ovoid forms and located in the central region of the splenium (20, 31-32) and other cerebral lesions sometimes accompanied the splenial lesion (32).

Besides those related to epilepsy and the AEDs, lesions involving the SCC have been reported with pathological conditions and diseases such as multiple sclerosis, ADEM, Marchiafava-Bignami disease, alcoholism, malnutrition, anorexia nervosa, vitamin B and folate deficiency, trauma, diffuse axonal damage, neoplasia, infarct, infection, AIDS-dementia complex, hydrocephaly, posterior reversible encephalopathy, lymphoma, fluid-electrolyte disorders, hypoglycemia, 5-fluorouracil chemotherapy, withdrawing of corticosteroid treatment discontinuation, extrapontine myelinolysis, hypertensive encephalopathy, adrenoleucodystrophy, and systemic lupus erythematosus (1,4,7-8,10,12,15,17,20,23-25,29-32,34). The lesions are not temporary and not limited to or isolated in the SCC in most of these conditions (24). Patients with a picture of slight encephalitis-encephalopathy accompanying the transient SCC lesions have been reported in recent years (14-15,18,20,23,28). Other possible diagnoses were discarded in our patient since the lesion was reversible and there was nothing of note in the patient history and no high fever or pathological neurological or laboratory findings.

The reason for the selective involvement of the SCC has not been clarified. No difference could be found in the splenium in terms of fiber thickness and composition when compared with other corpus callosum regions in anatomic studies (4). As a difference the splenium is supplied by the vertebrobasilar system while the other callosal areas are supplied by the carotis system (4, 29, 31); however, this fact does not explain the selective location of the lesions. In healthy subjects who underwent MRI T2 relaxation studies heterogeneity has been detected in the water content of the splenium and the internal capsule posterior leg, and the myelin water content was found to be higher. It is possible that the splenium has fluid mechanics that are more easily impaired compared to the surrounding tissues (10). It has also been suggested that the interhemispheric spread of seizure activity by means of splenial callosal fibers may have a role in the location of the lesion (7,26).

The appearance of transient lesions due to various pathological events and diseases perhaps by means of a common and not exactly illuminated mechanism in the splenium that has a selective vulnerability can be accepted as a syndrome. Knowing that SCC lesions can be temporary, especially when associated with epilepsy and AEDs, is rather important as it can help us avoid invasive examination and treatments.

REFERENCES

1. Appenzeller S, Faria A, Marini R, Costallat LT, Cendes F: Focal transient lesions of the corpus callosum in systemic lupus erythematosus. *Clin Rheumatol* 25(4): 568-571, 2006
2. Baumann CR, Regard M, Trier S, Schuknecht B, Siegel AM: Lipoma on the corpus callosum in a patient with schizophrenia-like episode: is there a causal relationship? *Cogn Behav Neurol* 19(2): 109-111, 2006
3. Brambilla P, Cerini R, Gasparini A, Versace A, Andreone N, Vittorini E, Barbui C, Pelizza L, Nose M, Barlocco L, Marella G, Gregis M, Tournikioti K, David AS, Keshavan MS, Tansella M: Investigation of corpus callosum in schizophrenia with diffusion imaging. *Schizophr Res* 79(2-3): 201-210, 2005
4. Bulakbaşı N, Kocaoğlu M, Tayfun C, Uçöz T: Transient splenial lesion of the corpus callosum in clinically mild influenza-associated encephalitis/encephalopathy. *AJNR Am J Neuroradiol* 27: 1983-1986, 2006
5. Carrara G, Ferlazzo E, Tampieri D, Andermann F, Melanson D: Transient edematous lesions of the splenium in epileptic patients. *Can J Neurol Sci* 32(3): 352-355, 2005
6. Cheung V, Cheung C, Mc Alonan GM, Deng Y, Wong JG, Yip L, Tai KS, Khong PL, Sham P, Chua SE: A diffusion tensor imaging study of structural dysconnectivity in never-medicated, first-episode schizophrenia. *Psychol Med* 22: 1-9, 2007
7. Cohen-Gadol AA, Britton JW, Jack JR, Friedman JA, Marsh WR: Transient postictal magnetic resonance imaging abnormality of the corpus callosum in a patient with epilepsy. *J Neurosurg* 97: 714-717, 2002
8. Conti M, Salis A, Urigo C, Canalis L, Frau S, Canalis GC: Transient focal lesion in the splenium of the corpus callosum: MR imaging with an attempt to clinical-physiopathological explanation and review of the literature. *Radiol Med(Torino)* 2007; 20 (Abs)
9. Da Rocha AJ, Reis F, Gama HP, da Silva CJ, Braga FT, Maia AC Jr, Cendes F: Focal transient lesion in the splenium of the corpus callosum in three non-epileptic patients. *Neuroradiology* 48(10): 731-735, 2006
10. Doherty MJ, Jayadev S, Watson NF, Konchada RS, Hallam DK. Clinical implications of splenium magnetic resonance imaging signal changes. *Arch Neurol* 62: 433-437, 2005
11. Downhill JE Jr, Buchsbaum MS, Wei T, Spiegel-Cohen J, Hazlett EA, Haznedar MM, Silverman J, Siever LJ: Shape and size of the corpus callosum in schizophrenia and schizotypal personality disorder. *Schizophr Res* 43(3): 193-208, 2000
12. Feitova V, Feit J, Krupa P: Therapy-related change of corpus callosum in a young patient with epilepsy. *Eur Radiol* 12: 345-347, 2002
13. Gürtler S, Ebner A, Tuxhorn I, Ollech I, Pohlmann-Eden B, Woermann FG: Transient lesion in the splenium of the corpus callosum and antiepileptic drug withdrawal. *Neurology* 65(7): 1032-1036, 2005
14. Hakyemez B, Erdoğan C, Yıldırım N, Gökalp G, Parlak M: Transient splenial lesion of corpus callosum associated with antiepileptic drug: conventional and diffusion-weighted magnetic resonance images. *Acta Radiol* 46(7): 734-736, 2005
15. Honda K, Nishimura J, Sato H, Munakata M, Kamada M, Iwamura A, Nemoto H, Sakamoto T, Yuasa T: Transient splenial lesion of the corpus callosum after acute withdrawal of antiepileptic drug: A case report. *Magn Reson Med Sci* 5(4): 211-215, 2006
16. Keshavan MS, Diwadkar VA, Harenski K, Rosenberg DR, Sweeney JA, Pettegrew JW: Abnormalities of the corpus callosum in first episode, treatment naive schizophrenia. *J Neurol Neurosurg Psychiatry* 72(6): 757-760, 2002
17. Kim JH, Choi JY, Koh SB, Lee Y: Reversible splenial abnormality in hypoglycemic encephalopathy. *Neuroradiology* 49(3): 217-222, 2007
18. Kim SS, Chang KH, Kim ST, Suh DC, Cheon JE, Jeung SW, Han MH, Lee SK: Focal lesion in the splenium of the corpus callosum in epileptic patients: antiepileptic drug toxicity? *AJNR Am J Neuroradiol* 20: 125-129, 1999
19. Maeda M, Shiroyama T, Tsukahara H, Shimono T, Aoki S, Takeda K: Transient splenial lesion of the corpus callosum associated with antiepileptic drugs: evaluation by diffusion-weighted MR imaging. *Eur Radiol* 13(8): 1902-1906, 2003
20. Maeda M, Tsukahara H, Terada H, Nakaji S, Nakamura H, Oba H, Igarashi O, Arasaki K, Machida T, Takeda K, Takanashi JI: Reversible splenial lesion with restricted diffusion in a wide spectrum of diseases and conditions. *J Neuroradiol* 33(4): 229-236, 2006
21. Mirsattari SM, Lee DH, Jones MW, Blume WT. Transient lesion in the splenium of the corpus callosum in an epileptic patient. *Neurology* 60: 1838-1841, 2003
22. Narita H, Odawara T, Kawanishi C, Kishida I, Iseki E, Kosaka K: Transient lesions in the splenium of the corpus callosum, possibly due to carbamazepine. *Psychiat Clin Neuros* 57: 550-551, 2003
23. Nelles M, Bien CG, Kurthen M, von Falkenhausen M, Urbach H: Transient splenium lesions in presurgical epilepsy patients: incidence and pathogenesis. *Neuroradiology* 48: 443-448, 2006
24. Nifle C, Couratier M, Jallade C, Sarfati Y, Mignon F, Pico F: Cas clinique hypersignal T2 transitoire du splenium du corps calleux chez une patiente non epileptique. *Rev Neurol (Paris)* 163: 6-7, 736-739, 2007
25. Nishimura K, Takei N, Suzuki K, Kawai M, Sekine Y, Isoda H, Mori N: A transient lesion in splenium of the corpus callosum in a patient with childhood-onset anorexia nervosa. *Int J Eat Disord* 39: 527-529, 2006
26. Oster J, Doherty C, Grant PE, Simon M, Cole AJ: Diffusion-weighted imaging abnormalities in the splenium after seizures. *Epilepsia* 44: 852-854, 2003
27. Polster T, Hoppe M, Ebner A: Transient lesion in the splenium of the corpus callosum: three further cases in epileptic patients and a pathophysiological hypothesis. *J Neurol Neurosurg Psychiatry* 70(4): 459-463, 2001
28. Prilipko O, Delavelle J, Lazeyras F, Seeck M: Reversible cytotoxic edema in the splenium of the corpus callosum related to antiepileptic treatment: Report of two cases and literature review. *Epilepsia* 46(10): 1633-1636, 2005

29. Renard D, Bonafe A, Heroum C: Transient lesion in the splenium of the corpus callosum after oral corticoid therapy. *Europ J Neurol* 14: e19-e20, 2007
30. Shimizu H, Kataoka H, Yagura H, Hirano M, Taoka T, Ueno S: Extensive neuroimaging of a transient lesion in the splenium of the corpus callosum. *Europ J Neurol* 14:e37-e39, 2007
31. Tada H, Takanashi J, Barkovich AJ, Oba H, Maeda M, Tsukahara H, Suzuki M, Yamamoto T, Shimono T, Ichiyama T, Taoka T, Sahma O, Yoshikawa H, Kohno Y: Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. *Neurology* 63: 1854-1858, 2004
32. Takanashi J, Barkovich AJ, Shiihara T, Tada H, Kawatani M, Tsukahara h, Kikuchi M, Maeda M: Widening spectrum of a reversible splenial lesion with transiently reduced diffusion. *AJNR Am J Neuroradiol* 27: 836-838, 2006
33. Takanashi JI, Barkovich AJ, Yamaguchi KI, Kohno Y: Influenza-associated encephalitis/encephalopathy with a reversible lesion in the splenium of the corpus callosum: A case report and literature review. *AJNR Am J Neuroradiol* 25: 798-802, 2004
34. Yaguchi M, Yaguchi H, Hoh T, Okamoto K: Encephalopathy with isolated reversible splenial lesion of the corpus callosum. *Internal Medicine* 44:1291-1294, 2005