HOSPITAL CHRONICLES 2014, 9(3): 202–207

CASE REPORT

Acute Hemorrhagic Leukoencephalitis: Multimodal Diagnosis and Treatment

Adamantia Sotiriou, MD[1], Sarantoula Ververaki, MD[2], Anastasios Chalkis, MD[3], Dimitra Riga, MD,[4] Spiros Zakynthinos, MD, PhD[1]

[1]*Department of Critical Care Medicine and Pulmonary Services,*
[2]*Department of Neurology,*
[3]*Department of Neurosurgery,*
[4]*Laboratory of Pathology,*
Evagelismos Hospital, Athens, Greece

KEY WORDS: *acute disseminated leukoencephalitis; decompressive craniectomy; Hurst disease; cerebral edema; epileptic seizures; multiple sclerosis*

Abbreviations
ADEM = acute disseminated encephalomyelitis
AHLE = acute hemorrhagic leukoencephalitis
CRP = C reactive protein
FLAIR = fluid attenuated inversion recovery
GCS = Glasgow coma scale
HLA = human leukocyte antigen
ICU = intensive care unit
MRA = magnetic resonance arteriography
MRI = magnetic resonance imaging
MRV = magnetic resonance venography
PML = progressive multifocal leukoencephalopathy
SV 40 = Simian virus 40

Correspondence to:
Adamantia Sotiriou, MD,
Critical Care Medicine, Evagelismos Hospital, Athens, Greece;
E-mail: mandiasotiriou@hotmail.com

Manuscript received September 25, 2013; Revised manuscript received January 23, 2014; Accepted March 21, 2014

Conflict of Interest: none declared

ABSTRACT

We report a case of a previously healthy 26-year-old male, admitted to the intensive care unit due to cerebral edema. The patient was admitted 3 days earlier to the neurological department because of sudden onset of headache and vision disturbances. Brain magnetic resonance imaging (MRI) on admission revealed an extended right parietooccipital lesion with marginal contrast enhancement and extension towards the corpus callosum. The patient quickly deteriorated, became comatose and was intubated and transferred to the intensive care unit. In order to control intracranial hypertension, decompressive craniectomy was decided which also allowed for a brain biopsy. According to clinical, radiological and laboratory data, acute disseminated encephalomyelitis was the working diagnosis. The patient was treated with high dose corticosteroids and plasmapheresis sessions and gradually improved and transferred to a rehabilitation center. Brain biopsy showed acute hemorrhagic leukoencephalitis or Hurst disease, a variant of acute disseminated encephalomyelitis.

INTRODUCTION

Acute fulminant brain dysfunction may derive from infectious, inflammatory, vessel-obstructive, vessel-inflammatory, demyelinating, neoplastic, metabolic or toxic processes. Causative spectrum is quite wide to be timely worked up when danger for life is present. Clinical evaluation, blood testing, brain computed tomography and lumbar puncture constitute the standard emergency diagnostic sequence. From the physician's perspective, narrowing the differential diagnosis to subgroups of entities with common treatment plan is highly desirable. Early recruitment of detailed brain imaging, i.e., brain parenchyma magnetic resonance imaging (MRI) together with arteriography and venography protocols (MRA, MRV) should be viewed as mandatory in this context.[1,2] On the contrary, specific laboratory investigations in blood and cerebrospinal fluid are often either not available or not informative in the early stage. In cases with ambiguous findings, targeted brain biopsy always remains an option.[1,3,4]

CASE REPORT

A 26-year-old previously healthy male patient was admitted via the Emergency Department complaining for severe headache and vision disturbances.

Medical history was remarkable for post infectious cerebellar dysfunction at the age of 7 years, aphthous stomatitis the previous year, and nasal congestion with myalgias 20 days earlier. Family history revealed the presence of non-Hodgkin lymphoma in his sister.

The patient reported abrupt onset of occipital headache and diplopia 3 hours prior to his admission. Clinical examination at the emergency room revealed right hemianopsia and positive left Babinski sign. There was no fever, nor nuchal rigidity. White blood cell count was $10.200*10^3/\mu l$ with lymphopenia and C-reactive protein (CRP) was 0.2 mg/dl. A brain computed tomography revealed cerebral edema localized in the right parietooccipital region without contrast enhancement. There was no midline shift; funduscopic examination showed absence of optic disc edema; clinical sings of "impeding" herniation were not evident and a lumbar puncture was safely undertaken. Opening pressure was 4 cm H_2O and cell count, glucose and protein were 4 per mm^3, 60 mg/dl (plasma glucose: 69 mg/dl) and 54 mg/dl, respectively. The patient was admitted to the Neurology Department.

The following day, headache was limited to the right retrobulbar area. General irritability, focal tonic-clonic seizures of the left upper limb and left hemiplegia sequentially emerged. Electroencephalogram was positive for focal brain dysfunction in the temporoparietal region (Table 2). Brain MRI (Fig. 1) revealed an extended right parietooccipital lesion with low signal on T1 sequence and high signal on T2 and FLAIR sequences, with marginal contrast enhancement and extension towards the corpus callosum. A second smaller lesion was identified in front of the first. Despite dexamethasone and valproic acid therapy, the patient sank gradually into coma and developed right mydriasis. He got intubated during the third day and a new brain computed tomography showed diffuse cerebral and brainstem edema. The patient was then transferred to the intensive care unit (ICU). Neurosurgical consultation suggested intraventricular catheter placement for intracranial pressure monitoring. First value was 60 mmHg. Decompressive right hemicraniectomy was undertaken. The ICU physician requested a brain biopsy sample.

Intracranial pressure was alleviated with surgery, but brain computed tomography images were still disappointing after days. Neurology consultant gave priority to acute disseminated encephalomyelitis as the working diagnosis. Clinical, radiological and laboratory data (Tables 1 & 2) were consistent with such a diagnosis. Tailored to this initial diagnosis, the patient received pulse dose of methylprednisolone 1 g/day. After 5 days patient was switched to prednisone 1 mg/kg along with

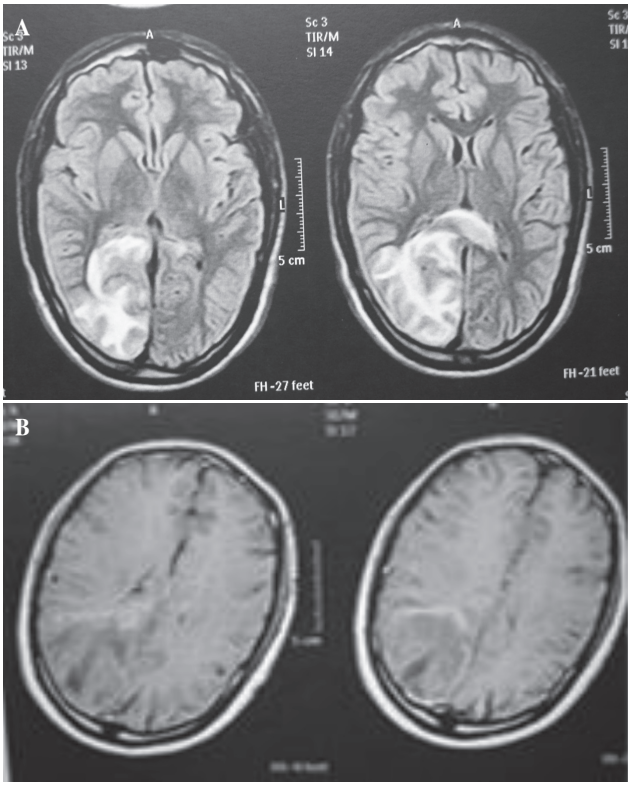

FIGURE 1. Brain MRI on admission. A: Extensive parenchymal lesion right parietooccipitally with inhomogenous signal in T2 and FLAIR sequences and low signal in T1 sequence. Marginal contrast enhancement and extension through the corpus callosum. **B**: Second little lesion with contrast enhancement in front of the main one. FLAIR = fluid attenuated inversion recovery; MRI = magnetic resonance imaging.

daily sessions of plasmapheresis, because of persistent cerebral edema. Additional treatment with antimicrobials (ceftriaxone, vancomycin, trimethoprim-sulfamethoxazol, azithromycin) and ganciclovir for three weeks was also provided. Histology report, available on the 20th day, made mention of the presence of immunohistochemic positivity for anti-Simian Virus 40 (SV40) antibody, but the concluded diagnosis was acute hemorrhagic leukoencephalitis (Fig. 2).

Gradual sedation withdrawal revealed a Glasgow Coma Scale (GCS) of 15, with left hemiplegia. Sedative drugs were continued until day 10. As protracted ICU stay was anticipated, the patient underwent early tracheostomy and gastrostomy. MRI follow-up on the 30th day disclosed brain lesion downsizing. After weaning from mechanical ventilation and completing 20 plasmapheresis sessions on the 45th day from admission, the patient was transferred to the intermediate care department. During the next 3 months, corticosteroids were gradually tapered and bone flap was restored. After another 3 months with physiotherapy and speech therapy, he got rid of tracheostomy

TABLE 1. Laboratory Findings

Blood chemistries			
Glucose	69 mg/dl	Uric acid	4.8 mg/dl
Urea	44 mg/dl	AST / ALT	19 IU/l/25 IU/l
Creatinine	1.03 mg/dl	Alkaline phosphatase	66 IU/l
Amylase	41 IU/l	γGT	12 IU/l
Total protein	7.43 g/dl	Bilirubin	0.68 mg/dl
Albumin	4.8 g/dl	Creatine kinase (CK)	78 IU/L
Globulins	2.63 g/dl	CK-MB	19 IU/l
Potassium	4.6 mmol/l	Lactic dehydrogenase	169 IU/l
Calcium	9.6 mg/dl	Cholesterol	196 mg/dl
Phosphorus	4.58 mg/dl	Triglycerides	70 mg/dl
Magnesium	2.06 mg/dl	C-reactive protein	0.2 mg/dl
Iron	46 µg/dl	ESR	14 mm/h
Blood counts			
Complete blood count			lymphopenia
White blood cell count			$11.6*10^3$/µl
Neutrophils (%)			72%
Lymphocytes (%)			20.7%
Monocytes (%)			6.45%
Red blood cell count			$6.32*10^6$/µl
Hematocrit			46.7%
Hemoglobin			16.2 g/dl
Platelet count			$217*10^3$/µl
Autoimmune disorders			
Antinuclear antibodies (ANA)			negative
Antineutrophil cytoplasmic antibodies (ANCA)			negative
AntidsDNA antibodies			negative
Anti-cardiolipin antibodies (ACA)			negative
Cryoglobulins			negative
Anti acquaporin 4			negative
Human leucocyte antigen (HLA) B51			positive
Muscle/vessel/skin biopsy			negative
Infectious agents			
Fluorescent antibody tests for viruses: HSV, CMV, VZV, EBV, Echo, Coxsackie, Adenovirus, Influenza A, B, measles, mumps, rubella			negative
Fluorescent antibody tests for bacteria: Listeria, Borrelia, Coxiella, Chlamydia, Mycoplasma, Legionella			negative
Human immunodeficiency virus (HIV) (Western blot and PCR)			negative
Blood disorders			
Thrombofilia			negative
Bone marrow aspirate			reactive
Peripheral blood immunophenotyping			Lymphopenia, no clonicity
Bone marrow immunophenotyping			Lymphopenia, no clonicity
Flow cytometry for NPH			negative
Immunoelectrophoresis			negative
Cold agglutinins			1:256
Cerobrospinal fluid examination			
Cells, protein, glucose (1) day 1			$4/cm^3$, 54 mg/dl, 60 mg/dl
Cells, protein, glucose (2) day 3			$50/cm^3$, 152 mg/dl, 60 mg/dl
Cells, protein, glucose (3) day 22			$2/cm^3$, 54 mg/dl, 90 mg/dl
Gram stain-culture			negative
Ziel Nielsen stain-culture			negative
PCR: JCV, HSV, EBV, VZV, Enterovirus, West Nile Virus, Toxoplama, Coxiella			negative
PCR for Cytomegalovirus			25 copies/µl
Oligoclonal bands			negative
Cryptococcus antigen			negative
Immunoelectrophoresis			Possible IgG production

ALT: alanine transaminase; AST: aspartate transaminase; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ESR: erythrocyte sedimentation rate; HSV: herpes simplex virus; JCV: John Cunningham virus; NPH: noctural paroxysmal hemoglobinuria; PCR: polymerase chain reaction; VZV: Varicella zoster virus.

TABLE 2. Imaging, Paraclinical and Histological Findings

Computed tomography(1) day 1	Right parietooccipital edema, no contrast enhancement
Computed tomography(2) day 3	Diffuse hypodense appearance in brain hemispheres and brain stem, midline shift to the left, probable herniation through the tentorium
Computed tomography(3) day 10	Diffuse hypodense appearance in brain hemispheres and brain stem, absence of midline shift
Magnetic resonance(1) day 2	Extensive parenchymal lesion right parietooccipitally with inhomogenous signal in T2 and FLAIR sequences and low signal in T1 sequence. Marginal contrast enhancement and extension along the corpus callosum. Second little lesion with contrast enhancement in front of the main one.
Magnetic resonance (2) day 30	Right hemicraniectomy and right ventricle dilatation. Large confluent area of T2 hyperintensity located in the white matter of right parietoccipital lobes and corpus callosum splenium. Downsizing of the area in comparison to previous imaging. Moderate ring contrast enhancement is still observed.
Cerebral angiography day 4	negative
Electroencephalogram day 2	High voltage activity in the right temporoparietal region
U/S cervical vessels day 2	negative
Fundoscopy day 1	negative
Brain biopsy day 3	Perivenular inflammatory infiltration with polymorphs, macrophages, perivenular hemorrhagic infiltration, perivenular myelinolysis, staining of oligodendroglia with SV40 antibody

FLAIR = fluid attenuated inversion recovery; SV40 = Simian virus 40; U/S = ultrasound

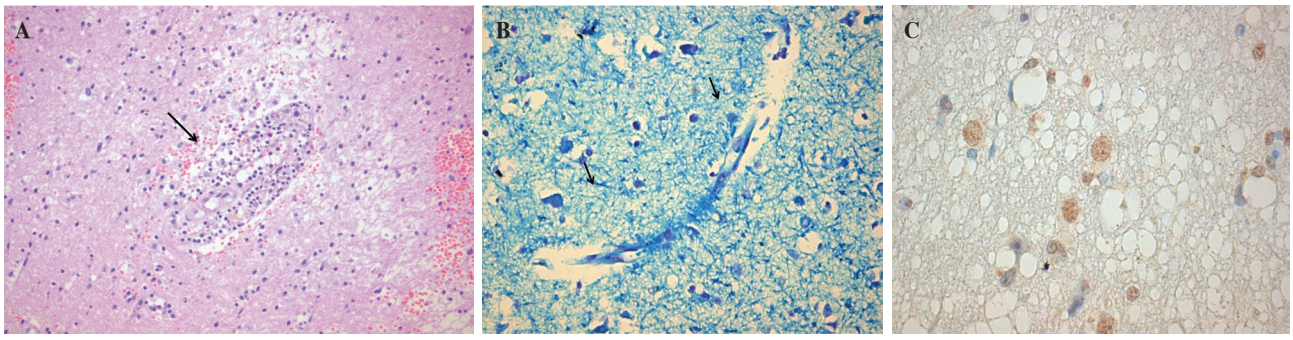

FIGURE 2. Histology, (a): Perivascular inflammation-perivenular lymphocytic infiltration (H+E x100); **(b):** Perivascular demyelination (arrows) (Kluver Barrera x 200); **(c):** Nuclear immunohistochemic positivity of oligodendrocytes to SV-40 antibody (DAB x 400)

and gastrostomy and was finally referred to a rehabilitation center. One year post-admission the patient was able to read, speak and walk with minimal help.

DISCUSSION

Acute disseminating encephalomyelitis is a rare clinical entity affecting mainly children and related to recent infections or vaccinations. Pathogenesis is related to activation of T-cells with neuro-crossreacting antigens, passage of T-cells through the perivenular space towards oligodendroglial dendritic cells for further antigen processing along with human leukocyte antigen molecules, inflammatory cell confluence in the brain and local production of direct neurotoxic substances, leading to variable degrees of myelinolysis.[5,6]

While children present with encephalopathy (i.e. acute behavioural change or alteration in consciousness) which has been established as a major criterion for diagnosis, initial symptoms in young adults usually imitate those of multiple sclerosis. Indeed, acute disseminated encephalomyelitis (ADEM) is considered to be the multiple sclerosis monophasic equivalent. Time to maximum intensity is usually between 2 and 7 days. Lumbar puncture and laboratory investigations are nonspecific. MRI of the brain is the investigation of choice and typically reveals more than one, asymmetrical, poorly margin-

ated lesions, settled in the deep white matter. T2 and FLAIR sequences are more helpful than T1.[6-8] Differential diagnosis in the typical case includes the group of demyelinating conditions (i.e., acute multiple sclerosis, neuromyelitis optica, transverse myelitis).[6,9] Treatment with high doses of corticosteroids (pulse therapy) accompanied by immunoglobulin, in cases with impossible to define or suboptimal response, usually are adequate for all forms of demyelinating diseases.[7,10,11] Active disease lasts 2-4 weeks and gradually resolves. Prognosis is favourable for acute survivors.

ADEM diagnosis is sufficiently set with clinical and radiological criteria.[12,13] Biopsy is not usually conducted since there are no detailed histopathological guidelines for unequivocal establishment of diagnosis.[14] The histologic hallmark is a perivenous mixed cell type inflammation along with myelinolysis. Location of lesions is highly sensitive for distinction against multiple sclerosis, but not exclusive as a finding.[15] Biopsy in our case was performed in order to take advantage of the hemicraniectomy, because diagnosis was at that time uncertain. Brain biopsy substantially contributed to the required quick exclusions, but also it was an important auxiliary tool for verifying the diagnosis. However, waiting for the definite histological diagnosis to decide the appropriate treatment would have been a pitfall.[14]

The hemorrhagic or hyperacute variant of ADEM is called acute hemorrhagic leukoencephalitis (AHLE) or Hurst disease, described first in 1941 and reproduced experimentally in 2008.[16] Basic histological particularities compared to ADEM are dominance of polymorphs in the inflammatory infiltrates, more vessel damage and less myelinolysis, the basic elements though being preserved.[17] Interestingly, this condition seems to resemble more neuromyelitis optica, except that its diagnosis does not require myelitis and eosinophils are not abundant in histology.[9] Hemorrhagic lesion transformation is sometimes evident in MRI.[2] In the case of AHLE, treatment intensity is maximised, adding prednisone 1 mg/kg after methylopredni-solone pulses and recruiting early plasmapheresis sessions.[18] Prognosis is, by all means, guarded.[2,19] Our patient was identified initially as usual ADEM and finally was ascertained histologically to fall into the hemorrhagic variant. By that time, treatment intensification had been implemented and clinical response had already been achieved.

Presence of anti SV40 antibody in oligodendroglial cells was an intriguing parallel finding. This feature awaits to be further elucidated by clinical follow-up as well as ongoing research in the fields of tumorigenic action of SV40 or properties of polyoma viruses, which share 70% DNA homology between each other.[20,21] Progressive multifocal leukoencephalopathy (PML), relating also to this group of viruses was readily ruled out because the patient was not formally immunosuppressed.[22] Relationship of SV-40 to multiple sclerosis could moreover be interesting,[23] as the age of the patient and the involvement of optic nerve are mentioned as predisposing factors for future demyelinating events.[7] Moreover, there exists a possibility of a random finding, as 3-5% of population in some countries are seropositive for the antibody,[24] as also are 7% of brain biopsies in normal human controls.[25]

CONCLUSION

Acute hemorrhagic leukoencephalitis has a mortality of at least 25%,[10] often necessitating decompressive surgery.[10,26,27] This is a death obliterating procedure but reversal of pathophysiology can be accomplished only through adequate immunosuppression. Both medical and surgical therapies were applied in our case, because fast clinical deterioration portended a dismal outcome. Along with clinical criteria- based approach, brain MRI was highly supporting ADEM because of selective devouring of the white matter. Additional identification of the AHLE variant via histology came to legitimize maximal therapeutic arrangements initially undertaken on the basis of a clinical emergency. Short and intermediate clinical course pursued as anticipated. Hyperacute post infectious encephalitis was thus thoroughly documented and successfully treated. A 5-year follow up is further required to authenticate diagnosis.[7]

REFERENCES

1. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: Clinical practice guidelines by the infectious diseases society of America. *Clin Inf Dis* 2008; 47:303-327.
2. Sonneville R, Klein I, de Broucker T, Wolff M. Post infectious encephalitis in adults: Diagnosis and management. *J Infect* 2009;58:321-328.
3. Rice CM, Gilkes CE, Teare E, Hardie RJ, Scolding NJ, Edwards RJ. Brain biopsy in cryptogenic neurological disease. *Br J Neurosur* 2011;25:614-620.
4. Franzini A, Leocata F, Giorgi C, Allegranza A, Servello D, Broggi G. Role of stereotactic biopsy in multifocal brain lesions: considerations on 100 consecutive patients. *J Neurol Neurosurg Psychiatr* 1994;57:957-960.
5. Becher B, Bechmann I, Greter M. Antigen presentation in autoimmunity and CNS inflammation: how T-lymphocytes recognize the brain. *J Mol Med (Berl)* 2006;84:532.
6. Lotze TE, Chadwick DJ. Acute disseminated encephalomyelitis in children: Pathogenesis, clinical features, and diagnosis. Up to Date, renewed November 2012. Available online.
7. Tenembaum S, Chitnis T, Ness J, Hahn JS; International Pediatric MS Study Group. Acute disseminated encephalomyelitis. *Neurology* 2007;68:S23-S36.
8. Murthy SN, Faden HS, Cohen ME, Bakshi R. Acute disseminated encephalomyelitis in children. *Pediatrics* 2002; 110(2 Pt 1):e21
9. Garg RK. Acute disseminated encephalomyelitis. *PostGrad*

Med J 2003;79:11-17.
10. Loetze T. Acute disseminated encephalomyelitis in children: prognosis and treatment. Uptodate, renewed September 2011. Available online.
11. Pohl D, Tenembaum S. T reatment of acute disseminated encephalomyelitis. *Curr Treat Options Neurol* 2012;14:264-275.
12. Krupp LB, Banwell B, Tenembaum S; International Pediatric MS Study Group. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology* 2007; 68(16suppl 2):s7-12.
13. Verhey LH, Branson HM, Laughlin S, et al. Development of a standardised MRI scoring tool for CNS demyelination in children. *AJNR Am J Neuroradiol* 2013;34:1271-1277.
14. Menge T, Kieseier BC, Nessler S, Hemmer B, Hartung HP, Stóve O. Acute disseminated encephalomyelitis: an acute hit against the brain. *Curr Opin Neurol* 2007;20:247-254.
15. Young NP, Weinshenker BG, Parisi JE, et al. Perivenous demyelination: association with clinically defined acute disseminated encephalomyelitis and comparison with pathologically confirmed multiple sclerosis. *Brain* 2010;133:333-348.
16. Pirko I, Suidan GL, Rodriguez M, Johnson AJ. Acute hemorrhagic demyelination in a murine model of multiple sclerosis. *J Neuroinflammation* 2008;5:1-5.
17. Hart MN, Earle KM. Hemorrhagic and perivenous encephalitis: a clinicopathological review of 38 cases. *J Neurol Neurosurg Psychiatry* 1975;38:585-591.
18. Ryan LJ, Bowman R, Zantek ND, et al. Use of therapeutic plasma exchange in the management of acute hemorrhagic leukoencephalitis: a case report and review of the literature. *Transfusion* 2007;47:981-986.
19. Lann MA, Lovell MA, Kleinschmidt-DeMasters BK. Acute hemorrhagic leukoencephalitis: a critical entity for forensic pathologists to recognise. *Am J Forensic Med Pathol* 2010;31:7-11.
20. Martini F, Corallini A, Balatti V, Sabbioni S, Pancaldi C, Tognon M. Simian virus 40 in humans. *Infect Agents Cancer* 2007;2:1-12, available on line.
21. Randhawa P, Viscidi R, Carter JJ, et al. Identification of species specific and cross reactive epitopes in human polyoma virus capsids using monoclonal antibodies. *J Gen Virol* 2009;90:634-639.
22. Koralnik IJ. Progressive Multifocal Leucoencephalopathy: Epidemiology, Clinical Manifestations and Diagnosis. Up to Date, renewed January 2013. Available online.
23. Ribeiro T, Fleury MJ, Granieri E, et al. Investigation of the prevalence of antibodies against neurotropic polyoma viruses BK, JCV and SV40 in sera from patients affected by multiple sclerosis. *Neurol Sci*. 2010;31:517-521.
24. Butel JS, Wong C, Vilchez RA, et al. Detection of antibodies to polyoma virus SV40 in two European countries. *Cent Eur J Public Health* 2003;11:3-8.
25. Bu X, Zhang X, Zhang X, Yi S. A study of simian virus 40 infection and its origin in human brain tumors. *Zhonghua Liu Xing Bing Xue Za Zhi* 2000;21:19-21.
26. Ahmed AI, Eynon CA, Kinton L, Nicoll JA, Belli A. Decompressive craniectomy for acute disseminated encephalomyelitis. *Neurocritic Care* 2010;13: 393-395.
27. Sekula RF Jr, Jannetta PJ, Rodrigues B, Brillman J, Frederickson AM, Crocker CS. Acute disseminated encephalomyelitis: a report of two fulminant cases and review of the literature. *Neurol Neurochir Pol* 2008;42: 458-462.