Case Report

Reversible Posterior Leukoencephalopathy Syndrome: A Retrospective Study in King Chulalongkorn Memorial Hospital†

Chaiwiwat Tungkasaereerak MD*,
Kammant Phanthumchinda MD*

† *This manuscript was presented at Annual Meeting of the Neurological Society of Thailand, March 2006*
* *Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok*

Background: *Reversible posterior leukoencephalopathy (RPLE) or reversible posterior cerebral edema syndrome is a syndrome characterized by transient focal or diffused neurological deficits and reversible neuroimaging changes. RPLE is often associated with hypertension and systemic illness. The classical Magnetic Resonance Imaging (MRI) feature of RPLE is predominately involvement of bilateral posterior cerebral white matter. Due to availability of MRI technology, this entity has been reported more frequently.*
Material and Method: *The clinical recordings were searched from data bases at King Chulalongkorn Memorial Hospital from 2003 to 2005. Keywords were "leukoencephalopathy" and "hypertensive encephalopathy". Neuroimaging criteria for the diagnosis of RPLE were bilateral symmetrical cortical-subcortical white matter lesions predominantly affecting the occipital lobe. The data were reviewed. Cases with RPLE were recruited and analyzed.*
Results: *Nine patients (female:male, 8:1), ranged in age from 17 to 39 years (average, 26 years) were analyzed. Five patients had acute hypertension associated with renal failure, 1 had acute hypertension without renal impairment, 2 had eclampsia and 1 was associated with cyclosporine therapy. Most common clinical symptoms were seizure and cortical blindness. MRI revealed bilateral occipital white matter edema in 7/8 patients while computerized tomography demonstrated this feature in 3/9 patients. Other MRI abnormalities were detected in frontal lobes, parietal lobes, deep grey nuclei, brainstem and cerebellum. The patients were treated with antihypertensive drugs, antiepileptics and withdrawal from immunosuppressive therapy. In 8 patients, the neurological deficits recovered within 2 weeks. The case with cyclosporine therapy had residuals in the form of limb weakness and spasticity.*
Conclusion*: RPLE is associated with hypertension, systemic autoimmune diseases, renal impairment, immunosuppressive therapy or eclampsia. The neuroimaging findings reveal characteristic white matter vasogenic edema in occipital lobes as well as other cortical areas and deep grey matter. Good clinical outcomes occur after prompt symptomatic treatment with antihypertensive drugs, antiepileptics or withdrawal from immunosuppressive therapy and repeated neuroimaging may not be necessary.*

Keywords: *Reversible posterior leukoencephalopathy syndrome*

J Med Assoc Thai 2008; 91 (3): 427-32
Full text. e-Journal: *http://www.medassocthai.org/journal*

Reversible posterior leukoenceplalopathy (RPLE) is an acute neurological syndrome usually associated with an abrupt increase in blood pressure[1-4]. This syndrome is related to vasogenic edema in the cerebral white matter. RPLE is often associated with systemic illness such as systemic lupus erythematosus[5], thrombotic thrombocytopenic purpura[6], hemolytic uremic syndrome[6-8], renal failure, cyclosporine induced neurotoxicity[1,7,9] and eclampsia[1-4]. Magnetic resonance imaging (MRI) is the diagnostic test of choice in RPLE[10-12]. Classical MRI features of RPLE are reversible bilateral posterior cerebral white matter

Correspondence to : Phanthumchinda K, Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, 10330, Thailand. Phone: 0-2256-4612, Fax: 0-2256-4630, E-mail: Kammant@hotmail.com

lesions with some involvement of adjacent grey matter[10-12].

Material and Method

During 2003-2005, clinical recordings from the database at King Chulalongkorn Memorial Hospital which is organized according to ICD10-TM tubular list of diseases 2003 were searched. Keywords were "leukoencephalopathy" and "hypertensive encephalopathy". Inclusion criteria consisted of cases with acute reversible cerebral symptoms (diffuse or focal) and neuroimaging (MRI and/or CT scan of the brain) compatible with RPLE. Imaging criteria for RPLE were bilateral symmetrical cortical-subcortical lesions which predominately involved posterior cerebral white matter. Clinical data including clinical syndrome of RPLE, systemic illness, medications and neuroimaging features as well as clinical course were analysed.

Results

Nine cases of RPLE were recruited and 8 patients were female only 1 was male. Age ranged from 17 to 39 years with an average of 26 years. MRI and CT of the brain (CT) were performed in 8 cases and 1 case had only CT. Five cases were acute hypertension, associated with renal failure (4 cases associated with lupus nephritis, 1 with IgA nephropathy), one case was acute hypertension without renal impairment (Takayasu's disease), 2 cases were eclampsia, and one case was receiving cyclosporine for acute myeloid leukemia after a bone marrow transplantation.

The most common clinical symptom was seizure which occurred in 7 cases. All 7 patients had generalized tonic-clonic seizures. Five cases had only one seizure, 2 cases had recurrent seizures and status epilepticus occurred in one who was receiving cyclosporine. Four cases had cortical blindness. Headache with nausea and vomiting were presented in 3 cases. Confusion and quadriparesis were presented in 1 case who was receiving cyclosporine therapy (Table 1).

In 8 cases, MRI of the brain revealed classical bilateral white matter edema with increased signal intensity in T2 weighted and fluid-attenuation inversion recovery (FLAIR) images in posterior cerebral region (Fig. 1). CT was performed in 9 cases and posterior cerebral white matter edema was documented only in 3 cases (Patient 5, 8, 9). The involved areas were the occipital in 8 cases. In these cases, the involvement was also documented in other areas i.e. parietal lobes 5 cases, temporal lobes 2 cases, frontal lobes 5 cases, midbrain 2 cases, pons 1 case, thalamus 1 case and cerebellum 2 cases. Only 1 case with classical clinical picture of RPLE had bilateral frontal lobe involvement without occipital and other lesions. Two cases had extensive lesions involving bilateral occipital, frontal, parietal lobes, brainstem and cerebellum (Patient 3, 7) as demonstrated in Fig. 2. In cases with occipital lobe involvement, the calcaline cortex and paramedian occipital lobe structures were spared. Since RPLE is a well documented clinical entity and due to a financial problem among the studied population, neuroimaging was not repeated in cases with complete clinical reversal. In case 7 who did not have a complete recovery, MRI was repeated within 4 weeks and revealed improvement of the lesions.

Patients were treated with antihypertensive medications, anticonvulsants and withdrawal of immunosuppressive drugs. Headache and vomiting promptly responded to antihypertensive treatment. Most of the cases had a complete neurological recovery within two weeks and none required long term antiepileptics. Only one case with cyclosporine therapy had residual guadriparesis and spasticity. Longterm antihypertensive medications are essential for cases with persistent hypertension.

Discussion

Classical clinical findings in RPLE are seizure, visual disturbances, headache, vomiting and confusion[1,7,13]. Other focal neurological deficits are

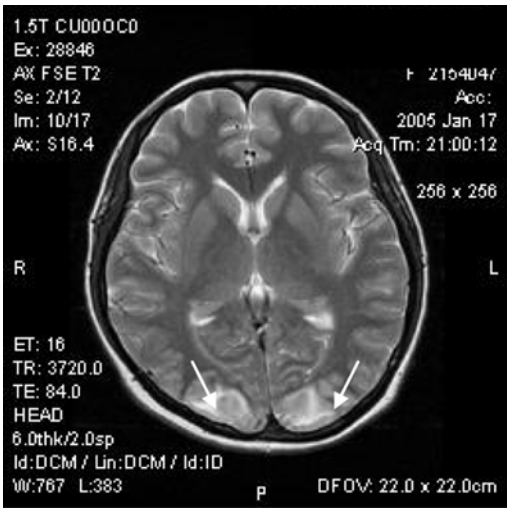

Fig. 1 Classical RPLE: T2-weighted MRI of patient 8, the images showed symmetric hypersignal intensity at bilateral occipital areas (arrow)

Table 1. Clinical and neuroimaging finding of 9 patients with reversible posterior leukoencephalopathy

Patient No.	Age (yr)/ Sex	Underlying diseases and/or precipitating causes	Clinical features	Hypertension	Neuroimaging findings MRI and CT scaning
1	39/F	Systemic lupus erythematosus, Hypertensive encephalopathy, Acute nephritis	Seizure, Cortical blindness	Yes (160/110)	Bilateral occipital, frontal, temporal, parietal lobes
2	26/F	Systemic lupus erythematosus, Hypertensive encephalopathy, Acute nephritis	Seizure, Cortical blindness	Yes (208/122)	Bilateral occipital, parietal, frontal, temporal lobes, Internal capsules
3	30/F	Systemic lupus erythematosus, Hypertensive encephalopathy, Acute nephritis	Seizure	Yes (166/112)	Bilateral occipital, parietal, frontal lobes, Cerebellum, Pons, Midbrain, Splenium of corpuscallosum, Internal capsules
4	33/F	Systemic lupus erythematosus, Hypertensive encephalopathy, Acute nephritis	Seizure	Yes (170/100)	Bilateral frontal lobes
5	34/F	Hypertensive encephalopathy, IgA nephropathy	Headache, Cortical blindness	Yes (230/130)	Bilateral occipital lobes
6	18/F	Hypertensive encephalopathy, Takayasu's arteritis	Hypertension, Headache	Yes (200/130)	Bilateral occipital, parietal, frontal lobes
7	17/M	Acute myeloid leukemia, Bone marrow transplantation, Cyclosporine administration	Drowsiness, Seizure	No	Bilateral occipital, parietal, frontal lobes, Deep gray nuclei, Cerebellum, Pons
8	19/F	Puerperal eclampsia	Seizure, Headache	No	Bilateral occipital lobes
9	19/F	Puerperal eclampsia	Seizure, Cortical blindness	Yes (150/100)	Bilateral occipital lobes*

* CT scaning only
M = male, F = female, yr = year

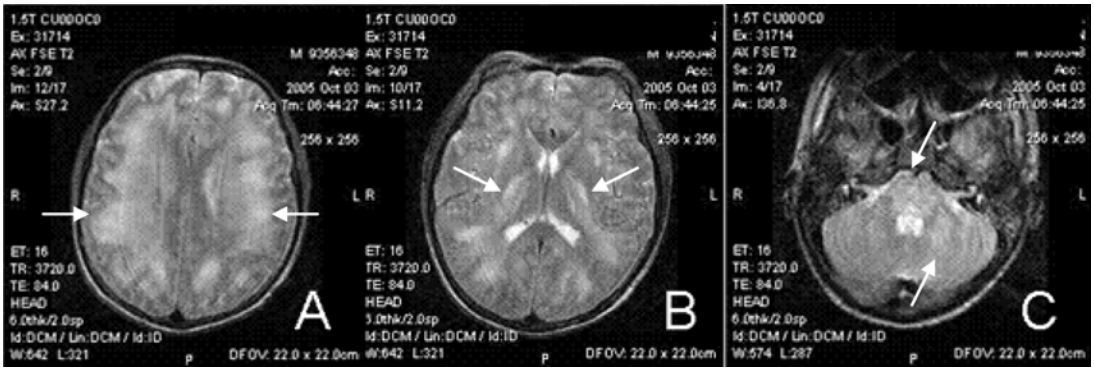

Fig. 2 Severe extensive RPLE: T2-weighted MRI of Patient 7, the images showed hypersignal intensity (A) widespread cortical-subcortical area, (B) internal capsules, (C) cerebellum and pons (arrows)

uncommon[1,4,13]. Seizures are usually generalized tonic-clonic and multiple[1] while status epilepticus occurs in severe cases. Visual loss manifested in the form of cortical blindness, visual field defect and visual neglect[14,15]. Moderate to severe diffuse headache with or without vomiting related to acute hypertensive episode or postictal state[1]. Patients are often confused[1] or drowsy but stupor and coma are uncommon[1]. RPLE may be associated with several systemic diseases especially autoimmune disease[5], renal impairment[10], immunosuppressive therapy[1,7] and eclampsia[1,3,4,13]. In the present series, the clinical pictures are similar to classical RPLE and the associated conditions are well-known documented risk factors for RPLE.

MRI is the investigation of choice for RPLE while CT scan is less sensitive[16]. White matter abnormalities are detected as increased signal intensity in T2 weighted and FLAIR images[16] which are usually bilateral and symmetrical. RPLE has been initially described as a condition predominantly affecting posterior cerebral white matter, however other cortical and subcortical grey matter such as frontal, temporal, parietal lobe, thalamus, basal ganglia as well as brainstem and cerebellum may be involved[1,7,11,17,18]. Sparing of the calcaline cortex and paramedian occipital lobe structures which are a prominent character in this syndrome[1], differentiates RPLE from bilateral posterior cerebral artery infarction[1]. Moreover, these imaging patterns in combination with the absence of hemorrhagic infarction, cord sign caused by hyperdense thrombosed vein can distinguish RPLE from superior sagittal venous sinus thrombosis. The neuroimaging findings in the present series followed these documented patterns.

Cerebral autoregulation keeps cerebral blood flow constant thereby protecting the brain from an abrupt increase in blood pressure[19]. Sudden increase in blood pressure causes cerebral vasoconstriction which limits cerebral hyperperfusion via cerebral autoregulation[2]. However, autoregulation may fail and results in vasodilatation, endothelial dysfunction with capillary leakage and disruption of the blood brain barrier[2]. The autoregulation failure may cause vasogenic edema of the white matter and hypertensive encephalopathy[1,11,13]. MRI changes in RPLE are prominent in posterior cerebral areas which are supplied by posterior cerebral circulation. The posterior region of the brain is more susceptible to RPLE due to less sympathetic innervation and less potent autoregulation of the vertebrobasilar and posterior cerebral arteries[2,4]. Anterior cerebral vasculature is richly innervated by sympathetic nerves from the superior cervical ganglion[4,17,19] and has more ability in protecting itself from an acute increase in blood pressure. However, in severe cases, diffuse autoregulation failure may occur and the involvements of the brain are more diffuse.

RPLE is common in SLE patients with mild elevation of blood pressure[5]. Postmortem investigations of the brain in SLE patients revealed small vessel angiopathy[20-24]. This angiopathy in combination with mild elevated blood pressure might predispose to the damage of blood brain barrier. The exact etiology of RPLE associated with immunosuppressants and cytotoxic drugs are still unknown and may be multifactorial[1]. These drugs might damage vascular endothelium and result in vasospasm which may cause reduction of tissue perfusion and activation of coagulation cascades[1]. In cases with cyclosporine neurotoxicity, blood vessel inflammation as well as minor ischemic lesions were documented in the watershed regions of the brain[26,27] and these changes may cause RPLE[25-28]. In eclampsia, several findings suggested that there are maternal endothelial dysfunction caused by secretion of trophoblastic cytotoxic factors originated from a poor perfusion of fetal-placental unit[29]. Maternal endothelial dysfunction in combination with fluid accumulation during the puerperium will promote cerebral edema and RPLE[29]. Renal impairment is a common cofactor in diseases causing RPLE and chronic uremia or fluid overload may be important predisposing factors for RPLE[13]. Although neuroimaging reveals extensive cerebral lesions, prognosis of RPLE is usually good. Most of the patients will have a complete neurological recovery within 2 weeks[1] and recurrent RPLE has rarely been reported[5].

In conclusion, RPLE typically presents with headache, visual loss, and seizures. It often occurs in the setting of accelerated hypertension especially in patients with systemic autoimmune diseases, immunosuppressive therapy, renal impairment or eclampsia. Classical clinical syndrome together with associated systemic illness and characteristic MRI findings are critical clues to definite diagnosis. MRI findings must be differentiated from bilateral posterior cerebral arterial infarction or superior sagittal sinus thrombosis. Early management might prevent progression to irreversible brain damage. In developing countries where financial problem is a constraint, repeated neuroimaging may not be necessary after clinical reversal.

References

1. Hinchey J, Chaves C, Appignani B, Breen J, Pao L,

Wang A, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996; 334: 494-500.
2. Vaughan CJ, Delanty N. Hypertensive emergencies. Lancet 2000; 356: 411-7.
3. Arora A, Chowdhury D, Daga MK, Arora N, Gaiha M. Reversible posterior leukoencephalopathy syndrome: a report of 2 cases. Neurol India 2001; 49: 311-3.
4. Sheth RD, Riggs JE, Bodenstenier JB, Gutierrez AR, Ketonen LM, Ortiz OA. Parietal occipital edema in hypertensive encephalopathy: a pathogenic mechanism. Eur Neurol 1996; 36: 25-8.
5. Thaipisuttikul I, Phanthumchinda K. Recurrent reversible posterior leukoencephalopathy in a patient with systemic lupus erythematosus. J Neurol 2005; 252: 230-1.
6. Bakshi R, Shaikh ZA, Bates VE, Kinkel PR. Thrombotic thrombocytopenic purpura: brain CT and MRI findings in 12 patients. Neurology 1999; 52: 1285-8.
7. Kwon S, Koo J, Lee S. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. Pediatr Neurol 2001; 24: 361-4.
8. Taylor MB, Jackson A, Weller JM. Dynamic susceptibility contrast enhanced MRI in reversible posterior leukoencephalopathy syndrome associated with haemolytic uraemic syndrome. Br J Radiol 2000; 73: 438-42.
9. Lanzino G, Cloft H, Hemstreet MK, West K, Alston S, Ishitani M. Reversible posterior leukoencephalopathy following organ transplantation. Description of two cases. Clin Neurol Neurosurg 1997; 99: 222-6.
10. Pavlakis SG, Frank Y, Kalina P, Chandra M, Lu D. Occipital-parietal encephalopathy: a new name for an old syndrome. Pediatr Neurol 1997; 16: 145-8.
11. Casey SO, Sampaio RC, Michel E, Truwit CL. Posterior reversible encephalopathy syndrome: utility of fluid-attenuated inversion recovery MR imaging in the detection of cortical and subcortical lesions. AJNR Am J Neuroradiol 2000; 21: 1199-206.
12. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. AJNR Am J Neuroradiol 2002; 23: 1038-48.
13. Garg RK. Posterior leukoencephalopathy syndrome. Postgrad Med J 2001; 77: 24-8.
14. Bakshi R, Bates VE, Mechtler LL, Kinkel PR, Kinkel WR. Occipital lobe seizures as the major clinical manifestation of reversible posterior leukoencephalopathy syndrome: magnetic resonance imaging findings. Epilepsia 1998; 39: 295-9.
15. Tallaksen CM, Kerty E, Bakke S. Visual hallucinations in a case of reversible hypertension-induced brain oedema. Eur J Neurol 1998; 5: 615-8.
16. Mukherjee P, McKinstry RC. Reversible posterior leukoencephalopathy syndrome: evaluation with diffusion-tensor MR imaging. Radiology 2001; 219: 756-65.
17. Sanders TG, Clayman DA, Sanchez-Ramos L, Vines FS, Russo L. Brain in eclampsia: MR imaging with clinical correlation. Radiology 1991; 180: 475-8.
18. De Klippel N, Sennesael J, Lamote J, Ebinger G, de Keyser J. Cyclosporin leukoencephalopathy induced by intravenous lipid solution. Lancet 1992; 339: 1114.
19. Sheth RD, Riggs JE, Bodenstenier JB, Gutierrez AR, Ketonen LM, Ortiz OA. Parietal occipital edema in hypertensive encephalopathy: a pathogenic mechanism. Eur Neurol 1996; 36: 25-8.
20. Johnson RT, Richardson EP. The neurological manifestations of systemic lupus erythematosus. Medicine (Baltimore) 1968; 47: 337-69.
21. Devinsky O, Petito CK, Alonso DR. Clinical and neuropathological findings in systemic lupus erythematosus: the role of vasculitis, heart emboli, and thrombotic thrombocytopenic purpura. Ann Neurol 1988; 23: 380-4.
22. Hanly JG, Walsh NM, Sangalang V. Brain pathology in systemic lupus erythematosus. J Rheumatol 1992; 19: 732-41.
23. Provenzale J, Bouldin TW. Lupus-related myelopathy: report of three cases and review of the literature. J Neurol Neurosurg Psychiatry 1992; 55: 830-5.
24. Hughson MD, McCarty GA, Sholer CM, Brumback RA. Thrombotic cerebral arteriopathy in patients with the antiphospholipid syndrome. Mod Pathol 1993; 6: 644-53.
25. Sloane JP, Lwin KY, Gore ME, Powles RL, Smith JF. Disturbance of blood-brain barrier after bone-marrow transplantation. Lancet 1985; 2: 280-1.
26. Velu T, Debusscher L, Stryckmans PA. Cyclosporin-associated fatal convulsions. Lancet 1985; 1: 219.
27. Wilson SE, de Groen PC, Aksamit AJ, Wiesner RH, Garrity JA, Krom RA. Cyclosporin A-induced reversible cortical blindness. J Clin Neuroophthalmol 1988; 8: 215-20.

28. Reece DE, Frei-Lahr DA, Shepherd JD, DoroviniZis K, Gascoyne RD, Graeb DA, et al. Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporin. Bone Marrow Transplant 1991; 8: 393-401.
29. Roberts JM, Redman CW. Pre-eclampsia: more than pregnancy-induced hypertension. Lancet 1993; 341: 1447-51.

กลุ่มอาการ โพสทีเรีย ลิวโคเอนเซฟฟาโลพาธี ที่กลับเป็นปกติได้ การศึกษาย้อนหลังที่โรงพยาบาลจุฬาลงกรณ์

ชัยวิวัฒน์ ตุงคะเสรีรักษ์, กัมมันต์ พันธุมจินดา

ภูมิหลัง: *โพสทีเรีย ลิวโคเอนเซฟฟาโลพาธี ที่กลับเป็นปกติได้ (อาร์พีแอลอี) หรือ โพสทีเรีย ซีรีบรัล อีดีมา ที่กลับเป็นปกติได้ เป็นกลุ่มอาการที่มีความผิดปกติทางระบบประสาทที่เป็นแบบชั่วคราวและให้อาการผิดปกติแบบเฉพาะที่ หรือแบบกระจัดกระจายร่วมกับการเปลี่ยนแปลงของภาพถ่ายของระบบประสาทที่กลับเป็นปกติได้ อาร์พีแอลอี มักเกิดร่วมกับโรคความดันโลหิตสูงและโรคทางกายอื่น ๆ ลักษณะภาพคลื่นแม่เหล็กไฟฟ้า (เอ็มอาร์ไอ) ที่เป็นแบบฉบับของอาร์พีแอลอี คือความผิดปกติของไวท์แมตเตอร์โดยเฉพาะบริเวณส่วนหลังของสมอง เนื่องจากมีการใช้เทคโนโลยีภาพคลื่นแม่เหล็กไฟฟ้ามากขึ้นกลุ่มอาการนี้จึงมีการรายงานเพิ่มขึ้น*

วัสดุและวิธีการ: *ได้ทำการรวบรวมบันทึกข้อมูลทางคลินิกจากฐานข้อมูลที่โรงพยาบาลจุฬาลงกรณ์ตั้งแต่ปี พ.ศ. 2546 ถึง พ.ศ. 2548 รหัสคำคือ "ลิวโคเอนเซฟฟาโลพาธี" และ "ไฮเปอร์เท็นซีพ เอ็นเซฟฟาโลพาธี" เกณฑ์สำหรับการวินิจฉัยอาร์พีแอลอีโดยภาพของระบบประสาทคือความผิดปกติของไวท์แมตเตอร์ส่วนคอติเคิล-สับคอติเคิลโดยเฉพาะบริเวณกลีบออ๊กซิปิตัลทั้งสองข้างและเป็นอย่างสมมาตร ข้อมูลได้รับการทบทวน ผู้ป่วยที่เป็นอาร์พีแอลอีถูกนำมาศึกษาและวิเคราะห์*

ผลการศึกษา: *ได้วิเคราะห์ผู้ป่วยจำนวน 9 ราย (ผู้หญิง:ผู้ชาย, 8:1) อายุระหว่าง 17 ถึง 39 ปี (อายุเฉลี่ย 26 ปี) ผู้ป่วย 5 รายมีความดันโลหิตสูงแบบเฉียบพลันร่วมกับภาวะไตบกพร่อง, ผู้ป่วย 1 รายที่มีความดันโลหิตสูงแบบเฉียบพลันโดยไม่มีภาวะไตบกพร่อง, ผู้ป่วย 2 รายเป็นภาวะครรภ์เป็นพิษ, และอีก1รายสัมพันธ์กับการรักษาด้วยยาไซโคลสปอริน อาการที่พบบ่อยที่สุดคือ อาการชัก อาการตามัว เอ็มอาร์ไอพบการบวมของไวท์แมตเตอร์บริเวณสมองส่วนอ็อกซิปิตัล 2 ข้างในผู้ป่วย 7/8 รายในขณะที่ 3/9 รายความผิดปกติถูกตรวจพบโดยซีที ความผิดปกติในตำแหน่งอื่น ๆ จากเอ็มอาร์ไอ พบที่สมองส่วนฟรอนทัล, พาเรียทัล, เกรย์แมตเตอร์ส่วนลึก, ก้านสมองและสมองน้อย ผู้ป่วยได้รับการรักษาโดยยาลดความดันโลหิต, ยากันชัก, และหยุดยากดภูมิคุ้มกัน ความผิดปกติทางระบบประสาทในผู้ป่วยจำนวน 8 รายหายเป็นปกติภายใน 2 สัปดาห์ ผู้ป่วยรายที่ได้รับยาไซโคลสปอรินยังมีกล้ามเนื้อแขนขาอ่อนแรง และแข็งเกร็งหลงเหลืออยู่*

สรุป: *อาร์พีแอลอีเกิดขึ้นในผู้ป่วยที่มีความดันโลหิตสูง, โรคภูมิคุ้มกันต่อเนื้อเยื่อตนเอง, ภาวะไตบกพร่อง, การได้รับยากดภูมิคุ้มกัน หรือ ภาวะครรภ์เป็นพิษ การตรวจภาพถ่ายของระบบประสาทจะพบลักษณะที่เป็นแบบฉบับ คือการบวมของไวท์แมตเตอร์ในสมองกลีบอ็อกซิปิตัล และสมองกลีบอื่น ๆ ตลอดจนเกรย์แมตเตอร์ส่วนลึก ผลการรักษาที่ดีเกิดจาก การรักษาแบบประคับประคองอย่างทันท่วงทีด้วยยาลดความดันโลหิต, ยากันชัก, หรือ การหยุดยากดภูมิคุ้มกัน และการตรวจภาพถ่ายของระบบประสาทซ้ำอาจไม่มีความจำเป็น*