

ETIOLOGY OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES)

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ABSTRACT

Objective: To study the causes and risk factors for the development of Posterior Reversible Encephalopathy Syndrome (PRES).

Design: Prospective hospital based study over a period of five years from July 1999 to June 2004.

Patients and methods: Patients with clinical and neuroimaging features consistent with PRES were included in the study. All patients had detail clinical evaluation on presentation, and recovery from PRES. All had CT and/or MRI brain scan and other hematological and serological investigations to determine the most likely cause of the syndrome. Most patients also underwent follow up neuroimaging to demonstrate resolution of brain lesions.

Results: Thirteen patients fulfilled the clinical and radiological features consistent with PRES. Seizures and altered conscious level were most common clinical manifestations. Main radiological feature on CT and /or MRI brain was extensive subcortical edema mainly confined to the posterior parieto-occipital lobes. Hypertensive encephalopathy, immunosuppressive treatment, renal failure and eclampsia were main causes of PRES in our study. We also found that this syndrome was more common in females than males. Clinically all patients recovered with control of blood pressure and discontinuation or reduction in dose of the offending drug within 2-7 days. There was almost complete resolution of radiological abnormalities within 2-4 weeks in patients who underwent follow up imaging.

Conclusion: Hypertensive encephalopathy, immunosuppressive treatment, renal failure and eclampsia are most common causes of posterior reversible encephalopathy syndrome with a greater predilection for females than males. Multiple factors may be contributory in some patients who develop PRES.

KEY WORDS: Reversible encephalopathy, hypertension, eclampsia, seizures.

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INTRODUCTION

The term Reversible Posterior Leukoencephalopathy Syndrome (RPLS) refers to clinicoradiologic entity characterized by headache, confusion, visual disturbances, seizures and neuroimaging evidence of characteristic subcortical edema without infarction in a relative symmetric pattern, which predominantly involves parietal and occipital lobes¹. These often striking imaging findings resolve on follow up studies after appropriate treatment². With recent advancements in magnetic resonance imaging and availability of FLAIR sequences, diffusion weighted imaging, and Apparent Diffusion Coefficient (ADC)

mapping, it has been found that the lesions in RPLS occur in both gray and white matter. Therefore a new name, Posterior Reversible Encephalopathy Syndrome (PRES) has been coined recently³. Hypertensive encephalopathy, immunosuppressive treatment, eclampsia and renal failure were main causes of RPLS in 15 cases described by Hinchey, et al¹. Since its initial description, this syndrome has been subsequently described in an increasing number of other medical conditions⁴. Cyclosporine and tacrolimus (FK-506) are most common immunosuppressive drugs associated with development of PRES^{5,6,7}.

The pathogenesis of the syndrome is poorly understood and two main mechanisms have been suggested⁸. One hypothesis is that cerebral vasospasm results in cerebral ischemia and subsequent development of T2 hyperintensity^{9,10,11}. Alternatively it has been suggested that there is a temporary failure of autoregulatory capabilities of the cerebral vessels, leading to hyperperfusion, breakdown of blood-brain barrier, and consequent vasogenic edema^{12,13,14}. The preferential involvement of the parietal and occipital lobes is thought to be related to the relatively poor sympathetic innervation of the posterior circulation^{1,15}. Drugs have been postulated to contribute to this physiological effect by cytotoxic effects on the vascular endothelium or by inducing or exacerbating hypertension^{1,13}. We undertook this study to find out the causes and risk factors for the development of PRES in our patients.

PATIENTS AND METHODS

This was a prospective study carried out in King Abdul Aziz Hospital and Oncology Center, Jeddah, Saudi Arabia. This hospital is a teaching hospital and secondary referral center for medical, surgical, obstetric and gynecological patients including major allied medical and surgical subspecialties. Hospital is also involved in active renal transplant programme and management of patients with acute and chronic renal failure due to various causes. It is one of the referral centers for management

of oncology patients in western region of Saudi Arabia. As a result, we were involved in the management of variety of cases who developed neurological manifestations. Our study was carried out over a period of 5 years from July 1999 till June 2004. Patients with predominantly white matter edema on CT or MRI brain and subsequent evidence of clinical recovery and / or radiological recovery were included in the study. However, it may be worth mentioning that none of the patients, where PRES was suspected at the time of admission to the hospital, died. Abnormalities on imaging were defined as areas of low attenuation of white matter on CT scan, as T1-weighted hypointense and T2-weighted hyperintense areas on MRI scans that partially or completely resolved on follow up scanning. All patients had detail clinical evaluation including history and examination. Routine hematological investigations included an ESR, CBC, BUN, creatinine, sodium, potassium, calcium, and magnesium estimations. Antinuclear antibodies, rheumatoid factor, and HIV serology were checked for all patients. A lumbar puncture was performed only when suspicion of CNS infection was very high especially in patients on immunosuppressive drugs. All patients had CT scan of brain and / or MRI brain. Follow up imaging was performed in majority of the patients despite clinical recovery to demonstrate radiological reversibility of the lesions. Serum drug levels for cyclosporine and tacrolimus (FK-506) were measured on admission and on recovery from PRES. Serum drug levels were also compared with the levels previously recorded in their files before the development of PRES.

RESULTS

We collected 13 patients who had clinical and radiological features consistent with PRES. The 13 patients (9 female and 4 male) ranged from 12 to 45 years (average, 25). All underwent CT scan of brain on admission and 10 patients had subsequent MRI brain within next 48 hours of their admission. A follow up CT or MRI brain was done in 11 patients after 2-4

weeks. Eight patients presented with generalized tonic clonic seizures and three with acute confusional state without seizures. One patient developed sudden onset of coma with quadriplegia and another presented with sub-acute onset of vertigo and truncal ataxia. Headache and vomiting were present in only one patient. Characteristic white matter abnormalities on imaging were present in the parietal and occipital lobes in 12 patients. One patient had brainstem and cerebellar edema with minimal supratentorial white matter edema and another patient had isolated changes confined to cerebellum. Main causes of PRES in our study were hypertension in 9(69%), immunosuppressive treatment 7(54%), renal failure 4(31%), and eclampsia 2(15.5%) cases. There was complete clinical and radiological recovery with management of underlying cause including control of BP and seizures, discontinuation or reduction of immunosuppressive drugs and regular dialysis if indicated.

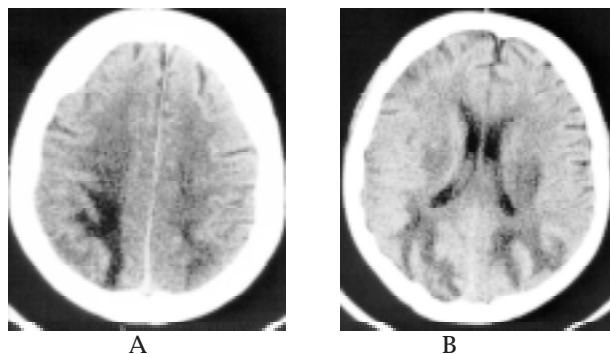


Fig 1: A&B. CT scan brain of one patient shows hypodensity in the parieto-occipital white matter.

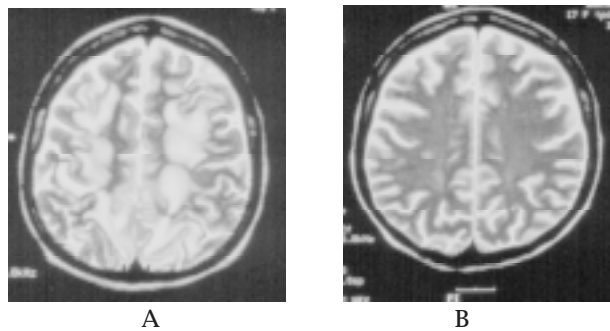


Fig 2: A. MRI brain T2WI shows widespread hyperintense signal abnormalities of white matter. B. Follow up scan shows almost complete resolution of the abnormalities.

HYPERTENSION

Nine of 13 patients in our study were found to have high blood pressure (BP). Five patients had grade 3 hypertension defined as systolic blood pressure (SBP) ≥ 180 or diastolic blood pressure (DBP) ≥ 110 . Two patient had grade 2 (SBP 160-179 or DBP100-109) and two patients had grade 1 hypertension (SBP 140-159 or DBP 90-99) at the time of presentation. Blood pressure was normal in four cases.

Immunosuppressive treatment

Seven patients who developed PRES were receiving immunosuppressive treatment. Three patients were receiving tacrolimus (FK-506), two cyclosporine A, one methotrexate and one high dose pulse therapy with methylprednisolone. Patients who were receiving tacrolimus (3 cases) and cyclosporine (2 cases) were post-renal transplant. Of these five cases, three had evidence of chronic rejection with elevation of BUN and serum creatinine and two had successfully functioning grafted kidney. Serum levels of immunosuppressive drugs were therapeutic in four and slightly above therapeutic value in one patient.

Renal failure

In our series, four patients had renal failure including three post renal transplant cases with chronic rejection. All patients with renal failure were hypertensive and receiving immunosuppressive treatment. The average serum creatinine was $569\mu\text{mol/l}$ with range from $345\text{-}1075\mu\text{mol/l}$. Serum sodium, potassium, magnesium and calcium levels were normal in these patients.

Eclampsia

Two patients with eclampsia showed features of PRES in our study. There was only mild to moderate hypertension in these cases and both recovered rapidly after control of their BP and emergency cesarean section.

DISCUSSION

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or Posterior Reversible Encephalopathy Syndrome (PRES) is a newly recognized clinicoradiological entity. It is characterized predominantly by subcortical edema without infarction mainly involving the parietal and occipital lobes bilaterally in a relative symmetric pattern¹. Most patients show complete clinical and radiological recovery on follow up imaging in 2-4 weeks². Hypertensive encephalopathy^{1,14,16,17}, renal failure¹, immunosuppressive therapy^{1,5-7} and eclampsia^{18,19} had been reported to be the major causes of this syndrome. Our study yielded similar results with hypertension, immunosuppressive therapy, renal failure and eclampsia being the main causes for the development of PRES. Few patients had more than one contributory factors especially patients with renal failure who were hypertensive and receiving immunosuppressive therapy as well. This implies that this disorder may be multifactorial in its pathogenesis.

The main cause of PRES is acute elevation of blood pressure, above the upper limit of cerebral blood flow autoregulation¹. Rapidly developing, fluctuating or intermittent hypertension carries a particular risk for hypertensive encephalopathy²⁰. The degree of hypertension required to induce encephalopathy depends on the baseline pressure^{21,22}. Severe hypertension is thus not mandatory for PRES to develop especially in patients who also have evidence of renal failure, vasculitis, immunosuppressive treatment or present with eclampsia. We found that only five of our patients had severe hypertension and BP was normal in four patients who developed PRES. There was poor correlation with degree of hypertension and development of PRES. One can argue that peak rise in BP could have been missed in some of these cases. However, we closely monitored all these patients in ICU and CCU setting until their complete clinical recovery and no intermittent rise in BP was noted in normotensive patients or those with mild hypertension. Most of our

normotensive patients were on immunosuppressive treatment. Therefore, we conclude that hypertension is commonly associated with PRES but is not universally present especially in the setting of immunosuppression. Similar observation has also been made in the past¹³.

Immunosuppressive treatment was second common cause of PRES in our study. Tacrolimus (FK-506) and cyclosporine A were two most common drugs in patients who developed PRES. One patient received methotrexate for treatment of osteosarcoma and another patient was on pulse therapy with high dose methyl prednisolone for autoimmune hemolytic anemia. Other immunosuppressive drug reported to cause PRES are vincristine²³, cisplatin¹², cytarabine²⁴, interferon- α ¹, and combination chemotherapy^{25,26}. Four of our patients had evidence of renal failure. There was no correlation between BUN / serum creatinine level and serum drug levels of immunosuppressive drugs in the development of PRES. Similar observation has been made in the past²⁷.

Eclampsia was the cause of PRES in two patients in our study. Both patients had mild to moderate hypertension. There is no significant correlation between symptoms of eclampsia and blood pressure levels¹⁹. Several findings suggest that maternal endothelial dysfunction, thought to be due to the secretion of trophoblastic cytotoxic factors originating from a poorly perfused fetal placental unit, play a role in eclampsia^{19,28-30}.

Other reported causes of PRES includes vasculitis especially SLE³¹, polyarteritis nodosa³², endocrine disorders including pheochromocytoma³³ and primary aldosteronism³⁴, porphyria³⁵, thermal injury³⁶, scorpion envenomation³⁷, thrombotic thrombocytopenic purpura³⁸, hemolytic uremic syndrome³⁹, hypercalcemia⁴⁰, and blood transfusion^{41,42}. PRES has also been reported to be caused by few other drugs like immunotherapy with interleukin⁴³, antiretroviral therapy in HIV infected patients⁴⁴, erythropoietin⁴⁵, granulocyte stimulating factor⁴⁶, intravenous immunoglobulins⁴⁷, and over-the-counter stimulants⁴⁸ like phenylpropanolamine, ephedrine and

pseudoephedrine.

An additional role of seizures has also been suggested as the cause of the PRES rather than manifestation of PRES^{49,50}. However, because seizures were not present in all patients in our study, they cannot be the only cause of the syndrome.

We found more females than males developing this syndrome. Similar observation has been made in the past^{1,13}. However, larger studies are needed to confirm this predilection.

All patients of PRES in this study improved with the management of underlying causes such as control of blood pressure and seizures, discontinuation or reduction in dose of immunosuppressive drugs in post renal transplant cases, and regular hemodialysis in uremic patients.

CONCLUSION

Posterior Reversible Encephalopathy Syndrome is a recently described clinico-radiological entity with well known causes like hypertensive encephalopathy, immunosuppressive treatment, renal failure and eclampsia. Its pathogenesis remains poorly understood. Clinical signs are non specific but neuroimaging are often characteristic and may be the first clue to the diagnosis. Diagnosing PRES has important implication because of its potential reversibility if managed appropriately.

REFERENCES

- Hinchey J, Chaves C, Appignani B, Breeb J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996;334:494-500.
- Yaffe K, Ferriero D, Barkovitch AJ, Rowley H. Reversible MRI abnormalities following seizures. *Neurology* 1995;45:104-8.
- 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. *Am J Neuroradiol* 2000;21:1199-1206.
- Lamy C, Oppenheim C, Meder JF, Mas JL. Neuroimaging in posterior reversible encephalopathy syndrome. *J Neuroimaging* 2004; 14: 89-96.
- Schwartz RB, Bravo SM, Klufas RA, et al. Cyclosporine neurotoxicity and its relationship to hypertensive encephalopathy: CT and MR findings in 16 cases. *Am J Roentgenol* 1995;165:627-31.
- Truwit CL, Denaro CP, Lake JR, DeMarco T. MR imaging of reversible cyclosporin A-induced neurotoxicity. *Am J Neuroradiol* 1991;12:651-9.
- Shutter LA, Green JP, Newman NJ, Hooks MA, Gordon RD. Cortical blindness and white matter lesions in a patient receiving FK506 after liver transplantation. *Neurology* 1993;43:2417-8.
- Port JD, Beauchamp NJ. Reversible intracerebral pathologic entities mediated by vascular autoregulatory dysfunction. *Radiographics* 1998;18: 353-67.
- Horn EH, Filshie M, Kerslake RW, Jaspan T, Worthington BS, Rubin PC. Widespread cerebral ischemia treated with nimodipine in a patient with eclampsia. *BMJ* 1990;301:794.
- Ito T, Sakai T, Inagawa S, Utsu M, Bun T. MR angiography of cerebral vasospasm in preeclampsia. *Am J Neuroradiol* 1995;16:1344-6.
- Trommer BL, Homer D, Mikhael MA. Cerebral vasospasm and eclampsia. *Stroke* 1988;19:326-9.
- Ito Y, Arahata Y, Goto Y, et al. Cisplatin neurotoxicity presenting as reversible posterior leukoencephalopathy syndrome. *Am J Neuroradiol* 1998;19:415-7.
- Ay H, Buonanno F, Schaefer P, et al. Posterior leukoencephalopathy without severe hypertension. Utility of diffusion-weighted MRI. *Neurology* 1998;51:1369-76.
- Hausser RA, Lacey DM, Knight MR. Hypertensive encephalopathy: magnetic resonance imaging demonstration of reversible cortical and white matter lesions. *Arch Neurol* 1988;45:1078-83.
- Dillon WP, Rowley H. The reversible posterior cerebral edema syndrome. *Am J Neuroradiol* 1998;19:591.
- Schwartz RB, Jones KM, Kalina P, et al. Hypertensive encephalopathy: findings on CT, MR imaging and SPECT imaging in 14 cases. *Am J Roentgenol* 1992;159:379-83.
- Sheth TN, Ichise M, Kucharczyk W. Brain perfusion imaging in asymptomatic patients receiving cyclosporin. *Am J Neuroradiol* 1999;20:853-6.
- Digre KB, Varner MW, Osborn AG, Crawford S. Cranial magnetic resonance imaging in severe preeclampsia vs eclampsia. *Arch Neurol* 1993;50:399-406.
- Schwartz RB, Feske SK, Polak JF, et al. Preeclampsia-eclampsia: clinical and neuroradiographic correlates and insights into the pathogenesis of hypertensive encephalopathy. *Radiology* 2000;217:371-6.
- Lamy C, Mas JL. Hypertensive encephalopathy. In: Mohr JP, Choi D, Grota JC, Weir B, Wolf PA. (Eds). *Stroke: Pathophysiology, Diagnosis and Management*. 4th ed. Edinburgh: Churchill Livingstone. pp810-35, 2004.
- Strandgaard S, Paulson OB. Cerebral autoregulation. *Stroke* 1984;15:413-5.

22. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990;2:161-92.
23. Hurwitz RL, Mahoney DH, Armstrong DL, Browder TM. Reversible encephalopathy and seizures as a result of conventional vincristine administration. *Med Pediatr Oncol* 1988;16:216-9.
24. Vaughn DJ, Jarvik JG, Hackney D, Peters S, Stadtmauer EA. High-dose cytarabine neurotoxicity: MR findings during the acute phase. *Am J Neuroradiol* 1993;14:1014-6.
25. Cooney M, Bradley W, Symko S, Patel S, Groncy P. Hypertensive encephalopathy: complication in children treated for myeloproliferative disorders-report of three cases. *Radiology* 2000;214:711-6.
26. Shin RK, Stern JW, Jans AJ, Hunter JV, Liu GT. Reversible posterior leukoencephalopathy during the treatment of acute lymphoblastic leukemia. *Neurology* 2001;56:388-91.
27. Covarrubias DJ, Luetmer PH, Campear NG. Posterior reversible encephalopathy syndrome: Prognostic utility of quantitative diffusion-weighted MR imaging. *Am J Neuroradiol* 2002;23:1038-48.
28. Roberts JM, Redman CWG. Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet* 1993;34:1447-50.
29. Savvidou MD, Hingorani AD, Tsikas D, Frolich JC, Vallance P, Nicolaidis KH. Endothelial dysfunction and raised plasma concentrations of asymmetric dimethylarginine in pregnant women who subsequently develop preeclampsia. *Lancet* 2003;361:1511-7.
30. Mas JL, Lamy C. Severe preeclampsia/eclampsia: hypertensive encephalopathy of pregnancy? *Cerebrovasc Dis* 1998;8:53-8.
31. Primavera A, Audenino D, Mavilio N, Cocito L. Reversible posterior leukoencephalopathy syndrome in systemic lupus and vasculitis. *Ann Rheum Dis* 2001;60:534-7.
32. Vora J, Cooper J, Thomas JP. Polyarteritis nodosa presenting with hypertensive encephalopathy. *Br J Clin Pract* 1992;46:144-5.
33. Seze JD, Mastain B, Stojkovic T, et al. Unusual MR findings of the brainstem in arterial hypertension. *Am J Neuroradiol* 2000;21:391-4.
34. Kaplan NM. Primary aldosteronism with malignant hypertension. *N Engl J Med* 1963;269:1282-6.
35. Kupferschmidt H, Bont A, Schnorf H, et al. Transient cortical blindness and bioccipital brain lesions in two patients with acute intermittent porphyria. *Ann Intern Med* 1995;123:598-600.
36. Popp MB, Friedberg DL, MacMillan BG. Clinical characteristics of hypertension in burned children. *Ann Surg* 1980;191:473-8.
37. Sofer S, Gueron M. Vasodilatation and hypertensive encephalopathy following scorpion envenomation in children. *Chest* 1990;97:118-120.
38. Bakshi R, Shaikh Z, Bates V, Kinkel P. Thrombotic thrombocytopenic purpura: brain CT and MRI findings in 12 patients. *Neurology* 1999;52:1285-8.
39. 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.
40. Kaplan P. Reversible hypercalcemic cerebral vasoconstriction with seizures and blindness: paradigm for eclampsia? *Clin Electroneurophysiol* 1998;29:120-3.
41. Ito Y, Niwa H, Iida T, et al. Post-transfusion reversible posterior leukoencephalopathy syndrome with cerebral vasoconstriction. *Neurology* 1997;49:1174-5.
42. Boughammoura A, Touzé E, Oppenheim C, Trystram D, Mas JL. Reversible angiopathy and encephalopathy after blood transfusion. *J Neurol* 2003;250:116-8.
43. Karp BI, Yang JC, Khorsand M, Wood R, Merigan TC. Multiple cerebral lesions complicating therapy with interleukin-2. *Neurology* 1996;47:417-24.
44. Giner V, Fernandez C, Esteban MJ, Galindo MJ, Forner MJ, Redon JG. Reversible posterior leukoencephalopathy secondary to indinavir-induced hypertensive crisis: a case report. *Am J Hypertens* 2002;15:465-7.
45. Delanty N, Vaughan C, Frucht S, Stubgen P. Erythropoietin associated hypertensive posterior leukoencephalopathy. *Neurology* 1997;49:686-9.
46. Leniger T, Kastrup O, Diener HC. Reversible posterior leukoencephalopathy syndrome induced by granulocyte stimulating factor filgrastim. *J Neurol Neurosurg Psychiatry* 2000;69:280-1.
47. Mathy I, Gille M, Raemdonck FV, Delbecq J, Depre A. Neurological complications of intravenous immunoglobulin (IVIg) therapy: an illustrative case of acute encephalopathy following IVIg therapy and a review of the literature. *Acta Neurol Belg* 1998;98:347-51.
48. Lake CR, Gallant S, Masson E, Miller P. Adverse drug effects attributed to phenylpropanolamine: a review of 142 case reports. *Am J Med* 1990;89:195-208.
49. Kassem-Moussa H, Provenzale JM, Lewis DV. Early diffusion-weighted MR imaging abnormalities in sustained seizure activity. *Am J Roentgenol* 2000;174:1304-6.
50. Obeid T, Shami A, Karsou S. The role of seizures in reversible posterior leukoencephalopathy. *Seizures* 2004;13(4): 277-81.