Posterior Reversible Encephalopathy Syndrome: Increasing Recognition of an Important Clinical Entity in Young Patients with Systemic Lupus Erythematosus

TANIA CELLUCCI and SUSANNE M. BENSELER

J Rheumatol 2011;38;1544-1545
http://www.jrheum.org/content/38/8/1544

Editorial

Posterior Reversible Encephalopathy Syndrome: Increasing Recognition of an Important Clinical Entity in Young Patients with Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic relapsing, remitting, multisystem disease[1]. Twenty percent of patients present at a younger age, with an onset of symptoms prior to age 18 years. Neuropsychiatric involvement is reported in a quarter of young lupus patients, of which 40% initially present with neuropsychiatric symptoms and 70% have their first manifestation within a year of diagnosis[2]. The diagnosis of neuropsychiatric lupus in children and young adults is based on the 1999 American College of Rheumatology nomenclature and case definitions[3,4]. Headaches, cognitive dysfunction, cerebrovascular disease, and seizures are among the most common clinical phenotypes in the spectrum of neuropsychiatric lupus[2]. Cerebrovascular disease includes cerebral vein thrombosis, microthrombotic vasculopathy, and inflammatory vasculitis, predominantly of the small vessels. Frequently, cerebrovascular disease and proliferative nephritis are concomitantly present in young lupus patients[5]. Headaches, seizures, and cerebrovascular disease were found to cluster, suggesting a common underlying vascular pathology[2]. Brain biopsies are rarely done. However, case reports demonstrated histological evidence of immune complex-mediated vasculitis[6].

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological entity of headaches, encephalopathy, and seizures associated with magnetic resonance imaging (MRI) findings of reversible vasogenic subcortical edema without infarction[7]. PRES was first reported in patients with hypertension and was thought to be purely a hypertensive encephalopathy. In 1996, Hinchey, *et al* first described the link of immunosuppressive medication, renal disease, hypertension, and PRES[8]. Subsequently, risk factors associated with development of PRES in lupus patients were identified including vascular disease with endothelial damage, disrupted blood-brain barrier, hypertension, systemic inflammation, and cytotoxic treatment regimens[9,10].

In 2010, Muscal, *et al* determined the characteristic MRI findings in young lupus patients with PRES[11]. They reported diffuse bilateral gray and white-matter findings in the majority, while only half the patients had the classical posterior fossa lesions. The authors identified reversible diffusion changes in all patients, providing guidance for neuroimaging evaluation of young lupus patients with suspected PRES[11].

The case series by Varaprasad, *et al* in this issue of *The Journal* adds to our understanding of the clinical spectrum of PRES[12]. The authors discuss the clinical and laboratory features, treatment, and outcomes of a group of 13 adolescents and young adults with SLE and PRES. In this study, the median disease duration prior to the onset of PRES was 6 months, which is significantly shorter than the mean disease duration of 61.8 months previously reported by Baizabal-Carvallo, *et al*[9]. This finding highlights the fact that PRES may develop early in the course of SLE, when disease activity is high. Active lupus nephritis was also identified in 10 of 13 patients, which is in keeping with previous studies that demonstrate an association between PRES and lupus nephritis[9,11,13]. Previous studies also documented renal insufficiency in over 75% of patients with SLE and PRES[9,14]. However, this new case series and another recent report of PRES in young lupus patients have shown a lower frequency of concurrent renal failure[11,12]. This suggests that disease activity, rather than fluid overload secondary to renal insufficiency, is a critical factor in the pathogenesis of PRES.

Common presenting features of PRES include headaches, seizures, decreased level of consciousness, temporary vision loss, and paresis[9,12,13,14]. PRES is typically associated with the sudden onset of severe hypertension[14,15]. However, Varaprasad, *et al* clearly demonstrate that patients with PRES may have blood pressure at near-normal, which broadens the clinical spectrum of this condition[12]. Previous reports have attributed the occurrence of PRES in normotensive patients to medications, such as corticosteroids, cyclophosphamide, and cyclosporine[8,16,17].

See Posterior reversible encephalopathy syndrome in SLE, *page 1607*

However, this study also identified PRES in treatment-naive patients with mild hypertension[12]. Further, several patients treated with cyclophosphamide were able to continue this medication without the recurrence of PRES after the acute episode had been treated[12]. These findings emphasize the complexity of the underlying pathogenic mechanisms leading to PRES.

The differential diagnosis for a patient with lupus who develops headache, hypertension, and seizures includes cerebrovascular disease, neuropsychiatric lupus and PRES. Since PRES may develop in the context of mild hypertension or normotension, blood pressure alone cannot differentiate these entities. All 3 may occur early in disease and in the presence or absence of immunosuppressive medications. However, neuroimaging may be more helpful in distinguishing among these conditions. Characteristic MRI findings in PRES include diffuse bilateral changes involving gray and white matter with altered diffusion[11]. In contrast, MRI lesions in neuropsychiatric lupus are typically small and multifocal, and predominantly involve the white matter[2]. Cerebrospinal fluid analysis may be normal in any of these conditions, although it is more likely to be normal in PRES[12]. Neurological recovery generally occurs more rapidly (within 7 to 10 days) following treatment in PRES compared to neuropsychiatric lupus.

The pathogenesis of PRES in lupus is multifactorial. The underlying susceptibility of the cerebrovascular system in addition to insults, such as inflammation secondary to active lupus, hypertension, nephritis, and cytotoxic medications, can lead to the development of the condition we recognize as PRES. The study by Varaprasad, *et al* in this issue widens the range of signs and symptoms that may be associated with PRES and broadens our understanding of the context in which PRES develops.

TANIA CELLUCCI, MD, HonBSc, FRCPC,
Clinical Research Fellow,
Division of Rheumatology, The Hospital for Sick Children,
University of Toronto;
SUSANNE M. BENSELER, MD, PhD,
Staff Physician,
Division of Rheumatology, The Hospital for Sick Children,
Associate Professor of Paediatrics,
University of Toronto,
Toronto, Canada

Address correspondence to Dr. Benseler.
E-mail: susanne.benseler@sickkids.ca

REFERENCES

1. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol 2010;6:538-46.
2. Benseler SM, Silverman ED. Neuropsychiatric involvement in pediatric systemic lupus erythematosus. Lupus 2007;16:564-71.
3. Singh S, Gupta MK, Ahluwalia J, Singh P, Malhi P. Neuropsychiatric manifestations and antiphospholipid antibodies in pediatric onset lupus: 14 years of experience from a tertiary center of North India. Rheumatol Int 2009;29:1455-61.
4. Muscal E, Bloom DR, Hunter JV, Myones BL. Neurocognitive deficits and neuroimaging abnormalities are prevalent in children with lupus: clinical and research experiences at a US pediatric institution. Lupus 2010;19:268-79.
5. Hiraki LT, Benseler SM, Tyrrell PN, Hebert D, Harvey E, Silverman ED. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: a longitudinal study. J Pediatr 2008;152:550-6.
6. Rizos T, Siegelin M, Hahnel S, Storch-Hagenlocher B, Hug A. Fulminant onset of cerebral immunocomplex vasculitis as first manifestation of neuropsychiatric systemic lupus erythematosus (NPSLE). Lupus 2009;18:361-3.
7. Lee VH, Wijdicks EF, Manno EM, Rabinstein AA. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. Arch Neurol 2008;65:205-10.
8. 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.
9. Baizabal-Carvallo JF, Barragan-Campos HM, Padilla-Aranda HJ, Alonso-Juarez M, Estanol B, Cantu-Brito C, et al. Posterior reversible encephalopathy syndrome as a complication of acute lupus activity. Clin Neurol Neurosurg 2009;111:359-63.
10. Punaro M, Abou-Jaoude P, Cimaz R, Ranchin B. Unusual neurologic manifestations (II): posterior reversible encephalopathy syndrome (PRES) in the context of juvenile systemic lupus erythematosus. Lupus 2007;16:576-9.
11. Muscal E, Traipe E, de Guzman MM, Myones BL, Brey RL, Hunter JV. MR imaging findings suggestive of posterior reversible encephalopathy syndrome in adolescents with systemic lupus erythematosus. Pediatr Radiol 2010;40:1241-5.
12. Varaprasad IR, Agrawal S, Prabu VN, Rajasekhar L, Kanikannan MA, Narsimulu G. Posterior reversible encephalopathy syndrome in systemic lupus erythematosus. J Rheumatol 2011;38:1607-11.
13. Kur JK, Esdaile JM. Posterior reversible encephalopathy syndrome — an underrecognized manifestation of systemic lupus erythematosus. J Rheumatol 2006;33:2178-83.
14. Leroux G, Sellam J, Costedoat-Chalumeau N, Le Thi Huong D, Combes A, Tieulie N, et al. Posterior reversible encephalopathy syndrome during systemic lupus erythematosus: four new cases and review of the literature. Lupus 2008;17:139-47.
15. Ni J, Zhou LX, Hao HL, Liu Q, Yao M, Li ML, et al. The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: a retrospective series of 24 patients. J Neuroimaging 2010 June 21. [Epub ahead of print]
16. Magnano MD, Bush TM, Herrera I, Altman RD. Reversible posterior leukoencephalopathy in patients with systemic lupus erythematosus. Semin Arthritis Rheum 2006;35:396-402.
17. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. AJNR Am J Neuroradiol 2008;29:1043-9.

J Rheumatol 2011;38:1544–5; doi:10.3899/jrheum.110774