Dr. Varaprasad and Dr. Agrawal reply

To the Editor:

It is an interesting proposition made by Dr. Park, *et al* regarding the pathogenesis of posterior reversible encephalopathy syndrome (PRES) in systemic lupus erythematosus (SLE)[1]. The report by Dr. Ortiz, *et al* points to the occurrence of PRES in various autoimmune conditions in which endothelial dysfunction might play a central role[2].

Various factors responsible for PRES in SLE include disease activity (mostly with associated nephritis), renal failure, hypertension, and drugs such as cyclophosphamide and steroids[3]. There are not enough data to understand the exact pathogenesis of PRES but it depends on 2 vital factors, hypertension and endothelial dysfunction, with variable contributions by each[4]. Severe hypertension can cause endothelial dysfunction and endothelial dysfunction *per se* can lower the threshold of cerebral autoregulation, deranging the blood-brain barrier and ultimately leading to vasogenic edema, with or without cytotoxic edema, depending on the severity. Immune-mediated endothelial dysfunction may play an important role in normotensive patients with PRES[5].

Many molecules are involved at different stages of vasogenic edema, such as vascular endothelial growth factors (VEGF), angiopoietins, aquaporins, and matrix metalloproteinases[6]. Aquaporin-4 autoimmunity is considered to predispose to PRES in neuromyelitis optica[7]. Reports of PRES in normotensive patients with thrombotic thrombocytopenic purpura with severe renal involvement also point to endothelial dysfunction and altered cerebral autoregulation. Altered function of P-glycoprotein, an adenosine triphosphate export pump, in proximal convoluted tubules and brain capillaries is implicated[8]. A similar role may be the cause for PRES in patients with postinfectious glomerulonephritis who have neurological manifestations before nephritis[9].

VEGF has an important role in angiogenesis and capillary permeability, and elevated levels are seen in various autoimmune diseases secondary to endothelial activation. Elevated VEGF levels (by inducing nitric oxide synthesis) are required for repair of glomerular endothelium in various nephropathies including lupus nephritis[10].

Patients with active lupus have elevated VEGF levels, and postmortem studies in PRES showed VEGF upregulation in the biopsy specimens[10,11]. But there are reports of occurrences of PRES in patients treated with bevacizumab, an IgG1 monoclonal antibody against VEGF used in the treatment of colorectal and renal cell carcinomas[12]. VEGF-A and angiopoietin-2 are important in the initial stages of edema, and antagonizing this by VEGF-A receptor chimeric protein and angiopoietin-1 administration in rodent models showed a decrease in edema size[13]. In contrast, VEGF-B and angiopoietin-1 are important for maintenance of the blood-brain barrier after an initial breach[6].

With the available data it is difficult to say whether elevated VEGF levels indicate a cause or a consequence in PRES. An imbalance between various isoforms of VEGF and their receptors may be crucial and accordingly, the targeted therapy might be complex.

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