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REVIEW ARTICLE

Posterior Reversible Encephalopathy Syndrome, Part 2: Controversies Surrounding Pathophysiology of Vasogenic Edema

W.S. Bartynski

SUMMARY: Posterior reversible encephalopathy syndrome (PRES) is a neurotoxic state accompanied by a unique brain imaging pattern typically associated with a number of complex clinical conditions including: preeclampsia/eclampsia, allogeneic bone marrow transplantation, solid organ transplantation, autoimmune diseases and high dose cancer chemotherapy. The mechanism behind the developing vasogenic edema and CT or MR imaging appearance of PRES is not known. Two theories have historically been proposed: 1) Severe hypertension leads to failed auto-regulation, subsequent hyperperfusion, with endothelial injury/vasogenic edema and; 2) vasoconstriction and hypoperfusion leads to brain ischemia and subsequent vasogenic edema. The strengths/weaknesses of these hypotheses are reviewed in a translational fashion including supporting evidence and current available imaging/clinical data related to the conditions that develop PRES. While the hypertension/hyperperfusion theory has been most popular, the conditions associated with PRES have a similar immune challenge present and develop a similar state of T-cell/endothelial cell activation that may be the basis of leukocyte trafficking and systemic/cerebral vasoconstriction. These systemic features along with current vascular and perfusion imaging features in PRES appear to render strong support for the older theory of vasoconstriction coupled with hypoperfusion as the mechanism.

The mechanism of posterior reversible encephalopathy syndrome (PRES) is not known. Two opposing hypotheses are commonly cited, but the issue is controversial: 1) The current more popular theory suggests that severe hypertension exceeds the limits of autoregulation, leading to breakthrough brain edema; 2) the earlier original theory suggests that hypertension leads to cerebral autoregulatory vasoconstriction, ischemia, and subsequent brain edema. The issues surrounding these theories are reviewed to summarize the potential values of each mechanism.

Current Popular Theory: Hypertension, Failed Autoregulation, Hyperperfusion

Severe hypertension with failed autoregulation, injury to the capillary bed, and hyperperfusion remains the most popular theory for the brain edema that develops in PRES.[1-4] This concept is naturally intuitive, due to the frequent presence of hypertension at toxicity, and was originally embraced as the cause of eclampsia, historically labeled as a "hypertensive disorder of pregnancy." The hypertension/hyperperfusion theory is primarily based on blood pressure exceeding the autoregulation limits of the brain.

Autoregulation

Autoregulation is an intrinsic function of the vasculature of the brain, designed to maintain a stable blood flow in the face of fluctuating blood pressure.[5,6] Under normal circumstances, brain vessels possess intrinsic vascular tone.[7] With autoregulation, vasodilation occurs as blood pressure drops and vasoconstriction occurs as blood pressure increases.[5-7] This function is regulated by the endothelium with release of relaxing factors (endothelium-derived relaxing factor: nitric oxide) and vasoconstriction factors (thromboxane-A2 and endothelin).[6] Approximately 80% of cerebrovascular resistance is related to the small arteries, arterioles, and capillary bed, with the remaining 20% contributed by postcapillary venules and veins.[7] Autoregulation is managed by the principal resistance vessels, the arterioles with a diameter of 30–300 μm.[6,7]

In humans, the lower limit of autoregulation is approximately 40–60 mm Hg mean arterial pressure (2/3 diastolic + 1/3 systolic pressure) with an upper limit mean arterial pressure of 150–160 mm Hg.[6,8-10] With reduced blood pressure beyond the lower limits of autoregulation, hypoperfusion occurs with potential infarction. With severe increase in blood pressure beyond the upper limit of autoregulation, animal studies demonstrate breakthrough with passive arteriolar dilation, pinocytotic fluid transfer, injury to the capillary bed, vasogenic edema, and vessel injury with altered arterial morphology.[8-10] Above a mean arterial pressure of 200 mm Hg, vessel morphologic changes tend to be permanent and hypocapnia develops.[9] In dog and cat studies, breakthrough perfusion occurs above a mean arterial pressure of approximately 170–180 mm Hg.[8-10]

Of importance, several factors can alter the upper limit by up to 30 mm Hg.[11] Cerebral vessels possess a rich sympathetic neural supply, and sympathetic stimulation will increase the upper limit of autoregulation.[5,7] The upper limit will also increase in the setting of chronic hypertension.[5]

Observations Supporting Hypertension with Autoregulatory Failure

The popularity of the hypertension/hyperperfusion theory is primarily related to the common presence of significant blood pressure elevation at toxicity. Moderate-to-severe hypertension is encountered in 50%–70% of patients with PRES at toxicity, and emergent hypertension treatment is associated with symptom improvement in hours, days, or weeks.[12-14] In

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some patients, hypertension can be quite severe, clearly challenging the upper limits of autoregulation.[15-18]

Investigating the brain effects of severe hypertension, a series of animal studies demonstrate that when the upper limits of autoregulation are exceeded, breakthrough occurs with the development of blood vessel alteration, capillary bed injury, vasogenic edema, and hyperperfusion.[8-10] To my knowledge, no large clinical series has been reported, but evidence of hyperperfusion has been suggested in isolated case reports of patients studied with technetium Tc99m-hexamethylpropyleneamine oxime (Tc99m-HMPAO) single-photon emission CT (SPECT) and induced hypertension studied by arteriovenous oxygen (O_2) difference.[3,4,19]

Problems with the Hypertension/Hyperperfusion Theory

Although intuitive, several problems exist with fully embracing the hypertension/hyperperfusion theory in PRES.

Blood Pressure. PRES is commonly seen without hypertension or with only minor increase of blood pressure at toxicity as noted in larger studies of eclampsia, allogeneic bone marrow transplant (allo-BMT), solid organ transplant (SOT), and a wide variety of case reports.[20-23] Equally important, even when significant hypertension is present, toxicity blood pressure does not typically reach the limits of failed autoregulation.[15,24-28] Also of note, increased sympathetic activation secondary to cyclosporine has been documented after heart transplantation.[29,30] As mentioned previously, the upper limit of autoregulation is increased in the presence of sympathetic stimulation.[5]

Hyperperfusion. Evidence documenting hyperperfusion is scant. Several isolated early case reports have suggested observing hyperperfusion in the setting of PRES.[3,19] More recently, a number of moderate-to-large series have demonstrated watershed hypoperfusion in eclampsia by technetium Tc99m HMPAO SPECT and reduced brain perfusion in the posterior brain or in regions of PRES by MR perfusion (MRP).[24,31-33] Abnormal radiopharmaceutical uptake could represent luxury perfusion due to loss of autoregulatory vascular tone as opposed to true hyperperfusion.[34]

Systemic Toxicity. PRES typically develops in the setting of a significant 'systemic process', including preeclampsia, transplantation (allo-BMT, SOT), infection/sepsis/shock, autoimmune disease, and cancer chemotherapy.[23] In toxemia of pregnancy (the best studied of these conditions), systemic vasoconstriction is present (including cerebral vasoconstriction) and is considered responsible for the developing hypertension.[35,36] Unfortunately, animal models used to test autoregulation have not been performed under these conditions but rather in healthy animals. Similar to the effects of sympathetic stimulation, the autoregulatory response of the brain may be altered in the setting of systemic toxicity (ie, toxicity-induced cerebral/systemic vasoconstriction).

Brain Edema. The extent of brain edema in PRES does not appear to increase with the severity of hypertension. In recent studies on PRES in patients with infection/sepsis/shock and in patients studied by catheter angiography (CA) and MR angiography (MRA), the extent of brain edema was statistically lower in those with severe hypertension at toxicity compared with those who were normotensive at toxicity.[24,37] This was also observed in PRES developing after SOT between liver (primarily normotensive with greater edema) and renal (severely hypertensive with low edema) transplantations.[38] If severe hypertension were the cause of PRES vasogenic edema, the opposite observations would be expected.

Early Original Theory: Vasoconstriction, Hypoperfusion, Ischemia

Early imaging reports of eclampsia, cyclosporine neurotoxicity, and severe hypertension demonstrated brain hypoattenuating areas by CT, particularly in the parietal/occipital region.[23] Parallel demonstration of parietal/occipital abnormality at CT and vasospasm at CA in patients with hypertension and eclampsia prompted several investigators to suggest that ischemia caused the brain parenchymal abnormality.[39,40] According to the traditional version of this theory, vasoconstriction secondary to evolving hypertension and autoregulatory compensation leads to reduced brain perfusion, ischemia, and subsequent vasogenic edema.[41]

For the past 20 years, the typical conditions that develop PRES are better recognized and the biology underlying toxicity in these patients is better understood. Although currently less favored, many of the clinical/imaging features now identified in these conditions fundamentally support the original basic concept of hypoperfusion/vasoconstriction in PRES.

PRES without Hypertension

Of critical importance, PRES develops in normotensive patients and in patients with only mild blood pressure elevation. In 20%–30% of patients who develop PRES, blood pressure is essentially normal at toxicity.[21,22] This has been observed in many large series, including those concerning women with eclampsia, cyclosporine toxicity after allo-BMT, broader PRES studies, and many isolated case reports.[15,20,26-28,42] Clearly the 'systemic process' is sufficient to establish a state in which neurotoxicity and the PRES imaging pattern develop. The vasogenic edema in these patients also resolves spontaneously without blood pressure management. PRES, therefore, develops and reverses in the face of systemic toxicity but in the absence of hypertension. In addition, though moderate-to-severe blood pressure elevation is observed in many patients with PRES, hypertension at toxicity does not reach the upper limit of autoregulation in most instances (mean arterial pressure $>$ 150–160 mm Hg). These are significant issues for the hypertension/hyperperfusion hypothesis, and any theory that attempts to postulate a mechanism in PRES must address these observations.

Clinical/Biologic Features Common to PRES-Associated Conditions

PRES is almost exclusively seen in the setting of a significant systemic process/condition, including transplantation (allo-BMT, SOT), infection/sepsis/shock, toxemia of pregnancy, autoimmune disease, and postcancer chemotherapy.[20,23] The clinical presentation at neurotoxicity and the imaging appearance of PRES are essentially the same in these conditions.[13] An important group of underlying biologic processes (Table) is also similar and sustained in these conditions including the following: 1) immune system activation (T-cells, related to transplant/microorganism), 2) endothelial cell activation (en-

Clinical features common to PRES-related conditions						
Feature	Preeclampsia	Allo-BMT	SOT	I/S/S	Autoimmune Ds	Chemo/Ca
Immune system antigen challenge	+ (Placenta)	+ (BMT)	+ (Transplant)	+ (Bacteria)	+ (Self?)	+ (Tumor Ag)
Microchimeric exchange	+	+	+	–	+	–
T-cell activation	+	+	+	+	+	+
Inflammatory cytokines: TNF-α, IL-1, IFN-γ	+	+	+	+	+	+
Endothelial activation: p-selectin, e-selectin, ICAM-1, VCAM-1	+	+	+	+	?	?
Endothelin-1 up-regulation	+	+	+	+	?	?
Endothelial injury: thrombocytopenia, schistocytes, LDH	+	+	+	+	+	?
Vascular instability: vasoconstriction, vasodilation	+	+	+	+	?	?
Organ hypoperfusion	+	+	+	+	?	?
MODS	+	+	+	+	+	?
VEGF elevation	+	?	?	?	?	?
Endothelial autoantibodies	+	+	+	–	+	–

Note:—I/S/S indicates infection/sepsis/shock; + = present; –, not present; ?, undetermined or not studied; Allo-BMT, allogeneic bone marrow transplant; SOT, solid organ transplant; TNF, tumor necrosis factor; IL-1, interleukin; IFN, interferin; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; LDH, L-lactate dehydrogenase; MODS, multiorgan dysfunction syndrome; VEGF, vascular endothelial growth factor; Ds, disease; Chemo/Ca, post chemotherapy with cancer; Ag, unique tumor antigens.

dothelial cell swelling, surface-marker expression, endothelin release), 3) endothelial injury, 4) vascular instability (systemic vasoconstriction), and 5) systemic/organ hypoperfusion in addition to procoagulant and metabolic effects. The best characterized, most familiar of these systemic conditions is toxemia of pregnancy.

Preeclampsia. The inciting mechanism in preeclampsia is considered endothelial activation and injury, with numerous systemic consequences.[35,36] A prominent inflammatory cytokine response is identified including the following: tumor necrosis factor (TNF-α), interleukin (IL)-1, interferon (IFN)-γ, and IL-6. The source of cytokine release may include the placenta and T-helper cells (Th1 and 2 cells); Th cell levels are altered in preeclampsia.[36] Subsequent endothelial cell activation results in endothelial cell swelling and augmented endothelial surface markers including the following: E-selectin, vascular cell adhesion molecule 1 (VCAM-1), and intercellular adhesion molecule 1 (ICAM-1). Inflammatory cytokine levels parallel detected levels of endothelial surface markers (VCAM-1).[36] TNF-α and IL-1 also up-regulate messenger ribonucleic acid for the potent vasoconstrictor endothelin-1 and stimulate its release from endothelial cells.[43-45]

Diffuse endothelial activation leads to systemic vasoconstriction, systemically labile blood pressure, and abnormal response to vasopressors.[35] Endothelial damage results in platelet adhesion (thrombocytopenia), platelet degranulation (thromboxane-A2, vascular tone/blood pressure effects), hemolysis (L-lactate dehydrogenase [LDH] elevation, schistocytes), protein/fluid leakage, and systemic edema. Glomerular endothelial swelling and dysfunction occur with magnesium, fluid, and protein loss.[35] Hepatic dysfunction from reduced perfusion leads to elevated liver enzymes (hemolysis elevated liver low platelets [HELLP] syndrome when coupled with hemolysis/low platelets).[35] Cerebral vasospasm and increased vascular resistance parallel the process in other organs.[40,46-50]

The placenta is fetal tissue (fetal human leukocyte antigens typing) and requires unique immune modulation to remain isolated from the maternal circulation.[36,51] Placental-maternal immune reaction has been postulated.[36] Anti-endothelial cell antibodies are detected in a high percentage of eclamptic women (50%) in comparison with healthy pregnancies (15%).[36]

Allo-BMT. After allo-BMT, features develop that parallel the underlying biology of preeclampsia. Acute graft-versus-host disease (GVHD) following allo-BMT is generally related to T-cell–mediated response of graft to host (in particular to host endothelium) and a response to preconditioning regimens.[21,25,52,53] The preconditioning regimens in combination with acute GVHD result in tissue injury with cytokine release (IL-2), monocyte/macrophage activation (release of TNF-α, IL-1, IFN) with resultant endothelial activation (surface marker up-regulation) or injury.[25,52-57] Endothelial injury is reflected in the development of BMT thrombotic microangiopathy (BMT-TM) with LDH elevation, schistocytes, and thrombomodulin release.[21,25,58] The coagulation system is undoubtedly triggered, with platelet adhesion/consumption/degranulation (thrombocytopenia, vasoconstriction, and blood pressure fluctuations supplemental to the endothelin). Reduced hepatic perfusion and hepatic injury develop, with elevated liver enzymes (veno-occlusive disease, similar to preeclampsia).

Transplant tolerance is aided by immunosuppression (cyclosporine/tacrolimus), limiting acute GVHD and graft rejection. The effects of cyclosporine/tacrolimus and problems related to transplantation often coexist.[59,60] Acute GVHD has been labeled a "distortion of the cellular response" to infection.[55] Cyclosporine induces diffuse endothelial injury with systemic effects.[61] Vasoconstriction develops (endothelin, sympathetic) with altered glomerular filtration, glomerular endothelial injury, proteinuria, and magnesium loss (resembling preeclampsia).[59,62] Chronic renal interstitial changes occur with prolonged exposure.

Chronic GVHD (a condition that resembles scleroderma or lupus) appears to be related to the development of autoantibodies (antiendothelial and antiphospholipid antibodies) similar to autoimmune diseases.[63]

Infection/Sepsis/Shock. Observations in infection/sepsis/shock are similar.[37,64] The septic/shock response likely reflects systemic toxicity similar to systemic inflammatory response syndrome or multiorgan dysfunction syndrome (MODS) and bacteremia, or endotoxins/exotoxins are considered potential triggers.[64-66] Cytokine response (TNF-α, IL-1) plays a critical role in development of this effect.[67,68]

Endothelial activation and injury are considered central to the development of the primary infection response and secondary septic response.[64,69-71] Inflammatory cytokine release (TNF-α, IL-1β) leads to endothelial activation with endothelial cell swelling, up-regulation of surface antigens (P-selectin, E-selectin, ICAM-1) with increased leukocyte adherence, altered vascular tone, altered vascular permeability, and coagulation.[64,71-73] Microcirculatory dysfunction develops due, in part, to leukocyte adherence and tissue migration (trafficking) with reduced tissue capillary/venule blood flow.[72] Altered vascular tone secondary to competing vasoconstrictive (platelet degranulation [thromboxane release], endothelin-1, angiotensin, vasopressin, central sympathetic stimulation) and vasodilatory (nitric oxide, prostacycline) effects are noted.[73] Significant vascular instability is seen in 50% of patients with sepsis.[74] TNF-α and IL-1 up-regulate and stimulate the release of endothelin-1,[43-45] and endothelin-1 is released at high levels in sepsis.[37,75] Endotoxin also promotes endothelin release.[76]

Gram-positive organisms are commonly seen in infection/sepsis/shock–associated PRES.[37] The mechanism of gram-positive sepsis is unique, with cell surface antigen and superantigen T-cell stimulation of cytokine release, compared with traditional T-cell trigger occurring with gram-negative organisms.[64,77-79] Superantigens demonstrate a marked interaction rate with the overall T-cell population (5%–20% of T-cells for superantigens versus 1 in 10^4–10^6 T-cells for traditional antigen) with broad T-cell stimulation/cytokine response.[64,78]

SOTs. In SOT, several processes are observed, including acute and chronic organ rejection, infections, and microchimerism secondary to circulation of transplanted organ immune cells. Graft rejection following SOT is related to a T-cell response to the graft along with the development of antivascular or antiendothelial antibodies (primarily against the transplant).[80,81] Acute rejection also involves up-regulation of T-cells and the endothelium. Leukocyte trafficking occurs in the transplant with inflammatory cell adhesion. Altered perfusion develops due to trafficking and the ongoing inflammatory response.

Late rejection (as in kidney transplants) generally involves CD4 T-cell activation to transplant endothelium with delayed-type hypersensitivity response (including TNF-α and -β, IFN-γ, and IL-1 cytokine expression) and progressive cytotoxic CD8 T-cell activation with direct endothelial/tissue injury.[80] The inflammatory response to the graft leads to endothelial adhesion molecule activation, leukocyte trafficking (T-cells, macrophages, other leukocytes), and organ hypoperfusion. Chemokine activation of neutrophils develops, and B-cell activation with antibody production can also occur. This chronic allograft inflammatory process results in the organ/stromal injury, which constitutes the histologically observed effects of rejection.[80]

Chemotherapy and Cancer. Immunologic reaction to cancer cells is well recognized.[82] Potential triggers include: 1) CD8+ T-cell recognition of unique tumor antigens expressed on tumor cell major histocompatibility complex type-I (MHC-I) molecules or 2) CD4+ T-cell recognition of unique tumor antigens expressed on antigen presenting cells (APC; ie dendritic cells or macrophages) MHC-II molecules.

PRES typically occurs several weeks after cancer chemotherapy[23] and tumor cell lysis, APC tumor antigen expression, CD4+ T-cell activation and monocyte/macrophage activation likely develops with subsequent cytokine expression.[82] Increased recognition of PRES with higher doses of chemotherapy could reflect immune response to unique tumor antigen and/or the direct effects of chemotherapy on the endothelial cell.[23,25]

Microchimeric Conditions

"Microchimerism" is a condition in which blood cell populations of different genetic composition coexist. The hallmark is allo-BMT, but this state may exist in SOT (in particular liver transplants), preeclampsia, and autoimmune disease.

Liver Transplants. The donor liver contains a significant number of mobile and intrinsic (Kupffer) immunologically active cells.[83] A large pool of T-cells/macrophages/stem cells present in the donor liver exits in the first 45 days posttransplantation, interacting with the recipient or establishing permanent residence within the host.[83] Mechanisms similar to allo-BMT (GVHD effect) could contribute to PRES, typically seen early after liver transplantation.[25]

Preeclampsia. The placenta is not a fully restrictive maternal-fetal barrier. Exchange of fetal blood with the maternal circulation occurs, particular at delivery (Rh exchange). Fetal leukocytes and DNA can be detected in the maternal circulation as early as 4–5 weeks into the pregnancy, increase during the course of the pregnancy, and can persist in the maternal circulation as long as 27 years after delivery.[84,85] Preliminary studies suggest the presence of preeclampsia, and the severity of preeclampsia may, in part, be related to the quantity of fetal-maternal cell exchange during the pregnancy.[86]

Autoimmune Diseases. Scleroderma, systemic lupus erythematosus (SLE), and Wegener's granulomatosis share recognized underlying histopathology traditionally labeled vasculitis.

In scleroderma, endothelial activation and cytokine production result in stimulation of systemic collagen deposition/fibrosis.[87] A high number of fetal Y-chromosome leukocytes have recently been demonstrated in the characteristic skin lesions and blood of women with scleroderma, apparently related to prior pregnancy (microchimersim).[88,89] The features of chronic GVHD resemble those of scleroderma,[63] and models of chronic GVHD are commonly used to study scleroderma and SLE.[90,91]

SLE is caused by incorrect Th cell control over B-cell function, with the errant production of self-antibodies or autoantibodies.[92] Build-up of antigen-antibody complexes results in vascular/endothelial injury/activation with multiorgan tissue injury and potential inflammatory cell attraction.

Wegener's granulomatosis is a necrotizing vasculitis that affects the kidney, lung, and other organs such as the sinonasal region, skin, and brain.[93] The specific trigger remains elusive, but prominent cytokine release is recognized (TNF-α) along with extensive autoantibody production (antineutrophilic cytoplasmic antibody) and potential antigen-antibody stimulation of neutrophil degranulation and endothelial injury.

Overall Observations in PRES-Associated Conditions

In the majority of patients who develop PRES, therefore, a complex underlying 'systemic process' is present with similar underlying biologic features (Table). T-cell activation and inflammatory cytokine production (TNF-α, IL-1, IFN-γ, and

IL-6) are common. Cytokines (TNF-α, IL-1) up-regulate endothelial surface antigens (P-selectin, E-selectin, ICAM-1, VCAM-1), and increased leukocyte adherence (trafficking) leading to microcirculatory dysfunction. Endothelial injury is noted with thrombocytopenia, schistocytes, and increased LDH. Endothelial activation and injury likely result in vasculopathy with altered intrinsic vascular tone from platelet aggregation, inflammatory cytokine expression (TNF-α, IL-1), cyclosporine/tacrolimus, or endotoxin (ie, vasoconstriction [endothelin-1, thromboxane-A2] and vasodilation [nitric oxide, prostacycline]). Enhanced systemic endothelial activation (swelling), leukocyte trafficking, and vasoconstriction, alone or in combination, would result in brain and systemic hypoperfusion.

Evidence of Hypoperfusion in PRES

An evolving systemic process with hypoperfusion/vasoconstriction and the development of parallel brain and systemic toxicity would more easily explain most of the observations in PRES.

Vasculopathy. Evidence of vasculopathy has been demonstrated in PRES, and the features reflect elements of vasoconstriction, vasodilation, and reduced perfusion as suggested from the common underlying biology described previously. CA and MRA demonstrate focal vasoconstriction, focal vasodilation, string-of-beads appearance, and vessel pruning, undoubtedly reflecting endothelial dysfunction (increased and decreased vessel tone) or reduced flow.[21,24,37,40,46,47,94-96] Diffuse vasoconstriction is also present.[24] These features have been noted in hypertensive as well as nonhypertensive patients and have been shown to reverse.

The PRES imaging pattern resembles a watershed distribution, further suggesting hypoperfusion, which has been demonstrated by technetium Tc99m HMPAO SPECT and MRP.[24,31,32,97] In addition, increased brain vascular resistance and cerebral vasospasm are suggested in preeclampsia/eclampsia by transcranial Doppler.[48-50]

Vasogenic Edema. Sustained hypoperfusion could explain the vasogenic edema in PRES. Toxicity-related hypoperfusion or vasoconstriction could lead to localized brain hypoxia. Hypoxia activates endothelial cells and stimulates angiogenesis.[98-100] Vascular endothelial growth factor (VEGF, previously called vascular permeability factor) is up-regulated in this setting due to tissue expression of hypoxemia-inducible factor 1α in the presence of hypoxemia.[101,102] With hypoxia, VEGF levels increase progressively for 6–24 hours and act on endothelial cells to stimulate angiogenesis and increase endothelial permeability.[101,102] The increased permeability appears threshold-dependent, occurring with increasing VEGF levels and requiring moderate-to-severe hypoxemia ($pO_2 < 8\%$) and is blocked by anti-VEGF antibodies.[101] Acidic extracellular pH 6.6 also increases VEGF levels, and brain proton spectroscopy has occasionally demonstrated lactate in PRES.[103,104] Permeability changes may relate to altered adhesion characteristics between endothelial cell tight junctions.[98] Systemic VEGF levels increase in preeclampsia.[35]

Brain Edema and Systemic Hypertension

If the cause of PRES is related to systemic toxicity, the quantity of brain edema will undoubtedly relate to features of the toxic process, including severity, duration, and regional brain vascular specificity. Recent evidence suggests that brain edema in PRES is reduced, not greater, in patients with severe hypertension.[24,37,38] If the underlying process is a systemic inflammatory response with resultant hypoperfusion, augmented systemic vasoconstriction and augmented hypertension may occur, representing a Cushing-like response, designed to increase perfusion and reverse brain hypoxemia. The role of hypertension may be that of a modulator in PRES.

With increasing hypertension, autoregulation could play a supplemental role, further modifying cerebral blood flow. Autoregulatory vasoconstriction superimposed on toxicity-induced brain vasoconstriction could further reduce brain perfusion and induce ischemia. Toxicity-blood-pressure reduction might lead to reduced autoregulatory vasoconstriction, improved perfusion, reversal of a watershed penumbra, and subsequent clinical improvement. Vasodilators and calcium channel blockers are commonly used antihypertensive agents in PRES, and apparent clinical recovery may be augmented by improved cerebral blood flow.[12,13,105]

Magnesium Revisited

It has been suggested that hypomagnesemia may be associated with and may augment PRES (cyclosporine neurotoxicity).[106] Magnesium wasting is well known in preeclampsia, due to glomerular dysfunction, and after transplantation, due to the effects of cyclosporine/tacrolimus on glomerular endothelium.[35,59] Magnesium is a competitive antagonist to calcium. It reverses cerebral vasoconstriction in laboratory animals and preeclamptics and is currently under study as a potential antivasospasm treatment after subarachnoid hemorrhage.[107-109] Although neural suppression is often suggested as the 'antiseizure' mechanism of action of magnesium sulfate,[35] its effect in preeclampsia could, in reality, be vasodilation with "PRES prevention". Of note, PRES has been observed in the setting of hypercalcemia.[23]

Summary of Systemic Toxicity with Hypoperfusion in PRES

The major clinical conditions that develop PRES demonstrate a similar clinical presentation, imaging appearance, and underlying biology. Toxicity occurs in the absence of hypertension, but elevated blood pressure may have a modulating effect. Immune system (T-cell) activation, endothelial cell activation and injury, and an inflammatory cytokine response predominate, with hypoperfusion intrinsic to these conditions, due to either leukocyte trafficking or vasoconstriction. Evidence of vasculopathy and cerebral hypoperfusion is present on most current imaging studies and is likely reflected in the watershed appearance of the vasogenic edema that develops in PRES. Parallel clinical, imaging, and underlying biology between preeclampsia and transplantation support an immune cause of placental intolerance.[36]

Conclusions

The mechanism of PRES remains controversial. Although the hypertension/hyperperfusion theory is favored due to the

common presence of elevated toxicity blood pressure and perceived response to hypertension management, key issues remain problematic, including PRES in normotensives, toxicity pressures rarely reaching autoregulatory limits, and brain edema lower in severe hypertensives. Hypertensive encephalopathy animal models do not reflect the systemic toxicity present, and hyperperfusion has not conclusively been demonstrated in patients.

Systemic toxicity leading to endothelial dysfunction with subsequent vasoconstriction or leukocyte trafficking or both appear to address the observations more comprehensively. Common underlying physiology/pathology in PRES-associated conditions, reversible vasculopathy identified at CA/MRA, and hypoperfusion as noted on most SPECT/MRP studies could lead to VEFG up-regulation and could better explain the watershed appearance on CT/MR imaging. Autoregulatory vasoconstriction superimposed on toxicity vasoconstriction/hypoperfusion with border-zone ischemia could be responding to antihypertensive/magnesium management, leading to perceived clinical improvement. Further investigations will be necessary to bring clarity and confirm the mechanism.

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