Medical Hypotheses 82 (2014) 619–622

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Posterior reversible encephalopathy syndrome: The endothelial hypotheses

A. Marra [a,*], M. Vargas [a], P. Striano [b], L. Del Guercio [c], P. Buonanno [a], G. Servillo [a]

[a] Department of Neuroscienze e Scienze riproduttive ed Odontostomatologiche-Anesthesiology and Intensive Care Medicine, University of Naples "Federico II", Italy
[b] Muscular and Neurodegenerative Disease Unit, 'G. Gaslini' Institute, University of Genoa, Italy
[c] Department of Sanità Pubblica – Vascular Surgery, University of Naples "Federico II", Italy

ARTICLE INFO

Article history:
Received 15 September 2013
Accepted 21 February 2014

ABSTRACT

Posterior reversible encephalopathy syndrome (PRES) is characterised by headache, visual disorders, seizures, altered mentation, consciousness disturbances and focal neurological signs. Initially described in patients with pre and eclampsia, severe hypertension, posterior reversible encephalopathy syndrome can occur in other clinical conditions such as infection, sepsis, shock, cancer chemotherapy, autoimmune diseases and hypercalcemia. Pathogenesis of brain lesions in PRES is not full understood and two opposite theories have been proposed. Both models are based on the central role of hypertension. According to the first theory, hypertension could cause a breakdown of the autoregulatory system in cerebral circulation, leading to brain edema. The second theory suggests that hypertension causes activation of autoregulatory system, which finally results in a vasoconstriction of brain vessels with hypoperfusion, ischemia and subsequent fluid leakage. However a large number of patients, with PRES, doesn't show hypertension. We here describe the hypothesis of the crucial role of endothelial dysfunction and activation in PRES pathogenesis. Our hypothesis offers a common pathogenetic mechanism in which every PRES-related condition can be set. In our model, the activation of immune system and the consequent endothelial activation start a molecular cascade which finally causes the production of molecules which alter the normal homeostasis of blood–brain barrier. This alteration consists in a weakening of brain vessel tight junctions, which allows fluid leakage and edema. In this scenario, hypertension would be an epiphenomenon of the underlying mechanism and not the cause and, for this reason, it can be present or not in PRES.
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Introduction

Posterior reversible encephalopathy syndrome (PRES) is characterised by headache, visual disorders, seizures, altered mentation, consciousness disturbances, and focal neurological signs [1]. Initially described in pre- and eclampsia, use of cyclosporine after transplantation, and severe hypertension, PRES can occur in many other clinical conditions such as infection, sepsis, shock, cancer chemotherapy, autoimmune diseases, and hypercalcaemia.

PRES shows a typical neuroradiological distribution of brain lesions; RMN images, in fact, reveal symmetrical areas of vasogenic edema of the white matter predominately localized in the territories of posterior circulation [2] even if signal alteration can involve, in most severe cases, other brain regions such as temporal and frontal lobes, basal ganglia, cerebellum, or brainstem [3].

Promptly recognized, symptoms and radiologic abnormalities of PRES may completely resolve; when unrecognized, the syndrome could progress to ischemia, brain infarction and death.

Pathogenesis of brain lesions in PRES is not fully understood and two opposite theories have been proposed so far [4]. The first and most popular theory is that of hypertension/hyperperfusion: in 50–70% of cases, PRES patients show a moderate-to-severe elevation of blood pressure; this finding initially suggested the hypothesis that hypertension could cause a breakdown of the autoregulatory system in cerebral circulation, leading to brain edema. Autoregulation is an intrinsic property of cerebral vessels which maintains the blood flow constant; in fact, a vasoconstriction occurs when blood pressure drops, whereas a vasodilatation is activated as blood pressure increases. This property is mediated by the endothelium itself through the release of relaxing (nitric oxide) or vasoconstriction (thromboxane A-2 and endothelin) agents. The second theory suggests that hypertension causes the activation of autoregulatory system, which finally results in a vasoconstriction of brain vessels with hypoperfusion, ischemia and subsequent fluid leakage.

* Corresponding author. Address: Department of Neuroscienze e Scienze riproduttive ed Odontostomatologiche, University of Naples "Federico II", Via Sergio Pansini 5, 80131 Naples, Italy. Tel.: +39 081 7463552.
E-mail address: marraannachiara@virgilio.it (A. Marra).

http://dx.doi.org/10.1016/j.mehy.2014.02.022
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Both models are based on the central role of hypertension but several clinical findings remain unexplained; in fact, a large number of PRES patients doesn't show hypertension and in many other cases, blood pressure doesn't exceed autoregulatory upper limit, suggesting a more general mechanism in PRES pathogenesis. Moreover, the extent of brain edema doesn't appear to correlate with the increase of blood pressure.

Hypothesis

We here describe the hypothesis of the crucial role of endothelial dysfunction and activation in PRES pathogenesis; in this model, hypertension is only an epiphenomenon of the underlying mechanism of endothelial activation which would be, in our opinion, the common final pathway of all clinical conditions precipitating PRES onset.

Evaluation of the hypotheses

Endothelial activation and damage in PRES onset

Our hypothesis rises from the observation that clinical conditions in which PRES can occur share some common features basically consisting in an activation of the immune system. Toxemia of pregnancy, autoimmune diseases, sepsis, transplantation, post-cancer chemotherapy are all systemic processes involving the entire organism which responses through its fundamental tools, i.e. the cells of the immune system and cytokines. T-lymphocytes, in particular, seem to have a pivotal role in driving and coordinating the immune response in PRES-related conditions along with molecules as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and interferon (IFN)-γ. The immune system would be responsible, in our hypothesis, of a systemic endothelial activation which eventually results in an increased vasal permeability; in this contest, PRES would represent the neurological manifestation of a more complex systemic process.

Molecular basis of endothelial damage in PRES

Immune system is activated every time an injury affects the organism; its effects can be exerted through the release of specific molecules, i.e. cytokines, which regulate the immune response and cause alterations in the normal homeostasis of tissues and organs. A central role is played by vasculature which is one of the most important target of the immune response. Changes in endothelial function and structure allow leucocytes to reach the sites where their activity is needed; but to do that, vessels have to express surface receptors to bind the cells and modify the intercellular junction to increase permeability and make cells pass through. Leukocytes recruitment and vascular permeability have to be therefore coordinated and it is not surprising that cytokines, which have pleiotropic functions, control both activities. TNF-α and IL-1, in particular, induce the expression of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule (VCAM-1), E-selectin, which are markers of endothelial activation. Leukocytes are sequestrated by activated endothelium and release cytotoxic mediators such as reactive oxygen species (ROS) and proteases, contributing to endothelial damage and subsequent fluid leakage. TNF-α can also induce the expression of vascular endothelial growth factor (VEGF), an important regulator of angiogenesis and vascular permeability; in addition, TNF-α is able to switch the expression of VEGF forms from anti-angiogenic splice variants to angiogenic ones [5]. Notably, VEGF induces ICAM-1, VCAM-1, and E-selectin expression in endothelial cells during inflammation, thus confirming the close functional relationship of these molecules in the inflammatory response [6]. Recently VEGF-A has been identified as an important driver of blood–brain barrier (BBB) permeability, lymphocytes infiltration, tissue damage, and clinical deficit. Argaw et al. have demonstrated that IL-1 β induces atrocytes to express molecules favoring vessel plasticity including hypoxia-induced factor 1α (HIF-1α) and its target gene coding for VEGF-A; this study also confirmed VEGF to be a potent inducer of BBB permeability. VEGF weakens tight junctions in brain endothelial cells, acting on claudins and occludins, which play key roles in junction formation and properties [7]. VEGF can also activate the Vesiculo-Vacuolar Organelle (VVO) which is supposed to provide the major route of extravasation of fluids and macromolecules [8] (Fig. 1).

The activation of immune system in PRES-related conditions causes the release of cytokines which up-regulate the expression of VEGF, opening the way to brain edema; notably, in preeclampsia, one of the first studied and most common clinical condition in which PRES can occur, circulating levels of VEGF-A are increased and preeclamptic plasma results in a 5-fold acute increase in vascular permeability [9].

Hypertension, in our opinion, would be a consequence and not the *primum movens* in PRES pathogenesis, due to endothelial dysfunction and activation determined by immune response; endothelial dysfunction consists in a insufficient production of nitric oxide (NO), a potent vasodilator, in response to stimuli that usually would cause a release of this factor. Another contributing factor to determine hypertension would be the endothelial activation which cause an altered cell trafficking through vessels wall, increasing cell adhesion and narrowing vasal lumen of microvasculature. This deficit of microvasculature also accounts for the microangiopathic haemolysis registered in many PRES-related conditions, causing the release in the circulation of red cells product such as lactate serum dehydrogenase (LDH). LDH is an intracellular enzyme which is present in many tissues; its concentration is about 500-fold lower in serum than in body cells. Tissue damage results in an enzyme release with a consequent increase in serum LDH activity [10]. Endothelial injuries may cause a narrowing of blood vessels and modifications in endothelial wall which make erythrocytes flow difficult leading to red cells mechanical stress and intracellular content release. Many clinical observations suggest the endothelial involvement in PRES pathogenesis. Schwartz et al. reported an association between PRES-related brain edema and serum LDH levels in patients with pre- and eclampsia but not in pre- and eclamptic patients who didn't show neuroradiological abnormalities compatible with PRES. Moreover, schistocytes were found in peripheral smear thus supporting the hypothesis of the microangiopathic status in PRES patients [11]. Demirtas et al. also found increased levels of serum LDH in pre- and eclamptic patients with magnetic resonance imaging suggestive of PRES [12]. Finally, Finocchi et al. [13] and Vargas et al. [14] demonstrated a significant raising in serum LDH activity in obstetric patients prior of the clinical onset of PRES symptoms. Microangiopathic status would determine a reduced perfusion of tissues and organs and subsequent hypoxia would further increase VEGF production through the induction of HIF-1α, especially in nervous system. Further studies should be conducted to confirm the overexpression of endothelial activation markers in the other PRES-related conditions in which these molecules have not been investigated so far. Bartysnki et al. reported increased levels of ICAM-1, VCAM-1, and E-selectin in different diseases as preeclampsia, allogeneic bone marrow transplantation (allo-BMT), solid organ transplantation (SOT), infection, sepsis, and shock [4]. Furthermore, many observations emphasize the role of VEGF in PRES pathogenesis: brain biopsy showed endothelial activation, T-cell trafficking, and endothelial/cellular VEGF expression in a case of PRES after cardiac transplantation [15] and in a patient with a non-Hodgkin lymphoma treated with different chemotherapy regimens [16]. Even PRES in systemic lupus erythematosus (SLE) has been recently

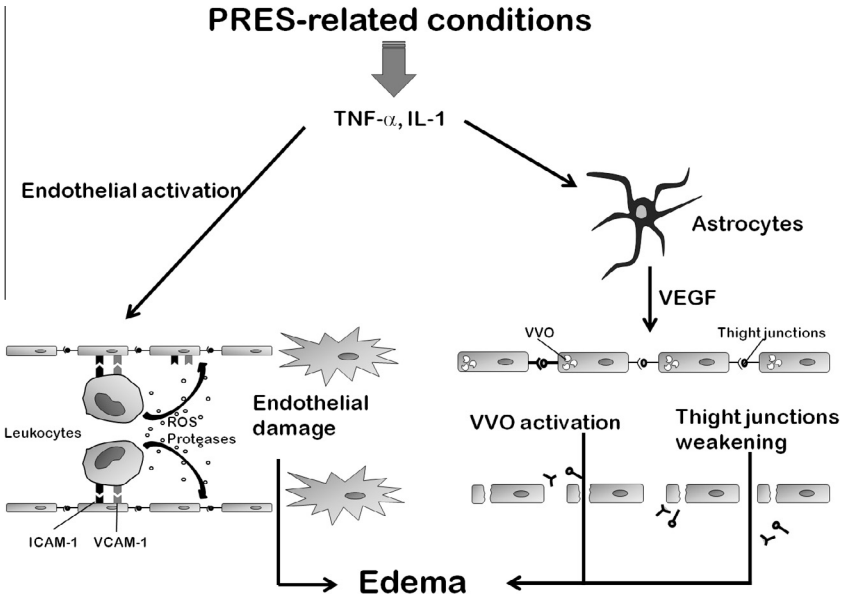

Fig. 1. PRES-related conditions cause the activation of the immune system and the release of cytokines such as TNF-α and IL-1. TNF-α and IL-1 induce the expression of the adhesion molecules ICAM 1 and VCAM 1 which interact with leukocytes, making them produce reactive oxygen species (ROS) and proteases leading to endothelial damage and consequent fluid leakage. TNF-α and IL-1 can also induce astrocytes production of VEGF which weakens the tight junction of brain vasculature and activates the Vesiculo-Vacuolar Organelle (VVO), thus contributing to edema formation.

supposed to be related with the increased level of VEGF [17], whose serum concentration was found to correlate with disease activity in a large number of autoimmune syndromes [18].

Consequences and discussion

PRES is a neurological entity that can occur in many clinical conditions. Promptly recognized, symptoms and radiologic abnormalities of PRES may completely resolve; when unrecognized, the syndrome could progress to ischemia, brain infarction, and death.

Immune response may play a central role in pathophysiology of PRES patients [4]. In normal conditions, endothelial cells were highly active, constantly sensing and responding to alterations in the local extracellular environment. Endothelial cell activation occurred as a normal adaptive response; the nature and duration of which depends not only on the type of stimulus, but also on the spatial and temporal dynamics of the system [19]. Endothelial cells activations may also occur under physiologic and pathophysiologic conditions. During the inflammatory response, the vascular endothelial cells were activated and induced many changes in gene expression to participate in inflammatory processes [20]. Once activated, the endothelial vascular cells began to secrete cytokines, chemokines and colony stimulating factors [20].

In the majority of patients who develop PRES, a complex underlying 'systemic process' was present as T-cell activation, inflammatory cytokine production, activation of endothelial surface antigens, endothelial antibodies, immune system antigens and VEGF elevation [4]. Cytokines (TNF-α IL-1) up-regulated endothelial surface antigens (P-selectin, E-selectin, ICAM-1, VCAM-1), and increased leukocyte adherence (trafficking) leading to microcirculatory dysfunction. Enhanced systemic endothelial activation (swelling), leukocyte trafficking, and vasoconstriction, alone or in combination, would result in brain and systemic hypoperfusion [4]. Furthermore, in our hypothesis patients with PRES may have a particular tendency to develop an overexpressed immune response associated with increased endothelial susceptibility to inflammatory stimuli.

However, PRES pathogenesis is not fully understood and the theories so far proposed don't account for all the different cases reported in literature. These previous theories give a central role to hypertension and autoregulation of blood flow in cerebral circulation. Our hypothesis, on the contrary, offers a common pathogenetic mechanism in which every PRES-related condition can be set; in this model, the activation of immune system and the consequent endothelial activation start a molecular cascade which finally causes the production of molecules, i.e. cytokines and VEGF, which alter the normal homeostasis of BBB; this alteration consists in a weakening of brain vessel tight junctions which allows fluid leakage and edema. In this scenario, hypertension would be an epiphenomenon of the underlying mechanism and not the cause and, for this reason, it can be present or not in PRES.

The exact comprehension of PRES pathogenesis is fundamental to find a targeted treatment; nowadays, the only way to contrast PRES is to treat the precipitating condition that led to syndrome development. Our hypothesis not only proposes a unifying molecular model of PRES pathogenesis, but, clarifying the complex pathway through which the syndrome develops, opens new perspectives to possible interventions. In fact, the action of the two principal molecules that drive endothelial activation and permeability, i.e. TNF-α and VEGF, respectively, could be antagonized by antibodies and receptor inhibitors yet available in clinical practice. TNF-α and VEGF, just like markers of endothelial activation e.g. ICAM-1 and VCAM-1, are not routinely determined in blood analyses and their measurement may have only an interest in research to clarify the mechanism of PRES pathogenesis in order to search for a more specific treatment. LDH, instead, could be a useful marker which can be easily and early detected in clinical routine to identify patients requiring more attention before the clinical onset of the syndrome, thus confirming the central role of endothelial instability in syndrome's pathogenesis.

Competing interests

The authors declare that they have no competing interests.

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