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NEW PROPOSAL ON THE PATHOGENESIS OF POSTERIOR REVERSIBLE ENCEPHALOPATHIC SYNDROME BASED ON DYSFUNCTIONAL PERICYTES

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ABSTRACT

Introduction: The posterior region of the brain is primarily affected by the, a reversible white matter vasogenic oedema as the hallmark of this neurological condition named as PRES or reversible encephalopathy syndrome, which is a typical endothelial dysfunction, which modify the cerebral autoregulation, cause the before mentioned reversible subcortical vasogenic oedema, leading to headaches, confusion, seizures, and visual disturbances. Whether a drug can induce PRES

The main goal of this review is to identify the novel diagnostic approaches and the most common drugs used.

Methods: from January 01, 2006, to May 31, 2025, following the PRISMA guidelines we searched the medical literature. We checked some scientific databases like PubMed Central, Scopus and Embase looking for the titles: " posterior reversible encephalopathy syndrome " OR " pathogenesis of PRESS " OR " aetiology of PRES " OR " management of PRES", OR "The role of pericytes in PRES"

Results: WE identified, 82 publications that were included in the final report. Notwithstanding, when we searched for PRES associated to Pcs dysfunction responding to drug therapy then no article was found.

Conclusions: It is the first investigation done regarding to the role of PCs in the pathogenesis of PRES. We released some hypotheses related with the above issue.

KEYWORDS: Posterior reversible encephalopathy syndrome, pathogenesis of PRES, aetiology of PRES, clinical features of PRES, pericytes.

BACKGROUND

PRES is primarily targeting the occipital lobes, typically associated reversible white matter vasogenic oedema as the hallmark of this neurological condition, characterized by endothelial dysfunction, altered cerebral autoregulation and reversible subcortical vasogenic oedema, leading to confusion, headaches, seizures, and visual disturbances. This syndrome was first described by Hinchey and collaborators [1]. From all hospital admissions, the incidence of PRES has been calculated to be around 0.01%. Still, it may not accurately reflect the fundamental values due to the number of underreported cases resulting from a lack of recognition and variable clinical features. Arterial hypertension among other conditions affecting brain autoregulation is crucial in its pathogenesis. PRES affect peoples of any age, more commonly seen in persons between the ages of twenty and fifty years. However, some children have also been reported. The comorbidity with other predisposing factors such as kidney disorders, immunological disorders, hypertension, eclampsia, and immunosuppressive therapies, among others, reflects the demographic distribution of PRES [2-5].

Apart from the affected parietal-occipital lobes, other involved cerebral regions, such as the cerebellum, brainstem, temporal and frontal lobes have been reported [6, 7].

The main aim of this investigation is to find the necessary information to answer our two research questions: 1. What is the most likely pathogenesis of PRES; 2. What is the most likely role played by pericytes in PRES?

2. MATERIALS AND METHODS

2.1. Search strategy

The search strategy included terms related to PRES and steroid medications. Publications were included in this research if they were peer-reviewed examining corticosteroids in PRES. We excluded all non-English, non-Spanish, and non-Portuguese publications, letters to the editor, editorials, or articles without appropriate primary

endpoints. All data on clinical features and demographics, imaging findings, drug therapy regimes, and prognosis were extracted. WE did not include any information on personal identification collected from the search performed. The study was done under the ethical principles established by the Declaration of Helsinki.

In this review, we selected observational studies, case reports or series. Exclusion criteria comprised articles written in languages other than English, Spanish, and Portuguese, letters to the editor, editorials, and studies which did not document the management of PRES. Two authors (Ibanez and Foyaca) independently reviewed all abstracts and titles of the selected papers using Rayyan QCRI.

All discrepancies among the investigators were discussed by the authors until reach unanimous decision. The selected full-text articles were then assessed based on the pre-established exclusion and inclusion criteria. The selected data such as year of publication, author's name, patient's clinical symptoms, sex, age, imagen findings, medical therapy, and outcomes were selected for further analysis.

We assessed the clarity of the diagnosis, various dimensions of bias, the validity of the outcomes and the precision of the reported intervention [8].

2.2. Exclusion criteria.

We applied exclusion criteria as follow: (1) investigations on animal model; (2) letter to editor, editorials, conference proceedings; (3) irrelevant clinicopathological data; (4) articles with unclear pathogenesis; (5); and inaccessibility to full text. Duplicates articles were removed.

2.3. Data extraction and quality assessment.

Using an electronic Excel database, the selected data was tabulated.

Quality and risk of bias.

Eighty-two series and case reports were selected for this study; most publications had a low-level risk of bias. Fourty-tree articles cases were rated with low risk of bias, twenty publications had a moderate risk, and nineteen publications showed a high risk.

3. RESULTS.

After removing duplicates and excluding records, a total of 1756 articles were selected. Eight hundred thirty-four selected articles were taken for assessment. Three hundred eleven studies were unavailable for evaluation. On top of that, five additional publications identified from list of references were also checked, 229 were removed lack of match with the selection criteria. Eighty-two articles were selected from these searches. Manuscripts relevant to PRES included the clinical features, investigations made, and drug therapy. We screened these papers based on their abstracts.

COMMENTS AND FINAL REMARKS

From our systematic review, we did not find any publication concerning the function played by Pcs on the pathogenesis of PRES, as it is shown in the Flow diagram of **Figure 1**

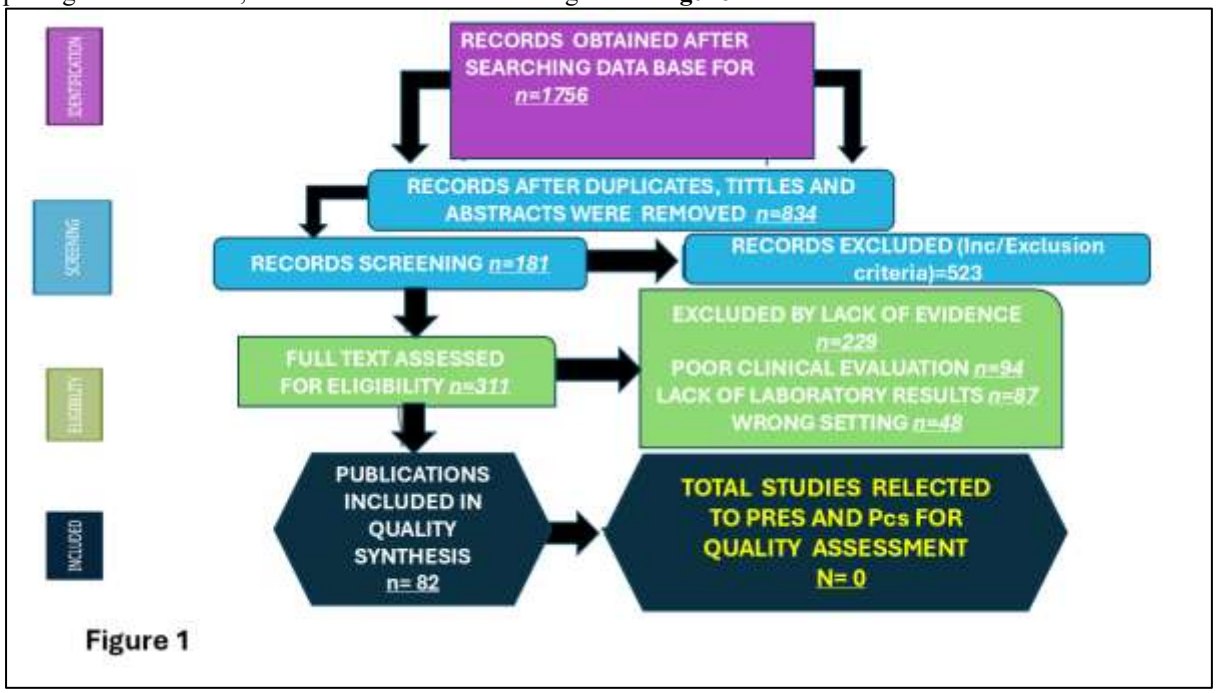

Figure 1: Following the PRISMA guidelines, this graphic shows a flow diagram of the selected publications.

Brief comments on drug therapy

From our systematic review, we determined that corticosteroids are the most administered standard treatment for PRES. We also found that steroids can be a cause of PRES in some peoples, a finding

supported by Srichawla et al. [5]. They documented that corticosteroid therapy may cause PRES by subsequent elevation of the cerebral blood flow, hypertension, and failure of cerebral autoregulation at the same time. Nevertheless, it may help in the management of PRES, leading to improved blood-brain barrier integrity, enhanced endothelial stability, and the provision of anti-inflammatory effects that may mitigate or reduce the formation of vasogenic oedema. Therefore, corticosteroid therapy may play a double role in PRES by decreasing swelling and avoiding the disruption of BBB or potentially inducing it condition through arterial hypertension.

On the other hand, it has been documented that the pathophysiology of PRES involves a critical malfunction of the endothelial cell (EC) and disruption of cerebral autoregulation, leading to vasogenic oedema [5,8]. However, the exact pathophysiological mechanism of PRES remains unknown. Nevertheless, we hypothesized that endothelial dysfunction may disrupt the BBB integrity, leading to subsequent vasogenic oedema formation, which plays a central role in this syndrome, as reported by other authors [9,10]. However, the role of pericytes in this process never been considered, as it is one of the most relevant goals of this study, which aims to answer the research question below.

Brief comments about the role of PCs on the pathogenesis of PRES.

Pericytes (Pcs), also named Rouget cells, which derived the French physiologist Charles Marie Benjamin Rouget, who described PCs in the 19th century for the first time. How PCs have different functions according to their location throughout the body [10, 11]. However, in this article, we will refer to the PCs located in the central nervous system (CNS) only. Nearly all brain's vasculature features have an extraordinary and complex capillary networks lined by pericytes (PCs). It has been well documented that PCs are multi-functional cells at the perivascular space surrounding capillary vessels (CV). The main functions of PCs are represented in **Figure 2.**

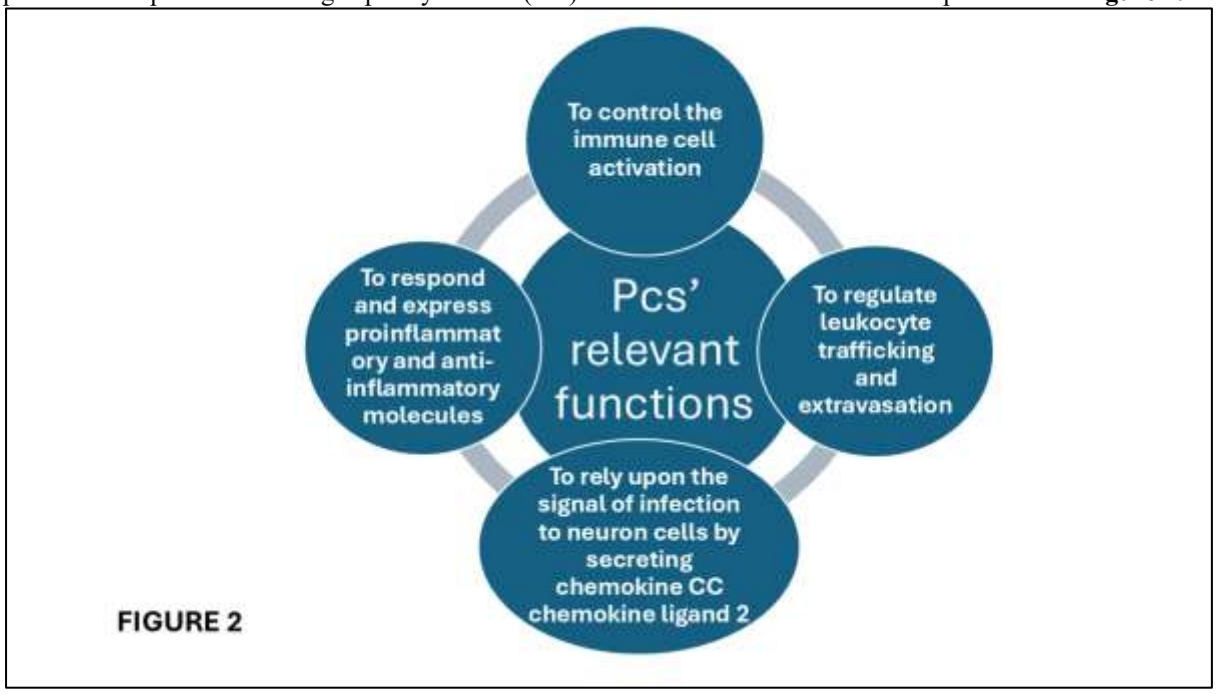

FIGURE 2: Shows graphically all functions of PCs.

As we mentioned before, the PCs have several functions, that we summarised as follows: **1**- The PCs integrate, coordinate, and modulate all signals coming from their surrounding cells to deliver the necessary responses to the brain and to support the vital activities in both sick and healthy peoples. **2-** PCs are involved in the control/modulation of angiogenesis (Ag) cerebral blood circulation, and the vascular stability of the neurovascular system. **3**- PCs also provide support to the development of BBB and its maintenance.**4-** PCs works with aquaporin 4 (AQP4), the glymphatic system (GS), meningeal lymphatic vessel (MLV), and corpora amylacea (CA) located at end plate in the feeding process of the astrocytes to clearance all metabolite waste to the lymph nodes at the cervical region from the brain supported by the CSF. **5**- PCs are involved in the recruitment of stem cell and the traffic of inflammatory cells. **6-** Finally, PCs coordinate crosstalk with other cell types, such as all kind of supporting cells and neurons, within the neurovascular unit [11]. We hypothesized that in cases with PRES, the associated BBB permeability and local reversible vasogenic oedema are strongly associated with PCs dysfunction that also causes damage of the CV, angiogenesis (Ag), regulation of the neuroinflammation (NI), impairment of the clearance of metabolites waste, damage of the capillary hemodynamic responses, and dysfunctional stem cell activity. We also believe that in PRES, there is not adequate intercommunication among the PCs and EC and by physical contact and through the CV paracrine signalling [11]. We also believe that the clinical manifestations of PRES related to vasogenic oedema, dysfunctional cerebral autoregulation and endothelial injury are due to disruption of the BBB secondary to transient PCs' disturbance. **See Figure 3.**

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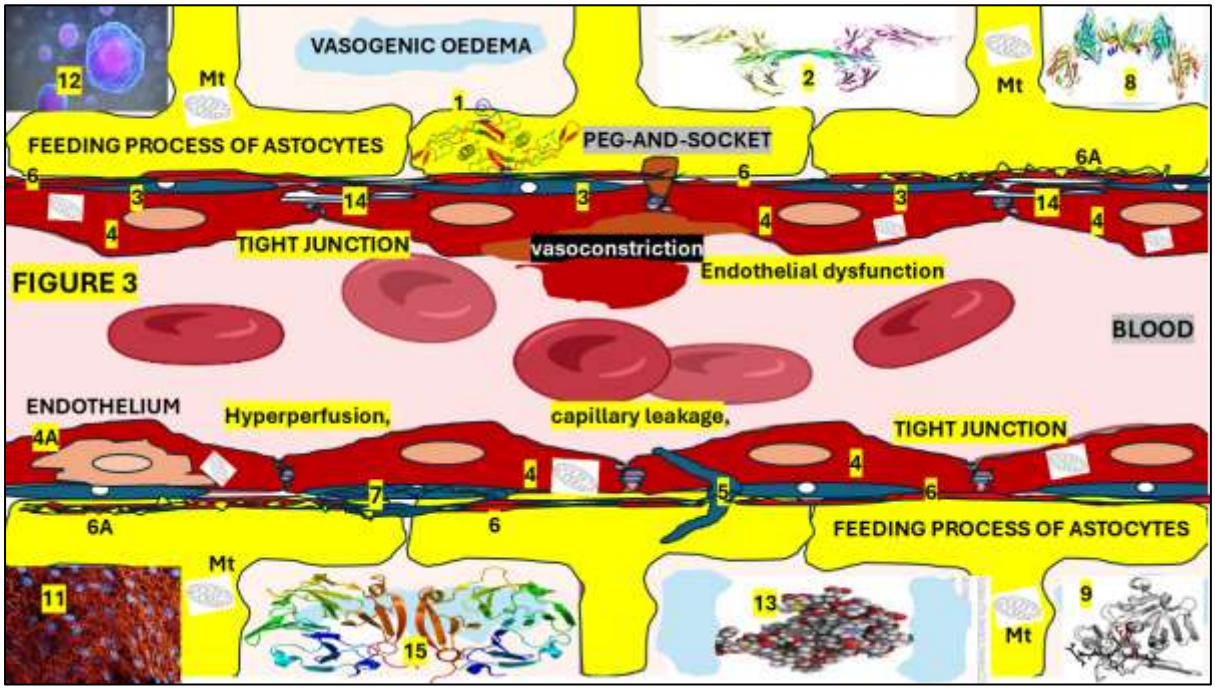

Figure 3: Shows a graphical schema of all components participating in the pathogenesis of PRES with Pcs involvement which are numbered as follow: 1- Transforming Growth Factor β 1 (TGF-β1). It is part of TGF-β cytokine family, (some proteins able to regulate cell behaviour). TGF-β1 is involved in both detrimental and beneficial processes, including bone growth, wound healing, and immune responses. 2.- Platelet-derived growth factor receptor beta. It is a protein belong to receptor tyrosine kinase family, encoded by the PDGFRB gene. PDGFRβ acts as a transmembrane protein, sending signals from the cell surface to the interior of the cell by signal transduction. It is activated when platelet derived growth factor (PDGF) binds to it, triggering a cascade of acts that modulate cell movement, growth, and survival. 3.- Pericytes processes cover between the 70 and 80% of the surface of capillary vessel and play a crucial role in the well-function of the tight junctions of endothelial cells, 4.-Tip cell (endothelial cell) moves to tubule formation managed by Tie-2/angiopoietin axis, to modulate CV neoformation, 5- detachment PCs, 6-Normal basement membrane, 6A-modified basement membrane, 7-Recruited/recovered PCs to stabilize newformed CV, 8. Vascular endothelial growth factor(VEGF) play a crucial role in stimulating BV formation (Ag). VEGF is created by several cells and interacts with endothelial cells (on specific receptors), the cells lining the BV, to promote their proliferation and migration. VEGF also participate in increasing vascular permeability and is associated with various pathologic and physiologic processes, including wound healing, development, and disease. 9-Proteases is an enzyme which breaks down peptides and proteins, 10-Mitochondrias, are membrane-bound organelles located in the cytoplasm of eukaryotic cells such as plants, animals, and fungi. They produce most of the cell's energy in the form of adenosine triphosphate (ATP), 11-Extracellular matrix (ECM) which is a three-dimensional dynamic network of macromolecules surrounding the cells delivering structural support and other essential functions for organs and tissues. the ECM also actively participate in cell growth, movement, signaling, and communication. 12- Cytokines that act as signaling molecules, primarily in the immune system, to regulate cell differentiation, growth, and activity. They are crucial for coordinating the immune response playing a role in cancer, inflammation, and other diseases, 13-Quemokine (a type of cytokine) is small proteins secreted by cells that attract primarily white blood cells, to areas of infection or inflammation. They play a vital role in the body's immunological response by guiding migration of other immune cells and leukocytes to specific locations 14- Tunnelling Nanotube (TNTs) are thin membranous between cells. They have a diameter of 50–200 nm that mediate communication among Pcs. In cases of PCs' mitochondrial (Mt) damage then healthy Mt might move to the affected site and provide the necessary energy support to the injured Pcs. 15- MMP-9, also known as matrix metalloproteinase-9. MMP-9 is a relevant enzyme working in the process of degradation of the extracellular matrix. It is involved in almost all normal physiological processes like wound healing, remodelling, and in inflammation and malignant process.

On the other hand, it is essential to highlight that the tight junction between endothelial cells of CV can facilitate those connections among the brain and the blood flow and can produce PCs' membrane invaginations, (also named as peg-and-socket contacts) and adhesion plaques, allowing PCs to transfer special contractile forces to the endothelial layer causing vascular constriction (See **Figure 3**) and CV dysfunction which can explain the presence of dysfunctional cortical neurons leading to hypersynchrony discharge and epileptic seizures apart from visual disturbance, headache and confusion among others clinical manifestations. Based on our previous investigations, we suggest that in patients presenting PRES, there is a transient alteration of the Transforming Growth Factor β 1 affecting the maturation of PCs progenitor cells and Platelet-Derived Growth Factor Receptor Beta expression which are attracted in the plexus of CV by EC expressing Platelet-Derived Growth Factor Subunit B. See

Figure 3.

We also reported that PDGF-B binds to PDGFRβ which is produced as PDGF-BB homodimers [11]. PDGF-BB may cause receptor dimerization and phosphorylation through activation of downstream signalling pathways, RasGAP, ER to modulate cell migration/proliferation, which is believed to be permanently altered in severe PRES, leading to poor outcomes. Figures 3 and 4 Represent PCs, which are the only elements located between EC and As at the NVU, prolonging their processes along capillaries, post-capillary venules and pre-capillary arterioles. Therefore, PCs are in direct contact with more than ninety percent of the total vascular length in the brain. The wall of CV has the highest Flow Resistance (FR) within the cerebrovasculature [11].

Furthermore, in cases of severe PRES, we hypothesize that PC loss it may causes a remarkable disruption of the BBB, that accumulation of amyloid-beta clearance leads passage of neurotoxic elements into the CNS, resulting in significant programmed cell death and a poor prognosis.

We previously documented that the most crucial element for brain homeostasis is the BBB, separating from the blood flow the extracellular fluid of the brain, impeding the non-selective transport of molecules into fluids from the blood circulation in the brain [11]. As shown in Figures 3 and 4, the BBB is composed of the capillary walls, which include endothelial cells and PCs attached to the basal membrane, and supported by oligodendrocytes, oligodendrocyte progenitor cells, and NG2. An intact BBB is crucial for keeping the brain homeostasis' capacity to protect the central nervous system (CNS) against pathogens and controlling the passage of essential nutrients into the brain, which are vital for proper network activity. PCs modulate the motility and cell development in central epithelial cells through the TGF-β-mediated induction of mesenchymal transition factors [11].

We hypothesized that PRES can be a transient pathological process responding to steroid therapy if
there is no permanent damage to Tunnelling Nanotubes (long intercellular channels), and their ability to transfer micronutrients and mitochondria among PCs is preserved. Taking into consideration that severe damage to the Mc and the incapacity of transferring Mc from the healthy sites to the affected regions will disturb the oxidative metabolism, affect reprogramming of differentiated cells, damage homeostasis of calcium and other functions like cell proliferation/ differentiation, signalling, and causing cell death trough PCD/RCD.

We hypothesized on the role played by the Fibroblast Growth Factor expression and Vascular Endothelial Growth Factor-A (vasogenic factors), markers for BBB damage and the endothelial barrier antigen immunoglobulin G in cases presenting with PRES. PCs' disturbances may lead to modifications in the vasculature of the brain, increasing activity of Ag markers, and BBB disruption caused by the aetiological elements responsible for PRES, as graphically represented in Figure 4.

We also hypothesized that in the case of PRES, there is a diminished immunological reaction to endothelial barrier antigen marker, prolong staining for IgG, hyperactivity of VEGF-A, VEGF2, and VEGF-A in surrounding As, and EC tube formation induced by dysfunctional PCs supported by our previous report on PCs function under different conditions [11].

We hypothesized that due to the short-term effect of eclampsia, hypertension, and the side effects of steroids and other pharmacological therapies, the process of angiogenesis (Ag) is not complete in
PRES, except in cases of a prolonged effect of these aetiological processes. Considering that Ag is a physiological process involved in the development and growth of new vessel creation, which is crucial in the healing mechanism, represented by fibrotic scar formation (FSF), we cannot rule out its presence due to endothelial dysfunction, vasogenic oedema, and loss of cerebral autoregulation. Angiogenesis (Ag) is defined as an encompasses of the development new BV from the existing vasculature in both pathological and physiological situations, and it also includes severe post-reperfusion oedema syndrome.

All regions of metabolically active nervous tissue require a healthy cardiovascular system for the adequate diffusion of oxygen and nutrients, as well as for the clearance of metabolic waste from the brain [12].

Under hypoxic/ischemic conditions caused by persistent vasogenic oedema in severe PRES, we hypothesized that PCs release VEGF, detach from the CV before translation of EC, and
that VEGF creates a potential force to guide EC, as occurs in different scenarios [13, 14].

We believe that in patients presenting PRES, the PCs are one of the first elements arriving into the affected regions in the parietal-occipital lobes and other cerebral lobes in severe PRES, contributing to PC proliferation and migration toward to the borders of the affected regions and remodelling of vasculature, followed by binding to EC secreted PDGF-BB and PDGFRβ (active on PCs), the main component of angiogenesis and PCs expression [15]. Other hypotheses about the role played by PCs in PRES also incorporate an increased activity of markers such as Ki-67, CD13, PDGFRβ and myeloid cells, as well as dendritic cells and endothelial cells in the target area. On the other hand, we considered that tyrosine kinase inhibitor blocking PDGFRβ signalling may cause PCs regression and detachment of affected CV surrounding vasogenic oedema, as has been proven under different circumstances [11]. Furthermore, PCs/Ag can control axonal regeneration/ growth along the vasogenic region, facilitating growth-permissive substrates through vascular bridging (pathological scenarios only) [15].

We believe in the ability of PCs/PRES to accommodate to the surrounding vasogenic oedema by liberating VEGF triggered by ischemia or hypoxia in respond to vasogenic oedema, direct compression of the surrounding tissue, PCs' CV vasoconstriction and their ability to intensify the activity of growth factors, (including cytokines/chemokines), as can be seen under different situations where PCs release a considerable amount of Chemokine Ligand 1 and Interleukin-6

(CXCL1) as we before cited [16]. Nevertheless, this report supports our hypothesis regarding the upregulation of inflammatory receptors in response to the activation of the proinflammatory mechanism following local ischemia and vasogenic oedema [17]. We hypothesized that the integrity of the BBB in patients with severe PRES is affected by PCs detachment, supporting the transference of harmful elements like fibrin and fibrinogen (See Figure 4) from capillary vessels into the brain, worsening NI and increasing Mg polarization; it is event contribute to the therapy with steroids medication and other therapies with the capacity to produce interleukin 33 and other trophic factors for a best anti-inflammatory results [18-20].

We hypothesized that the PCs in PRES have four remarkable functions: 1. To control immune cells expression (macrophages, B cells and T cells); 2. Regulation of extravasation and leukocyte trafficking; 3. Responding to and expressing anti-inflammatory and proinflammatory elements. In cases presenting severe PRES, we hypothesized that relying upon the warning of NC inflammation and glial cells by producing chemokine CC chemokine ligand 2, it can be the primary sensor of the global inflammatory process, as has been published by Duan et al. in cases with other different scenarios [21].

In cases with PRES, we hypothesized that PCs leukocyte extravasation (post-capillary veins) is elevated under the influence of interaction with capillary Pcs and the support of leukocyte migration, that occurs following inflammatory stimulation, causing crawling of an important group of sub-endothelial cells along PCs mechanism and transendothelial movements of white cells into the interstitial region. It can move across the gaps between nearest PCs, which lymphocytic expression supports- associated antigen-1, PCs- derived intercellular adhesion molecule-1, macrophage-1 antigen, and its white cells integrin ligands, which has been published by some investigators [22].

We also hypothesized that CCL2 mediates PC-monocyte interaction, macrophage migration-inhibitory factor, and neutrophil migration involving interleukin-8 (IL-8).

In previous publications, we documented the function of pro-inflammatory elements such as Interleukin 1 Beta and TNFα [23]. We speculate that PRES/Pcs exposure to proinflammatory cytokines facilitates the release of Matrix Metalloproteinase 9 plus other inflammatory molecules exacerbate BBB disruption. Considering our previous studies on cytokines (IL-1β, TNF-α, IFN-γ), an

interleukin-6 cytokine storm has been shown to induce proinflammatory states in EC and activated As/Mg, causing neuronal death. Therefore, we speculate that the something similar happen when PCs are exposed to cytokines, as has was reported by other investigators [24].

Beside proinflammatory elements produced by PCs, they can secrete anti-inflammatory elements, like C-X3-C motif Chemokine Ligand 1 and Interleukin 33, which promote an anti-inflammatory microglial phenotype, providing some benefits over the damage caused by prolonged vasogenic oedema and endothelial dysfunction [11].

We believe that patients with PRES have an interconnection between the Pcs and the EC, facilitated by the sharing of basement membrane through specific kind of integrin molecules, as observed in different scenarios [11].

Nonetheless, the relationship between PCs and EC is imperative to allow neoformation of working BBB, vascular stability, and Ag which supports the mechanism for reversing this process. Notwithstanding, if the basement membrane is not working for any reason, socket and peg contacts cause direct intercontact supported by connexin N-cadherin and 43. **See Figure 4.**

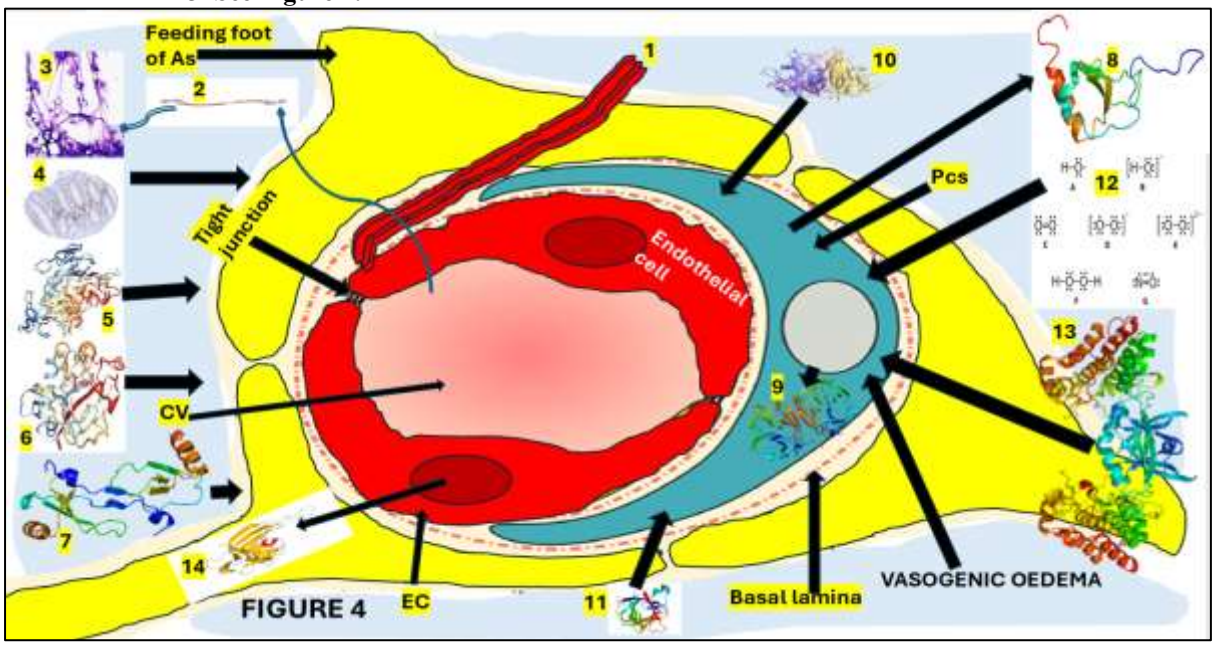

Figure 4: Show other elements involve in the pathogenesis of PRES with the participation of Pcs and dysfunctional BBB. 1Sproung angiogenesis is a process able to produce and grow new capillaries, small blood vessels, from pre-existing ones. 2-Fibrinogen is a protein involved in coagulation cascade which is synthesized

by the liver and released into the blood flow, 3-Fibrin strands (also called Factor Ia) is a fibrous, non-globular protein involved in the clotting of blood. It is formed by the action of the protease thrombin on fibrinogen, which causes it to polymerize ken, platelets are reacted, forming a platelet plug. It enters to the brain across disrupted BBB, 4-Periosn is a matricellular protein, that plays a vital role in inflammation, malignant tumor development and remodelling, 5- Angiopoien-1 (ANGPT1) plays a crucial role in maintenance and vascular development. 6-Angiopoien-2 (ANGPT2) plays an important role on vascular development and remodelling, acting as an antagonist to ANGPT1differently contribute to angiogenesis. 7-CCL2 chemokine is a protein that plays a crucial role in reacting immune cells, mainly monocytes, to the injury, area, site of the inflammation, and even to the malignant mass, 8-CX3CL1 also named as Fractalkine, is a transmembrane chemokine that work as a signaling molecule between microglia and neurons in the CNS. It also expresses immunological elements working with proinflammatory or anti-inflammatory response according to neuroimmnological conditions, 9-MMP9 produced by PCs responding to TNF-α. 10- IL-1β, 11-vasogenic oedema, 12-Reactive Oxygen Species. 13-TEK receptor, also named as TIE-2 or angiopoien-1 receptor. TEK is a tyrosine kinase receptor primarily activated in EC and it plays a vital role in blood vessel development, blood vessel maintenance and endothelial cell survival. TEK is activated by angiopoietin ligands, which are crucial for vascular homeostasis and Ag. 14- IL-33, Interleukin-33 is a protein which plays and important role in regulating NI and type 2 immune responses. IL-33 is produced by cells, stored in their nuclei, and released upon injury cellular or damage and work as an alarmin, alerting the immune system via its receptor ST2. particularly on T helper 2 cells, group 2 innate lymphoid cells (ILC2s), mast cells, and regulatory T cells. IL-33's involvement extends to various physiological processes, including cell proliferation, autophagy, and energy metabolism.

As a result, the healing process will be longer than usual, and a worse outcome is likely to occur [11].

Despite the roles played by PDGFB, VEGF, TGFβ, Notch, PDGFRβ-positive PCs, and S1P/S1PR1 signalling events in PCs and EC, the mechanism by which they modulate perilesional Ag in PRES remains unknown. Therefore, the forthcoming investigation might bring more clarity to this interrogation.

Based on what happens in other scenarios [25], we hypothesised that patients presenting PRESS can elaborate VEGF through a reciprocal interaction, and PCs-derived VEGF promotes cell recovering, sprouting of EC, proliferation/migration/stabilisation. Periostin (PT), (matricellular protein), is activated along with fibrocetin and laminin γ2 at basal levels, it participates in the process of wound healing and tissue regeneration,

particularly in the context of prolonged vasogenic oedema, and its ability to modulate differentiation, contraction, expression and activation of fibroblasts in various regions of the body. That's why it's include it in our hypothesis. **See Figure 4.**

AGP-1 plays a vital role in vascular development and Ag, which is considered in the pathophysiology of PRES-related PCs. A glycoprotein secretes this protein and activates the receptor by inducing its tyrosine phosphorylation. While AGP-1 mediates interactions between surrounding Matrix, EC and mesenchyme leading to complete blockage of EC permeability. ANG1 exhibits strong vascular protective action, characterized by plasma leakage suppression, vascular inflammation inhibition, and endothelial cell (EC) apoptosis prevention. Crosstalk between PCs and EC is also mediated by circular RNA [25]. See Figure 4.

In patients presenting PRES in ischemic /hypoxic scenario due to prolonged vasogenic oedema or PCs constriction, we think that the crosstalk/astrocyte is strongly related to BBB maintenance/ repairing with dysfunctional /loss of corpus amylacea/AQP4 and clearance failure from the damaged feeding food of As, poor modulation of cyclophilin A control (PC signalling) and PCs' migration plus BBB integrity which was previously reported under different circumstances [26, 27]. Notwithstanding, we hypothesized that vascular permeability factors such as CCL2 (secreted by PCs) in respond to ischemic/NI/hypoxia express Mg cells in perilesional oedema modulating the process of CV retraction of PCs and recruitment of monocyte which has been documented in some patients presenting malignant tumours [28], which mechanism of vasogenic oedema can be applied in patients presenting PRESS worsening its outcome due to cell's death mainly in cases presenting severe PRES or in situations where diagnosis is too delayed. We hypothesized about the role played by other anti-inflammatory cells secreted by PCs, which are also increased, like CX3CL1, which combines chemotactic for T cells and adhesion molecule, Interleukin 33 and monocytes. See **Figure 4;** it is a protein with the ability to release IL-4 , T helper-2, and a ligand for ST2, highly expressed in Th2 cells, mast cells, group 2 innate lymphocytes, dendritic cell, epithelial cells, osteoblast, fibroblasts, EC, and macrophages. In summary, fatal outcome in cases with PRES severe presentation may be due a failure of proper secretion of those anti-inflammatory Mg phenotypes.

Undoubtedly, the As has an essential role in the pathogenic mechanism of PRES, but details related to intrinsic mechanisms remain unknown. However, we believe that increased expression/ activation/signalling of As metabotropic Glutamate Receptors has a remarkably participation in the pathogenic mechanism of PRES. Our hypothesis is based on the findings reported by David et al. [29], although these findings were obtained under entirely different circumstances. We suspect that conducting large clinical trials to

explore new approaches to anti-seizure therapy may not be justified. Despite the close relationship between PCs and Perivascular Macrophages (PVMs) in the brain and their shared functions in

regulating cerebral vascular (CV) permeability and phagocytosis, we unfortunately lack sufficient information to build a credible hypothesis on the mechanism underlying this interaction in PRES.

Another component of this hypothesis is the participation of the Matrix Metallopeptidase 2 (MMP-2) in the PRES mechanism, which plays a crucial role in Ag, generating antiangiogenic factors, facilitating EC migration and mobilization of VEGF, managing lymph angiogenesis, using the MLV, that is the principal component of removing out brain death cell and metabolite waste from through the glymphatic system [11]. **See Figure 4**.
Currently, we did not get enough information to release new hypotheses about the process of its expression by extracellular proteinases and its capacity to decompose collagen located in the basement membrane of the CV in PRES, nor on how the scavenger receptors (CD36, CD47, and CD68) contribute to the modulation of this process. However, we release some hypotheses about the role of PCs in the pathogenic mechanism of PRES. Notwithstanding, other well-planned investigations must be done to support or reject our hypotheses. It is the first systematic review to examine the role of PCs in the mechanism of PRES production.

Limitations

We afford some limitations for this systematic review that must be acknowledged. The main limitations were related to most of the data obtained from case series and case reports, limiting the generalizability of the findings and introduce bias. Many publications did not report control groups. This issue presented a significant challenge for establishing causality.
We also found significant variability in the description of the pathogenesis of PRES. Therefore, this heterogeneity complicates the drawing of definitive conclusions based on the synthesis of data.
Underlying medical conditions and the concomitant use of multiple drug therapies were considered confounding variables, which interfered with the interpretation of the findings.
We note that the clinical features of the patients, underlying medical disorders, and drug therapies reported in case report cannot be apply to most clinical settings. The diversity of drug dosages, drug therapy protocols, demographics surely influences the risk of PRES development.
We believe that in most of the case reports, the duration of follow-up was not sufficient enough to capture the long-term outcomes fully to get a proper idea about the prognosis of drug therapy-induced PRES.
We also considered that retrospective data collection or inadequate documentation might affect the reliability of the findings of this investigation due to reporting bias.
Nevertheless, to elucidate the relationship between drug therapy and PRES properly, well-designed randomised controlled trials and prospective cohort studies are necessary. A better understanding of these mechanisms at the molecular level could shed more light on the development of targeted drug therapies. Long-term follow-up investigations are necessary to determine the best practices for managing chronic sequela and avoiding recurrence.
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DATA AVAILABILITY STATEMENT: The corresponding author will make all data supporting this manuscript's results available by reasonable request.

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