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Arginine Vasopressin and Posterior Reversible Encephalopathy Syndrome Pathophysiology: the Missing Link?

Bérenger Largeau[1] · Olivier Le Tilly[1] · Bénédicte Sautenet[2] · Charlotte Salmon Gandonnière[3] · Chantal Barin-Le Guellec[4] · Stephan Ehrmann[5]

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiological entity characterized by a typical brain edema. Its pathogenesis is still debated through hypoperfusion and hyperperfusion theories, which have many limitations. As PRES occurs almost exclusively in clinical situations with arginine vasopressin (AVP) hypersecretion, such as eclampsia and sepsis, we hypothesize that AVP plays a central pathophysiologic role. In this review, we discuss the genesis of PRES and its symptoms through this novel approach. We theorize that AVP axis stimulation precipitates PRES development through an increase in AVP secretion or AVP receptor density. Activation of vasopressin V_{1a} receptors leads to cerebral vasoconstriction, causing endothelial dysfunction and cerebral ischemia. This promotes cytotoxic edema through hydromineral transglial flux dysfunction and may increase endothelial permeability, leading to subsequent vasogenic brain edema. If our hypothesis is confirmed, it opens new perspectives for better patient monitoring and therapies targeting the AVP axis in PRES.

Keywords Leukoencephalopathy syndrome · Hypertensive encephalopathy · Antidiuretic hormone · Neurological adverse drug reactions · Blood-brain barrier

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinical and radiological entity where a bilateral white matter edema, occurring predominantly in the occipital and posterior parietal lobes, is associated with several neurologic symptoms [1]. Gao et al. [2] defined PRES based on the following criteria: (1) presentation with acute clinical symptoms; (2) presence of known risk factors (e.g., hypertension, history of antineoplastic therapy); (3) distributions of T2-weighted imaging or T2-fluid attenuated inversion recovery hyperintensities compatible with typical PRES imaging patterns (i.e., cortical-subcortical parietal-occipital-posterior frontal edema); (4) clinical and imaging abnormalities mostly or completely reversible; and (5) other possible causes of encephalopathy or vasogenic edema (e.g., reversible cerebral vasoconstriction syndrome, posterior circulation stroke) are ruled out.

Symptoms in PRES include hypertension (75–80%), encephalopathy (50–80%), headache (50%), visual disturbance (33%), focal neurological deficits (10–15%), seizures (60–75%), and status epilepticus (5–15%) [3]. Impaired renal function is highly prevalent during PRES: it may be present in up to 55% of all patients with PRES [3], and more than half of such patients have chronic hypertension [4]. PRES is generally considered to be a reversible entity both radiologically and clinically, although uncommonly cytotoxic edema, intracranial hemorrhage, or brain infarction may lead to long-term sequelae [2].

✉ Bérenger Largeau
berenger.largeau@etu.univ-tours.fr

[1] CHRU de Tours, Laboratoire de Biochimie et Biologie Moléculaire, Tours, France

[2] Université de Tours, Université de Nantes, INSERM, Methods in patients-centered outcomes and health research (SPHERE) - UMR 1246, CHRU de Tours, Service de Néphrologie-Hypertension artérielle, Dialyses et Transplantation Rénale, Tours, France

[3] CHRU de Tours, Service de Médecine Intensive Réanimation, Tours, France

[4] Université de Tours, Université de Limoges, INSERM, Individual profiling and prevention of risks with immunosuppressive therapies and transplantation (IPPRITT) - UMR 1248, CHRU de Tours, Laboratoire de Biochimie et Biologie Moléculaire, Tours, France

[5] Université de Tours, INSERM, Centre d'étude des pathologies respiratoires (CEPR) - UMR 1100, CHRU de Tours, Service de Médecine Intensive Réanimation, CIC 1415, réseau CRICS-TRIGGERSEP, Tours, France

The estimated incidence is about 0.4% in a pediatric intensive care unit (ICU), 0.69% in systemic lupus erythematosus (SLE) patients, and varies from 2.7 to 25% in recipients of allogeneic bone marrow transplants. However, as the scientific literature on PRES is almost exclusively represented by case series or many case reports, and since no comprehensive prospective study has evaluated PRES incidence based on MRI diagnosis, its epidemiology is unknown [3].

There is currently no specific treatment for PRES, but the disorder is usually reversible when the causal factor is controlled. Seizures and high blood pressure are treated with antiepileptic and antihypertensive agents respectively, but no studies are available to guide the prescription of specific pharmacological classes [3].

Given the great diversity of factors involved in PRES occurrence and of non-consensual pathophysiological mechanism, research in this area is not extensively developed. In an attempt to move forward, we extensively reviewed the literature regarding a plausible link between arginine vasopressin (AVP) and PRES, as we consider that it represents a new perspective, not only to better understand PRES occurrence but also to consider new therapeutic approaches.

Circumstances of PRES Occurrence

PRES etiologies can be schematically dichotomized into iatrogenic PRES and PRES-associated medical conditions.

Almost 100% of eclamptic patients have PRES [5], leading some authors to suggest that eclampsia represents an obstetric form of PRES. It also occurs in various conditions characterized by an excessive inflammatory response such as infection, sepsis, shock, and autoimmune disorders (e.g., vasculitis, SLE) [3]. Besides kidney transplant recipients who simultaneously combine several risk factors (i.e., calcineurin inhibitors (CNI), steroids, and immunologic conflicts), various kidney diseases may predispose to the development of PRES (Table 1).

Malignancies, including both hematologic and solid tumors, have been associated with PRES. In a retrospective cohort of 99 cases of PRES, 59% of patients had active cancer and 42% were under antineoplastic therapy [33]. In a review of 70 cases, cytotoxic-induced PRES was observed with platinum salts, anthracyclines, vinca alkaloids, nitrogen mustard, methotrexate, and 5-fluorouracil. The use of cytotoxics in combination represents a high-risk situation, as it was present in 74% of cases [22].

Drug-causality assessment in drug-induced PRES is difficult due to the fact that (1) the underlying diseases are also strongly linked to PRES (e.g., transplantation, active cancers, autoimmune disorders); (2) various drugs, often used in combination, can cause PRES (e.g., CNI, corticosteroids, mycophenolate mofetil) [34]; (3) delays of occurrence are extremely variable (e.g., usually in the first month after drug initiation but ranging from 24 h to 5 years in CNI-associated PRES, for example [34]); and (4) incriminated drugs can be reintroduced without iterative PRES recurrence [24].

Pathophysiology: Current Hypotheses

The pathogenesis of PRES has historically been dichotomized into two theories: the hyperperfusion hypothesis and the hypoperfusion/endothelial one [35]. According to the first theory, severe hypertension overcomes cerebrovascular autoregulation leading to increased capillary hydrostatic pressure, vasodilation, and disruption of the blood-brain barrier (BBB), resulting in interstitial extravasation of plasma and vasogenic cerebral edema. According to the hypoperfusion theory, endothelial dysfunction causes resultant hypoperfusion, ischaemia and subsequent edema. This theory of hypoperfusion is itself divided into three theories according to the nature of the initiating event (i.e., cytotoxics, immunogenic and neuropeptide). In cytotoxics theory, endotoxins or antineoplastic/immunosuppressive agents induce endothelial injury, mediated by release of chemokines and immune activation, leading to vasospasm, hypoperfusion and vasogenic oedema [3]. Then, the immunogenic theory has also been proposed, wherein immune system activation and endothelium dysfunction lead to vasogenic edema. The neuropeptide theory, very similar to the immunogenic one, hypothesizes that the trigger is the release of vasoconstrictors such as prostacyclin, endothelin-1, and thromboxane A_2, leading to vasospasm, ischemia and subsequent vasogenic cerebral edema (Table 2) [2]. Cerebral edema in PRES is a time-dependent continuum and usually has both vasogenic and cytotoxic components [36].

Hypersecretion of AVP as a Plausible Trigger for PRES

A recent observation illustrates an alternative pathophysiological approach of PRES. An 11-year-old girl with medulloblastoma was admitted into our institution and diagnosed with PRES following chemotherapy. She concomitantly presented a syndrome of inappropriate antidiuretic hormone secretion (SIADH). An analysis of the drugs taken showed that the anticancer agents she received (cisplatin, vincristine) were known to induce both PRES and SIADH. This case led us to thoroughly review the literature to analyze in depth a possible link between arginine vasopressin (AVP) hypersecretion and PRES. It appears that hyperstimulation of AVP axis indeed occurs in most of PRES etiologies. Therefore, this paper reviews these various conditions, especially in drug-induced PRES, and explores a potential contributory role of AVP as a trigger for PRES development and subsequent PRES symptoms.

Table 1 Circumstances of PRES occurrence

Etiologies	Main features	Ref.
Medical conditions associated with PRES		
Eclampsia	- Almost 100% of eclamptic patients had PRES	[5]
Inflammatory disorders	- PRES occurred in association with infection, sepsis or shock in 25/106 patients (23.6%)	[6]
	- Nearly half of patients with PRES have pre-existing autoimmune disease (e.g., vasculitis, SLE)	[3]
Kidney diseases	- Impaired renal function occurs in 55% of all patients with PRES	[3]
	- PRES has been associated with glomerulonephritis, ADPKD, ESRD, and dialysis	[7, 8]
Hypertension	- Acute hypertension occurs in 75–80% of PRES patients	[3]
	- More than 50% of PRES patients have chronic hypertension	[4]
Hyponatremia	- PRES due to severe hyponatremia and SIADH has been largely reported	[9–20]
Drug-induced PRES		
CNI	- Incidence of PRES in SOT varies between 0.4 and 0.6%	[3]
	- The average of time of PRES occurence varies according to the transplanted organ (e.g., liver transplantation 31 days, kidney transplantation 53 months)	[21]
Anticancer therapy		
Non-targeted	- Cytotoxics most represented include platinum salt, anthracycline, vinca alkaloids, nitrogen mustard, methotrexate, and 5-fluorouracil	[22]
	- The use of cytotoxics in combination increases the risk of PRES occurrence	
Targeted	- In bevacizumab-associated PRES, 57.7% of patients had a history of hypertension but all were hypertensive at the onset of PRES and 40% exhibited proteinuria	[23]
	- PRES has been associated with both antiangiogenic and non-antiangiogenic TKI	[24]
Corticosteroids	- PRES occurred in 44.4% of patients exposed to corticosteroids	[25]
	- Corticosteroids are considered as a treatment and as a precipitating factor of PRES	
Lithium	- The onset of PRES occurred between 3 and 10 days after lithium withdrawal	[26, 27]
Drug-abused	- The occurrence of PRES in alcohol withdrawal syndrome ranges from 3 to 8 days	[28–30]
	- PRES has been associated with cocaine/amphetamine use	[21, 28, 31, 32]

ADPKD, autosomal-dominant polycystic kidney disease; *CNI*, calcineurin inhibitors; *ESRD*, end-stage renal disease; *PRES*, posterior reversible encephalopathy syndrome; *SIADH*, syndrome of inappropriate antidiuretic hormone secretion; *SLE*, systemic lupus erythematosus; *TKI*, tyrosine kinase inhibitors; *SOT*, solid organ transplantation

Arginine Vasopressin

AVP, which is also known as the antidiuretic hormone (ADH), is a nonapeptide, mostly synthesized in the supraoptic nucleus and paraventricular nucleus of the hypothalamus, wherefrom it acts both as a hormone and a neurotransmitter. Copeptin, the C-terminal segment of the AVP prohormone, is largely used in vivo to monitor AVP variation. Indeed, copeptin is a more stable peptide derived from the same precursor molecule and released in an equimolar ratio to AVP [45].

AVP is involved in the regulation of renal water reabsorption, body fluid osmolality, blood pressure, cell contraction and proliferation, angiogenesis, adrenocorticotrophic hormone (ACTH) secretion, and corticotrophin releasing hormone (CRH) potentiation. AVP effects are mediated by the stimulation of specific receptors classified into V_{1a} vascular ($V_{1a}R$), V_{1b} pituitary ($V_{1b}R$) and V_2 renal (V_2R) [46]. $V_{1a}R$ is the main AVP receptor subtype in the brain and has a major role in modulating autonomic control of blood pressure, contributing to the setting of sympathetic outflow and baroreflex function. In the periphery, the activation of $V_{1a}R$ in blood vessels, the adrenal gland and kidneys induces vasoconstriction, platelet aggregation, secretion of aldosterone, and glucocorticoids and renin production. $V_{1b}R$ and CRH mediate secretion of ACTH and catecholamines from the pituitary and adrenal glands respectively [46]. V_2R are more densely

Table 2 Summary of the four pathogenesis theories of PRES

	Hyperperfusion theory	Hypoperfusion theory: the cytotoxics hypothesis	Hypoperfusion theory: Immunogenic and neuropeptide hypotheses
Location of CE [37]	- Often posterior brain (less sympathetic innervation), readily more diffuse	- Any part of the brain, often in watershed areas	- Any part of the brain, often in watershed areas
pathomechanism of CE	**MAP > 160 mmHg** → cerebrovascular autoregulation breakdown → increased capillary hydrostatic pressure →vasodilatation → extravasation of plasma proteins → **vasogenic CE**	Endogenous/exogenous toxins → ET-1, NO, ROS → **endothelial injury** → vasospasm/vasoconstriction → cerebral hypoperfusion → **vasogenic CE**	- **T-cell activation** → cytokine release → leukocyte adhesion and activation → VEGF up-regulation → weakening tight junction of the BBB → **vasogenic CE** - **Neuropeptides release** (ET-1, TxA2, prostacyclin) → vasospasm → **vasogenic CE**
Arguments [3, 35]	- High HTN prevalence (75-80%) - HTN severity (e.g., MAP = 200 mmHg [38]) - Direct evidence of hyperperfusion (SPECT, MRI)	- Direct evidence of vasoconstriction and hypoperfusion - Direct evidence of vasospasm on angiography - PRES occurred in normo- or hypotensive patients - Recovery with nimodipine [39, 40]	- Cytokine levels (IL-6 & IL-10) statistically greater in SLE with PRES [41] - Endothelial activation, T-cell trafficking and VEGF expression brain biopsies proven
Aetiologies explained	Severe acute HTN, eclampsia	Eclampsia, infection/sepsis, autoimmune disorders, hypomagnesemia, anti-VEGF therapy, CNI, ESRD	Infection/sepsis, anticancer drugs, autoimmune disorders, CNI
Potential biomarkers [42–44]	- Serum albumin offers conflicting results to discriminate CE type (vasogenic vs cytotoxic)	- LDH level correlates with the extent of vasogenic CE in PRES	
Limitations [3, 35)	- 15-20% of patients are normotensive/hypotensive - Less than 50% have MAP > 160 mmHg - No correlation or negative correlation between severity of HTN and severity of CE - Shock, autoimmune disorders, non-antiangiogenic TKI, corticosteroids-induced PRES, kidney diseases	- High HTN prevalence (75-80%): explained by Cushing reflex due intracranial HTN? Or as a consequence of primary endothelial dysfunction? - Most patients with PRES do not have demonstrable vascular narrowing imaging - PRES associated with alcohol and lithium withdrawal	- Correlation between vasculopathy and ischemia, suggesting a causal relationship between cytotoxic CE and larger areas of vasogenic CE [36] - Anti-VEGF therapy, PRES associated with alcohol and lithium withdrawal, kidney diseases

BBB blood-brain barrier, *CE* cerebral oedema, *CNI* calcineurin inhibitors, *ESRD* end-stage renal disease, *ET-1* Endothelin-1, *HTN* hypertension, *IL-* interleukin-, *LDH* lactate dehydrogenase, *MAP* mean arterial pressure, *MRI* magnetic resonance imaging, *NO* nitric oxide, *ROS* reactive oxygen species, *SLE* systemic lupus erythematosus, *SPECT* Single Photon Emission Tomography, *TKI* tyrosine kinase inhibitors, *TxA2* thromboxane A2, *VEGF* vascular endothelial growth factor

expressed in the renal distal tubules and collecting ducts where their stimulation induces water retention [46], and to a lesser extent in the brain [47, 48]. AVP also interacts with the immune system. Firstly, AVP appears to play a role in regulating lymphocyte homeostasis and self-tolerance [49, 50]; secondly, in inflammatory states (e.g., autoimmune disorders, sepsis) secretion of interleukin-6 (IL-6), induces AVP release [51, 52].

The vasopressin neuronal activity is regulated by many different neuropeptides/neuromodulators, such as apelin, brain-derived neurotrophic factor and humoral factors such as hyper-osmolality and angiotensin II [53].

AVP and Cerebral Edema

Cerebral edema occurs in PRES and in various other conditions, including stroke, traumatic brain injury (TBI), acute liver failure, and acute hyponatremia [54, 55]. Formation of cerebral edema is a highly dynamic process that evolves in stages, characterized by distinct morphological and molecular changes.

The involvement of AVP in the main etiologies of cerebral edema is established (Table 3). Although severe and rapid onset hyponatremia may cause brain edema, the pathogenesis of AVP in brain edema development can be independent of its action lowering serum sodium concentration through tubular water retention.

AVP hypersecretion can trigger cerebral edema formation through its action on regulation of hydromineral balance across cell membranes and ion transport across the BBB. Indeed, AVP increases the activity of sodium–proton exchangers (NHE) and Na^+-K^+-Cl^- cotransporters (NKCC) and can promote aquaporin-4 (AQP-4) upregulation in astrocytes, which is associated with increased sodium, chloride and water glial influx, and subsequent astrocyte swelling and BBB damage [57]. Interestingly, AQP-4 channelopathy appears to be involved in the pathogenesis of PRES [61].

AVP can also promote central angiogenesis through increased VEGF secretion induced by hypoxia resulting from the constriction of arterioles through $V_{1a}R$ stimulation [62, 63]. This triggers decreased expression of tight junction proteins, uncoupling of inter-endothelial tight junctions, and increased hydraulic permeability of vessels, and promotes cerebral edema formation [54]. However, like many mechanisms that produce cerebral edema, VEGF signaling is not purely maladaptive, but rather related to angiogenesis with an imbalance of anti- and proangiogenic factors [54] induced by AVP.

Other Clinical Manifestations of AVP over-Secretion

Due to its large spectrum of action, hypersecretion of AVP can produce various clinical manifestations, including renal dysfunction/proteinuria [64, 65] and hypertension [66]. The main clinical situations where AVP hypersecretion is systematically documented include SIADH and autosomal-dominant polycystic kidney disease (ADPKD). In SIADH, the levels of AVP are not sufficient to induce AVP-related symptoms. Conversely, in addition to its role in cyst growth, oversecretion of AVP is directly involved in hypertension and proteinuria of ADPKD patients through $V_{1a}R$ and V_2R stimulation, respectively [64]. Interestingly, hypertension and renal impairment are highly prevalent in PRES (Table 1).

Evidences of AVP Axis Hyperstimulation in Comorbid Conditions of PRES

Considering the fact that experimental data in PRES are almost non-existent, our review is based on a body of clinical and pharmacological observations. A key role for AVP is supported by the fact that hyperstimulation of the AVP axis occurs in

Table 3 AVP in pathophysiology of cerebral edema

CE etiology	Findings	Ref.
Stroke	- Plasma AVP levels were statistically higher in stroke patients than in control subjects	[56]
	- Plasma AVP levels correlated with the severity score of the neurologic deficit and the mean size of the lesion	
TBI	- AVP levels were independent of plasma osmolality and MAP - Increased AVP levels in multiple brain regions and in the cerebrospinal fluid	[57–59]
	- Astrocytic $V_{1a}R$ expression gradually increased in the traumatized parenchyma after TBI in rats	
	- Central inhibition of V_1R reduces brain edema formation, secondary brain damage, and neurological dysfunction in a time-dependent manner	
ALF	- Treatment with alpha-1 antichymotrypsin and AVP induce AQP-4 overexpression and astrocyte injury	[60]

AQP-4, aquaporin 4; *ALF*, acute live failure; *AVP*, arginine vasopressin; *CE*, cerebral edema; *MAP*, mean arterial pressure; *TBI*, traumatic brain injury; $V_{1a}R$, vasopressin V_{1a} receptor

most comorbid conditions associated with PRES. Stimulation of the AVP axis may arise from various mechanisms including the disease itself (e.g., eclampsia, inflammatory disorders), drugs stimulating AVP release (e.g., anticancer therapy), drugs inducing AVP receptors upregulation (e.g., CNI), or interruption of drugs inhibiting the AVP axis (e.g., corticosteroid/

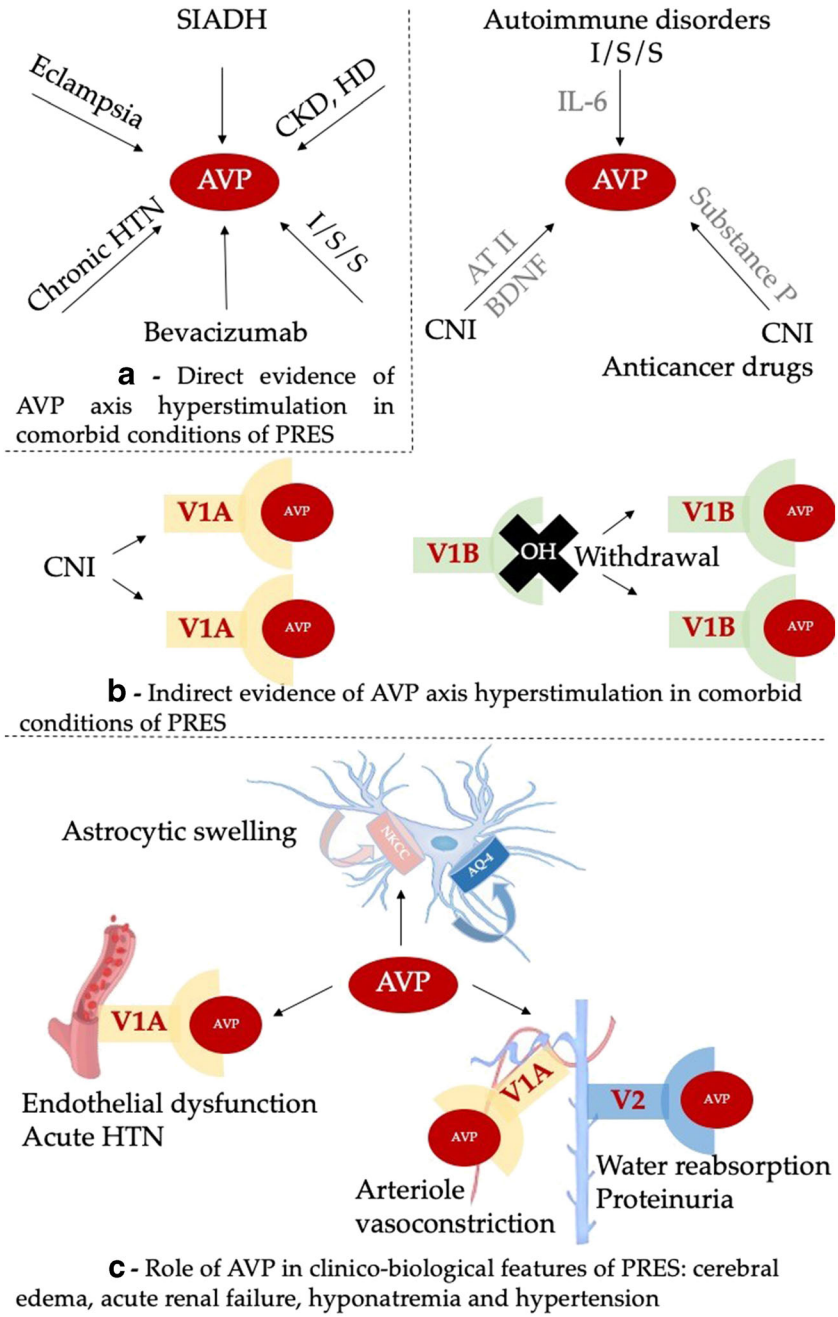

Fig. 1 A - Direct evidence of AVP axis hyperstimulation in comorbid conditions of PRES. Direct evidence refers to clinical situations where high copeptin/AVP levels are documented. B - Indirect evidence of AVP axis hyperstimulation in comorbid conditions of PRES. Indirect evidence refers to clinical situations where (i) the increase of mediators of AVP release is documented; (ii) drugs induce overexpression of AVP receptors; and (iii) there is interruption of drugs inhibiting the AVP axis. C - Role of AVP in clinico-biological features of PRES: cerebral edema, acute renal failure, hyponatremia and hypertension. Cerebral edema formation is mainly explained by the NKCC and AQP-4 dysfunction induced by AVP. Kidney injury, as a symptom of PRES, is explained by both proteinuria through V_2R stimulation and arteriole vasoconstriction due to $V_{1a}R$ activation. Hyponatremia is related to AVP effects on water reabsorption through renal V_2R. Acute hypertension, as a symptom of PRES, is explained by both endothelial dysfunction through $V_{1a}R$ stimulation and the increase of vascular tone and fluid overload. AVP, arginine vasopressin; AT II, angiotensin II; BDNF, brain-derived neurotrophic factor; CNI, calcineurin inhibitors; CKD, chronic kidney diseases; HD, hemodialysis; HTN, hypertension; IL-6, interleukin type 6; I/S/S, infection, sepsis, shock; OH, alcohol; PRES, posterior reversible encephalopathy syndrome, V1A, vasopressin V_{1a} receptor; V2, vasopressin V_2 receptor

lithium/alcohol withdrawal) (Fig. 1A, B). In many clinical situations such mechanisms may combine.

Eclampsia

A large body of recent literature suggests that AVP hypersecretion is involved in pre-eclampsia/eclampsia. Indeed, elevated plasma copeptin levels have been associated with pre-eclamptic pregnancies [67]. Moreover, chronic low-dose infusion of AVP in mice is sufficient to initiate pre-eclampsia symptoms [67, 68] and AVP receptors are known to regulate the major midgestational mechanisms of pre-eclampsia (i.e., vascular, angiogenic, immune, and renal dysregulation) in human patients [67]. Vasopressinase, the role of which is to catalyze AVP cleaving, was decreased during the third trimester in pre-eclamptic women [69]. Furthermore, a single-nucleotide polymorphism in the regulator of G protein signaling-2 (*RGS2*) gene, an endogenous negative regulator of the AVP axis, has been associated with pre-eclampsia [67], especially in overweight women [70].

Inflammatory Disorders

The immuno-neuroendocrine pathways connecting inflammation with AVP are now better defined and understood, explaining in part the role of hyponatremia in the setting of inflammatory states. Indeed, increasing evidence indicates that IL-6 is a key regulator of AVP secretion under physiological and pathophysiological conditions, by acting as an effector in brain areas that are involved in AVP release [51, 52].

Indeed, elevated plasma concentration of copeptin is strongly associated with sepsis and septic shock [45, 71–74]. In such circumstances, AVP release (e.g., through IL-6 secretion) beyond a critical threshold may trigger PRES development (Fig. 1B).

Interestingly, IL-6 also reflects disease activity in several autoimmune disorders, such as SLE [75] or vasculitis [76], which are known comorbid conditions/risk factors for PRES. Furthermore, serum IL-6 levels are significantly higher in SLE patients with PRES when compared with SLE patients without PRES and healthy controls [41].

Kidney Diseases

Kidney diseases appear to be both a cause/risk factor and a consequence/symptom of PRES (Fig. 1A, C). On the one hand, plasma copeptin levels are increased in various kidney conditions associated with PRES, such as ADPKD [65], end-stage renal disease (ESRD) [66], and hemodialysis [64]. During chronic kidney diseases, decline of renal function and the impairment of urine concentrating capacity are responsible for AVP accumulation and AVP hypersecretion respectively [64]. These high AVP levels may trigger PRES development in patients with chronic kidney diseases; but on the other hand, increase in AVP concentration could be the key component of acute kidney failure frequently observed during PRES (Table 1). Indeed, supraphysiologic concentrations of AVP induce kidney injury, by both proteinuria through V_2R stimulation and arteriole vasoconstriction due to $V_{1a}R$ activation [64].

Hypertension

As with kidney failure, hypertension appears to be both a symptom of PRES and a risk factor for PRES development and the clinical recurrence of PRES (Table 1). The relationship between AVP and hypertension involves three mechanisms: (1) stimulation of AVP release in supraoptic and paraventricular nuclei by renin angiotensin aldosterone system activation; (2) vasoconstriction due to direct effects on smooth muscle cells (via $V_{1a}R$) and by increasing renin secretion; and (3) effect of AVP on increased tubular sodium retention [64, 65]. Interestingly, recent evidence suggests that elevated blood pressure is associated with increased copeptin levels [64].

Hyponatremia

PRES due to severe hyponatremia has largely been reported [9–20]. However, although severe and rapid onset hyponatremia may cause osmotic brain edema, low plasma sodium concentration observed in PRES patients may be considered a collateral consequence of AVP axis hyperstimulation. SIADH is characterized by hypotonic hyponatremia and impaired urinary dilution without kidney disease or any identifiable non-osmotic stimulus known to induce AVP release [77, 78]. PRES has been associated with SIADH [9, 10], and desmopressin, a synthetic AVP analogue, can induce PRES [11, 12]. Furthermore, in patients suffering hemophagocytic lymphohistiocytosis, mild hyponatremia is a risk factor for PRES development [79]. In these cases, which do not meet SIADH's diagnostic criteria, hyponatremia may be a sign of AVP release.

Hypercalcemia

Hypercalcemia is frequently associated with PRES [80] and AVP receptors antagonists can abolish the high blood pressure induced by hypercalcemia [81]. Hypercalcemia alters V_2R responsiveness, resulting in acquired nephrogenic diabetes insipidus. Furthermore, hypercalcemia and parathyroid hormone-related peptide are involved in AVP release [81, 82].

Acute Intermittent Porphyria

Several reports have described acute intermittent porphyria as a trigger of PRES. Hyponatremia occurs in half of the

published literature [83]. Interestingly, when AVP monitoring is performed in an acute intermittent patient with PRES, high plasma AVP levels are detected [84]. The mechanism underlying the acute intermittent porphyria-induced increase in AVP levels is likely related to hypothalamic damage by δ-aminolaevulinic acid accumulation or abnormal heme activity with neuronal loss in supraoptic and paraventricular nuclei [85].

Drug-Induced PRES

Calcineurin Inhibitors

The effect of CNI on the AVP axis seems to be both direct, through effects on vascular smooth muscle cells, and indirect, through increased release of various neuropeptides and modulators of vasopressin neurons. Ciclosporin increases the response of rat vascular smooth muscle cells to AVP by upregulating $V_{1a}R$ expression [86]. This upregulation may cause both hypertension and, via renal vasoconstriction, reduced glomerular filtration. CNI-induced hypertension is also partly mediated by the action of AVP on V_2R through NKCC channels [87]. Given the fact that V_2R [47, 48] and NKCC are expressed in the brain and participate in the development of cytotoxic cerebral edema [54], it is probable that CNI-induced PRES results from V_2R/NKCC activation in the AVP axis. Second, CNI stimulate secretion of various neuromodulators and hormones, including brain-derived neurotrophic factor, substance P, and angiotensin II, which are known to modulate vasopressin neurons and AVP release [53, 88].

Anticancer Drugs

AVP hypersecretion in cancer patients may arise from at least three distinct mechanisms. The first one is ectopic production of AVP by tumor cells [89, 90]. The two others are related to anticancer drugs which can stimulate AVP secretion either by direct stimulation or through chemotherapy-induced nausea, which is the most potent stimulus for AVP release (Fig. 1B). The role of AVP is further supported by the perfect overlap that exists between anticancer agents responsible for PRES [22] and drug-induced SIADH [90], i.e., platinum salts, vinca-alkaloids, nitrogen mustard and methotrexate.

As anti-VEGF therapy is recognized to induce a pre-eclampsia-like syndrome (i.e., hypertension, renal failure) [91], the mechanisms of anti-VEGF drug-induced PRES may be extremely similar to those seen among pre-eclamptic women. As mentioned earlier, hypertension [64] and proteinuria/renal failure [64, 66] can arise from elevated AVP levels. Indeed, an increase in copeptin levels was shown after 6 weeks of a bevacizumab-containing chemotherapy [92]. Similarly, a phase II multicenter trial of aflibercept in combination with cisplatin and pemetrexed in non-small cell lung cancer was terminated prematurely because of the high prevalence of PRES (5/42 patients, 11.9%) [93]. The very high proportion of PRES in this cohort may be easily explained by the concomitant action of the anti-VEGF drug and cisplatin used in lung cancer patients. Indeed, lung cancers are the most prevalent malignancies associated with SIADH, cisplatin is one of the most trigger of drug-induced SIADH [90] and PRES [22], and anti-VEGF drugs are known to be associated with PRES [23] through their action on VEGF and probably AVP.

Hyponatremia has been largely reported with tyrosine kinase inhibitors (TKI) in cancer patients. Duchnowska et al. [20] report grade 3 hyponatremia that occurred concomitantly with PRES in a 71-year-old woman with sunitinib-induced PRES. Hyponatremia occurs in 23% of patients in the brivanib arm of a phase III trial comparing brivanib with sorafenib as first-line treatment for hepatocellular carcinoma [94]. In clinical trials, few investigations have been reported to determine the etiology of TKI-associated hyponatremia, but induction of SIADH seems to be one of the underlying mechanisms [90]. Some case reports mention an association between SIADH and other TKI (e.g., imatinib [95, 96], dasatinib [97]). In addition to central stimulation of AVP, erlotinib enhanced AQP-2 apical membrane expression in collecting duct principal cells in mice [98], suggesting also a peripheral action of AVP on V_2R.

Corticosteroids

The AVP theory does not explain corticosteroid-induced PRES and this effect may primarily depend on medical conditions for which these drugs are used, which are directly responsible for PRES. Conversely, the efficacy of corticoids in PRES can in part be explained by their effect on the AVP axis. Exogenous steroids are potent inhibitors of central AVP release [99–102]. Therefore, corticosteroid effectiveness may result from both normalization of the underlying disease activity (e.g., via decreased IL-6 secretion) and direct inhibition of the AVP axis, which is overstimulated in PRES. Another point that strengthens the involvement of the AVP axis in corticosteroid-induced PRES is based on the report of a 34-year-old SLE patient who developed PRES 6 days after she had suddenly stopped taking oral prednisone [103]. Given the fact that glucocorticoids inhibit the central AVP axis, this observation suggests a rebound effect after steroid therapy cessation, resulting in AVP hyperstimulation and therefore PRES development. This rebound effect of steroid cessation on AVP axis has been histologically demonstrated in humans [99].

Lithium

Lithium is known to induce nephrogenic diabetes insipidus by inhibiting the AVP-stimulated translocation of cytoplasmic

AQP-2 to the apical membrane of the collecting duct principal cells. Three case reports indicated an association between lithium and PRES [26, 27]. All cases occurred after lithium discontinuation. The onset of PRES occurred between 3 and 10 days after lithium withdrawal [26, 27]. As with corticosteroids, this chronology of events in PRES suggests a rebound effect of V_2R expression/stimulation when lithium was stopped.

Role of AVP in Drug Abuse-Induced PRES

The pathomechanism of PRES associated with chronic alcoholism [104–106] and alcohol withdrawal syndrome [28–30] seems very similar to that for corticosteroid- and lithium-induced PRES. The onset of PRES in acute alcohol withdrawal syndrome occurs between 3 and 8 days after withdrawal [28–30]. Recently, Godino and Renard [107] reviewed the effects of alcohol on the AVP axis. Ethanol is a potent inhibitor of the AVP axis and prolonged exposure to alcohol is associated with reduced AVP gene expression. Furthermore, a tolerance effect has been described in the inhibition of AVP neurohypophysial release after chronic alcohol consumption. Last but not least, acute alcohol withdrawal activates the hypothalamic-pituitary-adrenal axis [108, 109], and especially the amygdala AVP/V_{1b}R system [107]. As with corticosteroids, these data support a role for a rebound effect in the genesis of PRES induced by the abrupt cessation of substances inhibiting AVP release (Fig. 1B). PRES has also been linked to disulfiram intoxication, as reported in a 43-year-old man with a history of chronic alcohol abuse who continued drinking alcohol during administration of disulfiram [105]. Co-administration of alcohol with disulfiram is known to result in a significant increase in AVP expression in the paraventricular nucleus [110].

Association between cocaine/amphetamine use and PRES has been reported [21, 28, 31, 32]. The pathomechanisms proposed were acute high blood pressure and BBB disruption related to oxidative stress, endothelial dysfunction, and the vasopressors effects of cocaine [31]. Nevertheless, there is growing evidence that cocaine and methamphetamine interact with the central AVP axis though V_{1a}R [107].

AVP and PRES: Synthesis

PRES is a very heterogeneous disorder and it is probable that many different mechanisms are etiologically important in the different clinical situations. In this review, we have shown that AVP could be the trigger of PRES, in particular because of both its pathomechanism in brain edema formation and its involvement in most PRES etiologies/risk factors.

The AVP Theory: General Scenario

The initiating event, whatever its nature, causes AVP axis stimulation through its ability to increase AVP secretion (e.g., eclampsia, anticancer therapy) or to increase AVP receptor density (e.g., CNI) (Fig. 1A, B). Thus, the following scenario may occur (Fig. 2): (1) V_{1a}R stimulation leads to platelet aggregation, constriction of cerebral vessels, and increased sympathetic tone [46], causing both endothelial dysfunction and cerebral ischemia; (2) combination of these effects promotes dysregulation of ionic/water transglial flux, through astrocytic Na^+/K^+ ATPase, NKCC, AQP-4 dysfunction [57] and subsequent cytotoxic edema; (3) brain ischemia can trigger actin-dependent endothelial cell rounding and VEGF overexpression and increased endothelial permeability [54], leading to vasogenic brain edema; and (4) V_{1b} R activation thus promotes ACTH/CRH secretion [46] and potentially subsequent hypertension due to both the increase of peripheral vascular resistance, and fluid overload caused by glucocorticoids, aldosterone, and renin release. This salt and water retention can be perpetuated through V_2R activation and may potentially lead to hypertension and renal impairment [46, 64, 66]. Although inconsistent, hypertension can perpetuate cerebral aggression.

In PRES, the effectors of the AVP axis are stimulated both through central receptors (i.e., V_1R) and through peripheral ones (i.e., V_2R). Schematically, V_1R appear to be involved in the genesis of PRES, while V_2R are more likely to be responsible for PRES symptoms/complications. So, in light of this scenario, we can legitimately ask ourselves why patients with SIADH do not have PRES; and, conversely, why all patients with PRES do not have SIADH? The hyponatremia in SIADH is mainly related to peripheral/renal activation of V_2R. This explains why SIADH is neither necessary nor sufficient for the development of PRES. Conversely, the predominant role of V_1R compared with V_2R explains why not all occurrences of PRES are complicated by SIADH.

The AVP Theory: Individual Susceptibility

In most cases, patients with PRES concomitantly present complex conditions (e.g., transplantation, cancer, shock) with multiple risk factors (e.g., hypertension, renal failure, inflammatory state). Nevertheless, in rare cases, PRES can occur in patients without apparent risk factors [111]. Clinical recurrence, which occurs in about 5–10% of cases, has been associated with primary hypertension as an etiology [3]. In other words, the trigger factor of PRES can reoccur without clinical relapse. In some cases of drug-induced PRES, the

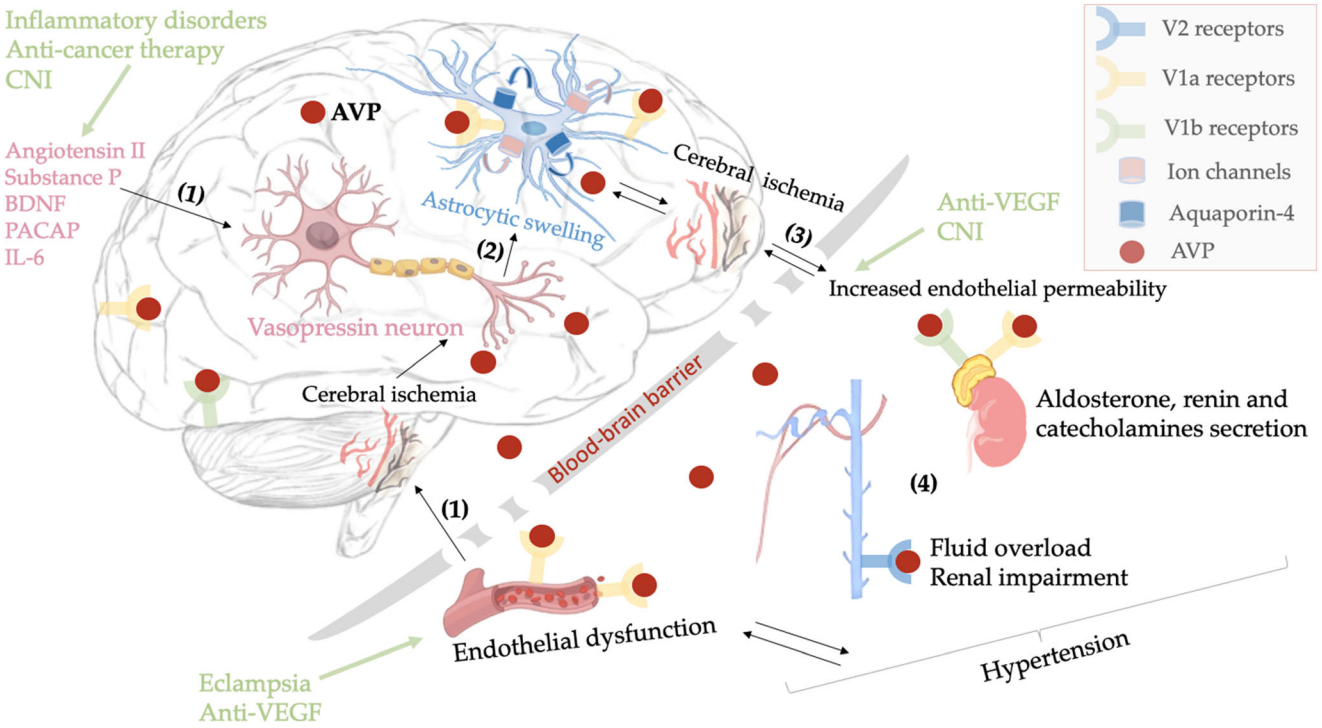

Fig. 2 Possible AVP pathway involved in PRES. The initiating event is responsible for the following scenario: (1) stimulation of vasopressin neurons and subsequent AVP release or direct $V_{1a}R$ stimulation leads to platelet aggregation, constriction of cerebral vessels, and increased sympathetic tone [46], causing both endothelial dysfunction and cerebral ischemia; (2) combination of these effects promotes dysregulation of ionic/water transglial flux through astrocytic NKCC, aquaporin-4 dysfunction [57], and subsequent cytotoxic edema; (3) brain ischemia can trigger actin-dependent endothelial cell rounding, VEGF overexpression and increased endothelial permeability [54], leading to vasogenic brain edema; and (4) V_{1b} R activation may thus cause hypertension due to both the increase of vascular tone and fluid overload caused by glucocorticoids, aldosterone, and renin release. This salt and water retention can be perpetuated through V_2R activation and may potentially lead to hypertension and renal impairment [46, 64, 66]. Although inconsistent, hypertension can perpetuate cerebral aggression. BDNF, brain-derived neurotrophic factor; CNI, calcineurin inhibitors; IL-6, interleukin type 6; PACAP, pituitary adenylate cyclase activating polypeptide; VEGF, vascular epithelial growth factor

incriminated drug could be safety reintroduced [24], suggesting that PRES development is a time-dependent process. Thus, we hypothesize that some individual risk factors must be present simultaneously to lead to PRES symptoms.

This raises an interesting hypothesis that exogenous/endogenous parameters altering AVP functions or genetic polymorphisms in the AVP axis could explain variable phenotypes (i.e., recurrent PRES or PRES without risk factor). Patients with PRES may have a particular tendency to develop a disproportionate response to AVP secretion stimuli. First, it may be due to the combination of several components involved in AVP release/potentiation (e.g., underlying disease, nausea, drugs) associated with risk factors for endothelial dysfunction and hypertension (e.g., hypomagnesemia, anti-VEGF therapy). It may also be caused by the convergence of various processes that induce stimulation of AVP axis in genetically predisposed patients. Indeed, we can imagine that some patients with PRES may have genetic polymorphism causing a decreased threshold for activation of vasopressin neurons. These polymorphisms could concern the AVP gene, genes of AVP modulators (e.g., as *RGS2* in eclampsia [67]) or AVP receptor genes.

Can Biomarkers Be Used to Move Forward?

Biomarker analysis in PRES is poorly studied. Currently, no studies have examined the pathophysiology of PRES at a molecular level. Only Merayo-Chalico et al. [41] analyzed a specific biomarker in PRES. Serum IL-6 levels, one of the most important activator of AVP release [51, 52], were significantly higher in SLE patients with PRES when compared with SLE patients without PRES and healthy controls [41]. Apart from Merayo-Chalico et al. [41], studies have focused only on non-specific biomarkers (e.g., transaminases, albumin, lactate dehydrogenase), which did not allow to specifically access to the pathophysiology of PRES (Table 2). Therefore, there is still a lack of experimental data in PRES. In the sole case report of PRES to date where AVP was measured, high plasma AVP levels (20.1 pg/mL) were detected [84].

Precise understanding of PRES pathophysiology is fundamental to develop targeted treatments. Our literature analysis shows that patients with PRES may have an AVP axis that is very sensitive to stimuli, usually physiologic, and may have high concentrations of AVP. As copeptin has a longer half-life than AVP, we expect it to be less susceptible to physiological changes over the course of the day, which is described for AVP measured in the plasma of rats [112]. Ideally, measurement of copeptin kinetics, with a first analysis carried out at the onset of neurological signs, should allow more precise investigation of the sequence of events.

A very exciting perspective would be to analyze the association between PRES and different genetic polymorphisms related to the AVP axis. This could be done either through hypothesis-driven studies, analyzing the association between selected genes and PRES but also through opened genome-wide association studies.

The AVP Theory: Therapeutic Implications

Early accurate diagnosis is critical for effective treatment for patients with PRES. So far, the focus of PRES treatment has been the removal of any predisposing factors and treatment of the underlying causes. Therapeutic management is based on correction of electrolyte disturbances, antihypertensive therapy, and anticonvulsant agents if necessary. Suppression of AVP hypersecretion and/or of its pharmacologic effects by antagonizing AVP receptors should be a promising therapeutic approach for AVP-associated brain edema and subsequent PRES.

Vaptans (V_2R antagonists) are aquaretic drugs which correct hyponatremia by producing a selective water diuresis without affecting sodium and potassium excretion. Tolvaptan has been approved in the USA for oral therapy of euvolemic and hypervolemic hyponatremia and in the European Union only for the treatment of hyponatremia secondary to SIADH [113]. The pathogenesis of AVP and the prognostic value of plasma copeptin are now established in various types of cerebral edema [55, 114, 115]. The recent understanding of these molecular mechanisms provided the rationale for evaluating the efficacy and safety of the use of conivaptan, a dual V_{1a} and V_2 receptors antagonist in the treatment of cerebral edema in intracerebral hemorrhage (NCT03000283). Studies reviewed by Ameli et al. [114] showed that conivaptan may have valuable treatment implications in a number of overlapping brain conditions, including cerebral edema and increased intracranial pressure after stroke, intracranial hemorrhage, and TBI. Considering the fact that it is the entire axis of the AVP that appears overstimulated in brain edema of PRES, the most attractive approach would be to combine both reduction of AVP secretion and pharmacological blocking of its effectors (i.e., $V_{1a}R$ and V_2R). This dual action could be achieved by combining corticosteroids and conivaptan therapy. After having defined a beneficial window of antagonizing AVP and under close natremia monitoring, the use of conivaptan could become a targeted/specific treatment for PRES. Conivaptan is contraindicated in cirrhosis, because blockage of $V_{1a}R$ effects may increase portal blood flow and precipitate variceal bleeding. Contrary to tolvaptan, conivaptan has not been specifically associated with elevation of liver enzymes [113, 116].

Conclusion

Clinical situations associated with PRES remain complex. Our review points to a common mechanism involving AVP hypersecretion. Depending on the situation, increases in AVP secretion may be caused by the underlying disease alone (e.g., eclampsia), or by several factors including pathophysiological states and treatments (e.g., transplantation). According to the AVP theory, the involvement of AVP in drug-induced PRES can be explained by (1) drug effects on stimulation of the AVP axis (i.e., increased AVP release, increased density of AVP receptors); (2) the association of PRES with abrupt cessation of drugs inhibiting the AVP axis (e.g., corticosteroids, lithium, alcohol); and (3) drugs inhibiting the AVP axis that can be used in PRES treatment (e.g., corticosteroids). Taken together, exploration of the AVP axis seems to be a particularly promising approach in PRES, not only for its diagnosis but also for its therapeutic management.

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Compliance with Ethical Standards

Competing Interests The authors declare that they have no conflict of interest.

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