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POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IN ECLAMPTIC PATIENTS: NEURORADIOLOGICAL MANIFESTATION, PATHOGENESIS AND MANAGEMENT

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Summary
Introduction. Eclampsia is one of the most serious complications of hypertensive disorders of pregnancy, defined as the occurrence of one or more convulsions superimposed on preeclampsia. Besides the ordinary course of the disease, ranging from a mild to a severe form, with culmination in eclamptic seizures, there is a significant percent of cases where eclampsia starts unexpectedly, without typical premonitory symptoms and signs, which makes it difficult to prevent. Neuroradiological Characteristics and Pathogenesis of Eclampsia. Neuroradiological signs of eclampsia are described as posterior reversible encephalopathy syndrome, and are manifested by nausea, vomiting, headache, visual disturbances, altered mental status, convulsions and coma, together with characteristic findings on computed tomography or magnetic resonance imaging scan of the head, indicating the presence of vasogenic brain edema. The topic of this article are possible mechanisms of the development of posterior reversible encephalopathy syndrome in pregnancy and modalities of acute treatment of this emergency state.

Management of Eclampsia. Magnesium sulphate is nowadays the drug of choice for the treatment and prevention of eclamptic seizures. Labetalol is considered to be the agent of choice in the treatment of hypertensive emergencies of pregnancy, followed by hydralazine, nifedipine, nicardipine, urapidil, nicardipine and sodium nitroprusside (in most refractory cases). Angiotensin converting enzyme inhibitors and angiotensin blocking drugs are contraindicated in pregnancy. Captopril and enalapril are allowed during lactation. Conclusion. Posterior reversible encephalopathy syndrome in eclamptic patients is completely reversible if adequate diagnosis is promptly made and intensive treatment immediately administered.

Key words: Posterior Leukoencephalopathy Syndrome; Eclampsia; Neurologic Manifestation; Tomography, X-Ray Computed; Magnetic Resonance Imaging; Signs and Symptoms; Disease Management; Pregnancy Complications; Hypertension, Pregnancy-Induced; Female

Sažetak

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Introduction

Eclampsia is one of the most serious complications of hypertensive disorders of pregnancy [1–3]. It complicates one in 100 - 1700 pregnancies in developing countries and one in 2000 - 3450 pregnancies in the western world [4, 5]. Preeclampsia/eclampsia is responsible for 10–18% direct obstetric deaths [6–10].

The disease is defined as the occurrence of one or more convulsions superimposed on preeclampsia [1]. Neurologic symptoms include nausea, vomiting, occipital or frontal headache, blurred vision, cortical blindness, altered mental status, convulsions and coma [10–16]. Diagnostic parameters of hypertensive disorders of pregnancy are well defined [1, 6, 7, 12, 17–20], but clinicians should be aware of the existence of atypical forms of preeclampsia, with symptoms ranging from mild hypertension with or without proteinuria to severe hypertension with/or without proteinuria and/or end organ damage [2, 5, 6, 12, 21]. Hypertension is considered to be the hallmark of the diagnosis of eclampsia; nevertheless, patients may be normotensive in even 16-30% of cases [3, 15]; severe hypertension was found in 47% of eclamptic patients [10, 15].

The ordinary course of the disease goes from a mild to a severe form of preeclampsia, culminating in eclamptic seizures. However, according to recent data, eclampsia starts unexpectedly, without premonitory symptoms and signs of preeclampsia in up to 20% of cases [4].

Eclampsia can be complicated by several serious conditions, such as cerebral hemorrhage or stroke, pulmonary embolism, acute renal or liver failure, disseminated intravascular coagulopathy (DIC), syndrome of hemolysis, elevated liver enzymes and low platelet count (HELLP), abruptio placentae, temporary or permanent neurologic abnormalities and cognitive impairment later in life [4, 5, 10, 15, 22–24]. Perinatal morbidity and mortality is high (5.6–18%), related to severe growth restriction and prematurity.

Neuroradiological Characteristics and Pathogenesis of Eclampsia

Neuroradiological signs of eclampsia are described as Posterior Reversible Encephalopathy Syndrome (PRES). PRES, as a relatively new neuroradiological entity, was described by Hinchey et al. in 1996 [25]. The authors connected it with hypertensive encephalopathy, autoimmune diseases, sepsis, renal insufficiency, transplantation, exposure to immunosuppressants and eclampsia [3, 12, 25–31]. PRES is a transient state, manifested by the above-mentioned clinical signs and symptoms, together with characteristic findings on computed tomography (CT) or magnetic resonance imaging scan (MRI) of the head [2, 4, 11–13, 15, 29, 30, 32]. The widespread application of MRI has allowed more precise recognition of PRES [26]. It typically shows bilateral focal regions of signal intensity alterations, indicating the presence of brain edema [4, 13, 27, 31]. In vast majority of cases it is vasogenic edema, presented by high signal intensity on T2 weighted imaging and fluid attenuated inversion recovery (FLAIR), increased apparent diffusion coefficient values (ADC) and hypointensity or no change of intensity on diffusion weighted imaging (DWI) [2, 3, 13, 33, 34]. An increased DWI signal combined with a decreased ADC and a decreased or normal FLAIR, indicates the presence of cytotoxic edema, which used to be seen in much lower percent of eclampsia cases [26].

There are two opposing hypothesis trying to explain the brain edema formation in PRES [4, 5, 11–13, 28, 33, 34]. According to the prevailing, forced dilatation theory; a rapid rise in blood pressure (BP), which exceeds the upper limit of cerebral autoregulation, leads to the blood brain barrier (BBB) dysfunction, cerebral vasodilatation and local hyperperfusion, manifested by vasogenic edema present in 93–100% of eclamptic women. Vasospasm theory; severe hypertension promotes cerebral overregulation, vasoconstriction, ischemia, infarction and cytotoxic edema.

Although vasogenic edema is far more common, autopsy findings have shown the predominance of cytotoxic edema, infarction and hemorrhage in the subcortical white matter in women who died from eclampsia. The explanation might be that vasogenic brain edema occurs in the first, reversible stage of the disease, which, if not promptly treated, progresses to cytotoxic edema, ischemic damage and hemorrhage with worse prognosis [2, 3, 12, 15, 29, 32].

The fact that PRES in an eclamptic patient can develop without a significant rise in BP and in cases where upper limit of autoregulation is not reached, makes this issue even more controversial [2, 3, 5, 11, 13, 28, 29]. We have to keep in mind, however, that it could be the case of “relative hypertension” when BP rises from a low baseline level (as in the young women with average BP levels of 90/60 mm Hg out of pregnancy) [13]. In addition, even normal pregnancy causes a decrease in the small brain vessel resistance when BP is elevated, which promotes enhanced BBB permeability and edema formation [11]. During pregnancy, autoregulation of cerebral blood flow (CBF) is shifted to the lower range of pressures; in preeclampsia/eclampsia this is even more pronounced [5, 11].

Abbreviations

PRES – posterior reversible encephalopathy syndrome
MRI – magnetic resonance imaging scan
ADC – apparent diffusion coefficient
DWI – diffusion weighted imaging
BP – blood pressure
BBB – blood brain barrier
MgSO4 – magnesium sulphate
ACE – angiotensin converting enzyme
One more crucial factor for PRES formation is present in eclampsia: **endothelial damage** [13, 28]. From what we know so far, immunological intolerance between the fetal and maternal tissues develops also in susceptible women (the presence of risk factors). This leads to abnormal trophoblast invasion of uterine blood vessels and to placental ischemia. Abnormal placentation provokes excessive production of reactive oxygen species, abnormal nitric oxide and lipid metabolism, excessive inflammatory response, activation of leukocytes, platelets and complement cascade, predominance of procoagulant and antiangiogenic factors, which all together lead to vascular endothelial damage and dysfunction [1, 6, 8, 21, 23, 28, 35–39]. All organ systems are affected, and so is cerebral vasculature. The enhanced BBB permeability per se is sufficient to provoke seizure activity. The passage of albumin into interstitial space and the presence of proinflammatory cytokines (such as tumor necrosis factor (TNF)), or aquaporines (AQP4), can lower the seizure threshold and also provoke seizure itself [5, 11].

Parieto-occipital brain region is affected in 94–98.7% of cases, but other parts might be involved as well: the frontal lobe in 77–78.9%, the temporal lobe in 64–68%, and the cerebellum in 53% of cases [3, 12, 13, 27, 29]. The predominant involvement of posterior brain was explained by the findings of less dense sympathetic innervation that makes vertebrobasilar system more susceptible to the breakthrough of the autoregulation limits. There is also an increased capillary density in the posterior brain region with an increased possibility of transcapillary filtration and edema formation [5].

PRES usually resolves in several days if prompt, aggressive management of seizures and BP is initiated [12, 15, 17]. Definitive therapy for preeclampsia/eclampsia is the delivery, especially removal of the placenta, as the placenta is the central organ in the pathogenesis of hypertensive disorders of pregnancy [3, 6, 10, 21].

**Management of Eclampsia**

During or immediately after a convulsive episode, cardiovascular and respiratory support, treatment of seizure, prevention of maternal injury and aspiration have the priority in the management [40].

The drug of choice for treatment and prevention of convulsions is magnesium sulphate (MgSO₄) [1, 4–6, 10, 13, 14, 24, 40, 41]. As an N-methyl-D-aspartate (NMDA) receptor antagonist, magnesium acts as an anticonvulsant. It reduces cerebral endothelial permeability and protects BBB as a calcium antagonist. Magnesium also acts as a vasodilator (the effects on systemic vasculature are more pronounced than on cerebral circulation) and a tocolytic agent [5, 28, 42].

Therapy starts with 4 - 6 g of MgSO₄ iv over 15 – 20 min (loading dose), followed by a continuous infusion of 1 - 2 g/h [6]. Side effects could be nausea, headache, and weakness. Overdose leads to the depression of neuromuscular transmission and the loss of deep tendon reflexes, respiratory depression and cardiovascular arrhythmias and collapse. Urine output, magnesemia, tendon reflexes and respiratory function should be monitored during the treatment. The first sign of magnesium toxicity is the loss of patellar reflexes. At that point, MgSO₄ should be discontinued and, if necessary, an antidote given (1 g of calcium gluconate over 2 min) [7, 13]. In cases of refractory seizures, therapy should be more aggressive and traditional anticonvulsant agents added (pentobarbital, phenytoin).

The next step in management of eclampsia should be the reduction of BP.

One of the challenges of treating hypertensive disorders in pregnancy is to decide when to start using antihypertensive medications. In case of mild to moderate hypertension, there is no evidence of obvious benefit of antihypertensive treatment in outcomes, preterm birth, and neonatal death [18, 19, 36]. However, there is no doubt in case of severe hypertension-therapy should immediately be initiated for the benefit of the mother [18, 23, 41, 42]. According to the opinion of the American College of Gynecology and Obstetrics (ACOG) Committee expressed in 2011 **“Acute onset of severe systolic (more than 160 mmHg), or severe diastolic (more than 110 mm Hg) hypertension, or both, in pregnant women, persisting more than 15 min, is considered hypertensive emergency”** [43]. Hypertensive emergency is a life threatening condition with evidence of target organ damage, in which therapy must be started within one hour [10, 27, 44, 45]. Severe systolic hypertension is the most important predictor of cerebral complications [43].

Another important question is what level of BP to target in order to prevent and treat severe hypertension and its possible complications on the one hand, and avoid (iatrogenic) hypotension with cardiac, cerebral and fetoplacental hypoperfusion in a patient who might be intravascular volume depleted, on the other hand. In such a case, continuous infusion of short-acting titratable antihypertensive agent is the best choice [45]. The immediate goal is to reduce MAP by 25% over 30 – 60 min and to reach 160/110 mmHg during the next 2 to 6 hours [44]. The long-term goal is to keep BP at 140-150/90-100 mmHg, because lower levels of arterial pressure could jeopardize uteroplacental circulation and fetal wellbeing as well as coronary and cerebral circulation of the mother in preeclampsia/eclampsia [12, 17, 20, 24, 30].

The choice of antihypertensive agent in pregnancy and lactation is limited because of their possible impact on fetal/neonatal development. Labetalol is nowadays the antihypertensive agent of choice in treatment of severe hypertensive disorders of pregnancy [9, 42]. This is a and non-selective β-blocker (β-effect being 7 times more pronounced than α-effect is). Labetalol decreases systemic vascular resistance (SVR) without reducing systemic vascular resistance (SVR) without reducing.
Peripheral blood flow, so it does not affect uteroplacental perfusion [9, 18, 45]. It reduces myocardial oxygen consumption by slowing the heart rate. The following side effects have been reported: dizziness, nausea, vomiting, postural hypotension, bronchospasm, fetal bradycardia. Labetalol is contraindicated in patients with asthma and heart failure [9, 27, 44, 45]. Treatment begins with 20 mg iv bolus given over 2 min. If there is no response, doses of 20-80 mg could be repeated every 10-15 min. Maximum cumulative dose is 300 mg [19, 45].

Hydralazine, a peripheral arteriolar dilator, is recommended in boluses of 5-10 mg every 10–20 min to a maximum cumulative dose of 30 mg [9, 20]. Hydralazine is unsuitable for the first line treatment of hypertension in pregnancy due to its delayed onset of action, prolonged duration (up to 12 hours), unpredictable hypotensive effect, reflex tachycardia, and increased intracranial pressure [9, 42–45].

In spite of being an oral agent, Nifedipine has been used in hypertensive emergencies, and proved to be as effective as hydralazine, but with a fewer side effects [9, 20]. It induces arteriolar dilatation and decreases the afterload without a reduction in the uteroplacental blood flow by blocking the calcium entry into the cells [42]. Acting as a selective renal arteriolar dilator, it increases urinary output. Its side effects are headaches, facial flushing, and tachycardia, and increased intracranial pressure [9, 42–45].

Nitroglycerin, being mostly venodilator, reduces preload and cardiac output (CO), so it is effective in patients with pulmonary edema or acute coronary syndrome. Its side effects are headaches, reflex tachycardia, and hypotension. The onset of action is in 2 min, half life 1 – 4 min. Infusion regime starts with 5 µg/min and can be doubled every 5 min, to maximum of 100 ng/min [9, 44].

Diuretics are avoided because of volume depletion in majority of hypertensive patients, except in cases of pulmonary edema, congestive heart failure or renal failure [19, 42].

Angiotensin converting enzyme inhibitors and angiotensin receptors blocking drugs are a very effective group of medications, but, unfortunately, contraindicated in pregnancy [9, 17, 23]. They can be used in cases refractory to other agents, when its benefit surpasses the risk [9]. Captopril and enalapril are allowed during lactation [9, 23, 46].

Conclusion

Eclampsia, one of the most serious complications of hypertensive disorders of pregnancy, can occur without prodromal signs or elevation in blood pressure in up to 20% of cases.

Neurological (headache, blurred vision, cortical blindness, nausea, vomiting, altered mental status, seizures, and coma) and radiological signs on magnetic resonance imaging scan (presence of bilateral focal regions of brain edema - predominantly vasogenic) in patients with eclampsia are described as posterior reversible encephalopathy syndrome.

Posterior reversible encephalopathy syndrome is completely reversible if adequate diagnosis is promptly made and intensive treatment immediately undertaken.

Magnesium sulphate is the anticonvulsive agent of choice.

Labetalol is considered to be the agent of choice in treatment of hypertensive emergencies of pregnancy. Hydralazine, urapidil, nicardipine, nifedipine, nitroglycerine and sodium nitroprusside (in most refractory cases) are recommended as well. Angiotensin converting enzyme inhibitors and angiotensin blocking drugs are contraindicated in pregnancy. Captopril and enalapril are allowed during lactation.


