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Review

Changes in the structure and function of the brain years after Pre-eclampsia

Olayemi K. Ijomone*, Philemon Shallie, Thajasvarie Naicker

Optics and Imaging Centre, School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, South Africa

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ABSTRACT

Pre-eclampsia (PE) is a pregnancy specific syndrome that affects multiple organs including the brain. PE resolves after delivery of the placenta. Nonetheless, PE is a predisposing factor for cardiovascular disorders and hypertension later in life. These conditions are associated with a cognitive decline and dementia later in life. Studies have suggested that there may be long term pathological changes within the brain of the woman after PE/eclampsia and PE may be a risk marker for early cerebrovascular impairment. The aim of this review is to provide an insight into the possible long-term effect of PE and eclampsia on the brain structure and function with the probability of PE being a risk factor for neurodegenerative development. Long term effects of PE include cognitive impairment such as memory loss, attention deficit and motor speed impairment. Also, the pathology of the brain seems to be much affected later in life in women with history of PE/eclampsia. Certain changes in the structure and function of the brain observed among women with history of PE/eclampsia are similar to neurological disease like Alzheimer's disease (AD) and dementia.

1. Introduction

Certain pregnancy hormones have been reported to remodel the maternal brain at the neuronal level (Kinsley and Lambert, 2006). Examples of maternal brain modifications caused by some pregnancy hormones include an increase in dendritic spine density and neuronal excitability in the dentate gyrus, white matter regeneration, mediation of neurogenesis in the forebrain and enhancement of hippocampal spike transmission (Shingo et al., 2003; Kinsley and Lambert, 2006; Rosenblatt et al., 1988; Maguire et al., 2009). Despite the tissue structural modification of the brain, a more marked functional remodeling of the hippocampus occurs during pregnancy (Chan et al., 2015).

Pre-eclampsia is a pregnancy specific condition, identified as the leading global cause of maternal and foetal morbidity and mortality with a prevalence of 3–10%. It is characterised by new onset of hypertension (systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg, measured on two occasions at least four hours apart) in a previously normotensive women and by the presence of proteinuria (> 0.3 g per 24 h). Additionally, other features associated with PE with or without proteinuria may include thrombocytopaenia (platelet count < 100000/μl), renal insufficiency (serum creatinine concentration > 1.1 mmg/dl or a doubling of the serum creatinine concentration in the absence of other renal disease), liver function impairment, pulmonary oedema and cerebral/visual problems (Duley, 2009; Lindheimer et al., 2015).

A 2017 report demonstrated racial and socio-economic disparities in prevalence of PE. The report showed that rate of PE/eclampsia was higher in black women compared to white, and also higher in women who resided in poorest areas compared to those in wealthy area (Fingar et al., 2006). Also, Fokom-Domgue and Noubiap, 2015, suggested that the commonly accepted definition of PE should be reassessed and readjusted to the African context, as black women had higher BP compared to their white counterparts, either during or in absence of pregnancy (Fokom-Domgue and Noubiap, 2015). Also, endemic infection such as malaria may also be confounding factors for PE in Sub-Saharan African women. Additionally, Goldenberg et al., 2015 showed that a prenatal care program that consist of testing for hypertension and proteinuria, increase in use of hospitalization for caesarean section/induction of labour would more significantly reduced maternal mortality in PE compared to increasing interventions with $MgSO_4$ (Goldenberg et al., 2015). Acute cerebral complications such as eclampsia, cerebral oedema and intracranial haemorrhage accounts for up to 75% of maternal fatalities in Europe. Earlier data from the UK indicated that eclampsia accounts for 6% of direct maternal deaths, while pre-eclampsia accounts for nearly 50% of reversible, pregnancy-related ischemic strokes (Zeeman, 2009). Reports from South Africa between 2005–2007 showed 622 deaths associated with hypertensive disorders of pregnancy. Eclampsia accounted for 55% of deaths, while pre-eclampsia accounted for 28%. 45% of the final cause of death was due to cerebral complications, while about 23% and 25% where due to cardiac and respiratory failure respectively (Moodley, 2011). It is

* Corresponding author.
E-mail address: 215082646@stu.ukzn.ac.za (O.K. Ijomone).

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possible that PE patients that survive these outcomes into later life may be at higher risk for further neurological damage associated with old age.

PE affects multiple organs including the kidney, liver and brain (Aukes et al., 2012, 2009; Duley, 2009; Aukes et al., 2007). The pathogenesis and pathophysiology of PE involve genetic and environmental factors. Apart from the pathogenomic endothelial cell dysfunction, persistent activation of systemic maternal inflammatory cell response and elevated inflammatory cytokines are implicated in the pathogenesis of PE (Tosun et al., 2010). Macrophages are implicated in pathophysiology of PE. Numbers of macrophages are altered PE patients. Most studies indicate increase macrophages in decidua of PE patients. This appear to be consistent with increase in occurrence of macrophage chemotactic factors such as M-CSF, IL-8 and MCP-1 in PE patients. Also, macrophages may be differentially activated in PE, in a manner consistent with increase in pro-inflammatory cytokines and decrease in anti-inflammatory cytokines in placenta of PE women (reviewed in Faas et al., 2014). Neuroinflammation is the recruitment and rapid activation of resident immune cells in the brain, these immune cells, also known as the macrophages of the central nervous system (CNS), constitute approximately 10% of the brain parenchyma cells (Streit et al., 2004). Activation of the immune cells of the brain resembles that of the activation of the monocytes in the peripheral tissues (Tilleux and Hermans, 2007). Neuroinflammation is a critical factor in the advancement of different neurological and neurodegenerative disease (Chen et al., 2015). The mechanism of how systemic inflammation relays signals to the brain and contributes to increased CNS inflammation and injury still remains to be fully elucidated (Mallard et al., 2003). However, D'Mello et al., (2013), demonstrated that increase in monocyte specific rolling and adhesion along cerebral endothelial cells (CECs) may contribute to cerebral changes that influence behaviour in response to systemic inflammation. The study indicated that TNFα-TNFR1 signalling and adhesion of P-selectin are vital mediators of these monocyte-CECs adhesive interactions (D'mello et al., 2013).

Adaptive immune mediated cells (T and B lymphocytes) and innate immune cells initiate neuroinflammatory disease (Baik et al., 2014; Ferretti et al., 2016; Van Eldik et al., 2016). Disruption of tight junctions at the blood brain barrier (BBB) mediates a greater transport of molecules from the peripheral to the CNS contributing to hypoperfusion and inflammation. This may in turn initiate or contribute to a "vicious cycle" of most neurodegenerative disease (Oby and Janigro, 2006; Zlokovic, 2005; Marchi et al., 2011).

This review aims at presenting findings from the literature on the long-term effect of pre-eclampsia and eclampsia on the brain structure and function whilst elucidating the possibility of PE being a risk factor for neurodegenerative disease development. Eclampsia is a severe complication of PE characterised by the onset of seizures (convulsions). Evidence suggests that long-term pathological changes within the brain may occur in eclampsia (Postma et al., 2014a,b). The association between PE/eclampsia and neurodegenerative disease are yet to be fully elucidated. PE/eclampsia might be a risk marker for early cerebrovascular impairment (Aukes et al., 2012).

2. Brain size in PE

During pregnancy, there is shift in focus of women from the survival of the pregnant woman to the care and well-being of her offspring (Kinsley and Lambert, 2006; Moya et al., 2014). This shift is mediated by variable amounts of different hormones secreted by the placenta, ovaries and brain during pregnancy (Szarka et al., 2010; Aagaard-Tillery et al., 2006), which may causes a change in the structure of the brain (Moya et al., 2014). With the use of T1 (spin lattice) weighted magnetic resonance imaging (MRI), a decrease in brain size and concomitant increase in ventricular zone was observed in pregnant women. The decrease in brain size with increase in ventricular zone demonstrates the overall decrease in brain volume during healthy pregnancy (Oatridge et al., 2002). The latter study reported a significant decrease in brain size in PE compared to healthy pregnant women during pregnancy and 40 weeks after delivery but no difference in the ventricular zone between the groups. The mechanism underlying the difference in brain size in PE is unclear but a complication like chronic renal failure in pre-eclampsia may influence size and volume of brain. The brain size was reported to decrease up to 52 weeks post-delivery in a pre-eclamptic patient with renal failure (Oatridge et al., 2002).

Mielke et al. (2016) found that hypertensive pregnancy disorders are associated to smaller brain volume later in life when compared with women without history of hypertensive pregnancy disorders in their study of 1279 women who participated in the Family Blood pressure Project Genetic Epidemiology Network of Arteriopathy (GENOA) (Mielke et al., 2016)

3. Gray matter and PE

There is a paucity of data on gray matter, the major component of the CNS in pregnancy and its associated complications. Gray matter is composed of neuronal cell bodies, dendrites, myelinated and unmyelinated axon, synapses, vascular structures and glial cells (Purves et al., 2008). Hoekzema et al. (2017), reported pronounced changes in gray matter pre- and post-pregnancy in primiparous and nulliparous women. In pregnancy there was an extensive gray matter volume reduction in the anterior and posterior cortical midline and bilateral prefrontal and temporal cortex zones. The reduction in gray matter volume remained up to 24 months post pregnancy (Hoekzema et al., 2017). Moreover, a recent study on brain MRI of women with a previous history of PE (5–15 years later) demonstrated a reduction in the volume of cortical gray matter in women with a history of PE compared to those with a normotensive pregnancy. This reduction in gray matter volume was also noted at the subcortical structure of the brain, thereby exacerbating the overall reduction in the total gray matter (Siepmann et al., 2017). Variations in gray matter signals extracted from MRI indicate various processes, including changes in the number of synapses, the number of glial cells, the number of neurons, structure of the dendrites, vasculature, blood volume and circulation, and myelination (Hoekzema et al., 2017) Notwithstanding the MRI, no studies have to-date been able to pinpoint specific molecular mechanisms underlying the volume reduction of gray matter both in pregnancy and PE.

4. White matter and PE

Alteration in white matter integrity is a predictor for the development of stroke and dementia later in life (Debette and Markus, 2010). White matter lesions are recently thought to be a direct consequence of small vessel pathology (Pantoni, 2010). White matter lesion is defined as a region found within the hemispheric white matter of the brain seen under T2 weighted magnetic resonance imaging to be hyperintense (Pantoni, 2010). Meta-analysis has revealed that women with history of PE, particularly those with early-onset pre-eclampsia, have an increased risk of hypertension, ischaemic and haemorrhagic stroke, both fatal and non-fatal, in later life, therefore PE is an independent risk factor for white matter lesions later in life (Bellamy et al., 2007).

Notably, in both elderly and young individuals one of the risk factors in the development and progression of white matter lesion is the presence of hypertension (Kuller et al., 2010; Jeerakathil et al., 2004, De Leeuw et al., 2002; Hopkins et al., 2006). Aukes et al. (2012) reported severe white matter lesion with a 41% prevalence in women with 5-6-year history of eclampsia and a 37% prevalence in women with history of PE compared to 17% in women with a history of normotensive pregnancy. Despite adjustment for factors like age, pre-existing hypertension and current hypertension, PE and age were independently associated with white matter lesion (Aukes et al., 2012).