Chapter 2.

Neuroradiological imaging in (pre)-eclampsia: a review

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Submitted

Abstract

Objective

To describe the neuroimaging findings in (pre)-eclampsia; to relate these findings to possible mechanisms in the pathogenesis of the cerebrovascular disturbances.

Study design

Pubmed was searched from 1980 – 2004 using the key words “preeclampsia, eclampsia, computed tomography (CT), magnetic resonance imaging (MRI). All articles were cross-referenced.

Results

CT and MRI primarily demonstrate transient lesions consistent with vasogenic edema in the (sub)-cortical regions of the parieto-occipital lobes. With diffusion-weighted MRI evidence for cytotoxic edema is now also found. Up to a fourth of, seemingly asymptomatic eclamptic women demonstrate permanent infarctions.

Conclusion

Eclampsia may represent the end stage of at least 2 different pathophysiological pathways; vasospasm versus increased cerebral blood flow. MR diffusion sequences may characterise the cerebral edema. Reversible Posterior Leucoencephalopathy Syndrome (RPLS) may serve as a model for eclampsia. The two conditions have many pathologic, radiologic, and clinical features in common. However, eclampsia should not be conceptualized as a solitary event but as a disorder with possibly lifelong sequelae

Eclampsia: Incidence, mortality and autopsy

Eclampsia is defined as the occurrence of tonic-clonic convulsions in pregnant or recently postpartum women with preeclampsia. Other dramatic neurological presentations, albeit uncommon, include blindness, altered state of consciousness and coma. Recent estimates of the incidence of eclampsia in the United States range from 0.6 to 3/1000 live births [Mattar 2000, Abi-said 1995, Saftlas 1990.] Eclampsia is considerend one of the most frequent causes of maternal death; approximately 50,000- 65,000 deaths occur per year worldwide [Lancet 1995 collaborative, confidential enquiries.] In the USA, the United Kingdom, and other developed countries such as Sweden, (pre)-eclampsia is the 2nd leading cause of maternal mortality [Kaunitz 1985, Rochat 1988, Moller, Douglas.] In The Netherlands (pre)-eclampsia is the leading cause of maternal death; 35 % of women classified as direct maternal death died due to complications of (pre)-eclampsia [Schuitemaker 1998.] In the USA 23 % of maternal deaths recorded in 1997 were related to pregnancy hypertension. [Williams Obstetrics] The acute cerebral complications of (pre)-eclampsia such as intracranial hemorrhage or massive cerebral edema account for at least 75 % of such fatalities, particularly in the presence of HELLP syndrome [Llopez Llera 1982, Okanloma 2000, Isler 1990.]Less well known is that (pre)-eclampsia also accounts for nearly 50 % of, mostly clinically reversible, pregnancy-related ischemic strokes [Sharshar 1995, Kittner 1996, Wiebers 1985.] Improvement in antenatal and intensive care has reduced the incidence of and death attributable to eclampsia in western countries over the past decade. Modern maternal mortality rates of < 0.5 % are now reported [Sibai 1990, Pritchard 1984.]

Pathogenesis

Information whether pregnancy elicits physiologic adaptations in cerebral blood flow is virtually non-existent compared with our knowledge of the alterations in other vascular beds during gestation. This is partly due to technical difficulties associated with in vivo studies of blood flow in the human brain. Obviously, there are ethical and logistic problems using angiography or other techniques involving radioactive tracers during pregnancy. Transcranial Doppler velocimetry of the middle cerebral artery has been employed most widely to study cerebral blood flow velocity Belfort 1999, 1999, Williams 1993, 1994. The interpretation of these Doppler data is limited since cerebral blood flow velocity measurements can not be extrapolated into flow volume measurements without making several assumptions.

There remain many unanswered questions regarding the pathogenesis of the cerebral manifestations of eclampsia. Human experimental data regarding the cerebral responses to hypertensive disease in pregnancy are scant. In addition, there is obvious difficulty in relating the histopathologic data with the hemodynamic information. By necessity, the central nervous system histopathology of eclampsia is based on autopsy specimens from women who died of the condition, while the hemodynamic data are taken from surviving patients with (pre)-eclampsia. Over the years, two theories have been proposed to explain the cerebral abnormalities associated with eclampsia. First, cerebral overregulation with vasospasm is thought to occur in response to acute severe hypertension Ito 1995, Trommer 1988**.** Alternatively, “forced” vasodilation is thought to occur in response to a breakthrough of cerebral autoregulation Strandgaard 1984, Hauser 1988, Schwartz 2000, Paulsen 2002. These two distinct theories will be discussed in more detail in the paragraph concerning cerebral autoregulation.

Prior to the 1980’s only electroencephalography (EEG) was available in the armamentarium to evaluate the cerebral response in the eclamptic patient. The EEG is acutely abnormal and shows diffuse or focal slowing with delta or beta waves Moodley 1993 Sibai 1984 and gradually returns to normal 6-8 weeks postpartum. The patterns described are not pathognomonic of eclampsia as similar patterns are seen in a variety of conditions Royburt 1991. Several recently developed neuroradiological imaging techniques have greatly improved our understanding of the correlation between the neurological symptoms and neuroanatomic pathological changes characteristic of (pre)-eclampsia.

Autopsy findings

The few autopsy series that exist describe gross intracerebral hemorrhage occurring in up to 60 % of patients [Melrose 1984, Sheehan 1973, Richard 1988, Govan 1961]. The incidence of cerebral hemorrhage in nonfatal eclampsia is unknown. The other principal macroscopic postmortem lesions consist of cortical petechial hemorrhages [Sheehan 1973]. Histologically, these lesions are composed of numerous small hemorrhages, 0.3-1.0 mm in diameter, arranged in streaks of 2-4 cm running radially in the cortex. They may appear anywhere on the gyral surface and are most common in the occipital lobes and least common in the temporal lobes. Many occur in the border zones between major cerebral arterial supplies. Other frequently found macroscopic major lesions described include multiple nonhemorrhagic areas of “softening” throughout the brain, small hemorrhagic areas in the white matter, single large hemorrhage in the white matter, and hemorrhage in the basal ganglia or pons, often with rupture into the ventricles. The classic microscopic vascular lesions consist of fibrinoid necrosis of the arterial wall and perivascular hemorrhages. Interestingly, in several cases numerous small areas of the cortex are infarcted [Sheehan 1973]. These infarcts vary from about 0.3-1.0 mm in diameter and are sometimes confluent. Small hemorrhages are commonly present inside the infarcts and a number of the precapillaries show stasis and thrombosis. These histopathologic findings correspond to several of the neuroimaging findings as discussed in this review.

The purpose of this systematic review is to describe the neuroimaging findings of women suffering (pre)-eclampsia as they have emerged over the last 2 decades with the use of CT and MRI scanning. Based on this literature, current considerations regarding the etiopathogenesis of cerebrovascular disturbances in (pre)-eclampsia as well as implications for clinical practice will be presented.

Search and study selection

Prior to 1980 no reports on cerebral imaging in (pre)-eclampsia were available. PUBMED/MEDLINE was searched from 1980 through 2004 and all articles cross-referenced. The following key words were employed: preeclampsia, eclampsia, computed tomography (CT) and magnetic resonance imaging (MRI). Single case reports are not necessarily quoted unless revealing important new or unique information.

Results

Neuroimaging of cerebral edema

Computed tomography

In the early 1980's the first single case reports describing the appearance of cerebral edema in eclampsia using computed tomography (CT) were published Benedetti 1980, Baker 1982, Grimes 1980, Beck 1981, gaitz 1982, Waldron 1985, Colosimo 1985, Naheedy 1985.

Localised hypodense lesions at the gray-white matter junction are typically found primarily in the parieto-ocipital lobes (Figure 5). Less commonly, such lesions may be found in the frontal and inferior temporal lobes [Brown 1988]. Deep white matter abnormalities have also been reported along with hypodense lesions of the basal ganglia and thalamus [kirby 1984, Kokcu 1993]. Several case series showing evidence of reversible cerebral edema have since been added to the literature [Koyama 1997, Sarma 2003, Moodley 1993]. Surprisingly, some CT scans in eclamptic women did not demonstrate any lesions [Sibai 1990]. This may represent true absence of such lesions or limitations of the contemporaneous technique in detecting more subtle lesions. Generally, the hypodense lesions are completely reversible but not all reports document the availability of follow up scans. Importantly, cerebral infarcts have been demonstrated with CT in eclampsia [Moodley 1993, Gaitz 1982]. In the absence of eclamptic seizures or other serious neurological symptomatology CT and MRI findings are not abnormal in women with severe preeclampsia. In addition, the hypodense lesions typically found

in eclampsia are not usually seen in normotensive pregnancies nor in pregnant women with chronic hypertension [Milliez 1990].

Some reports deserve special mention. Widespread diffuse cerebral edema instead of the more typical low density areas is described in women with persistent neurologic symptoms such as lethargy, confusion and blindness [Richards 1986, Cunningham 2000]. In these cases mass effect was present as demonstrated by a marked compression or even obliteration of the cerebral ventricles (Figure 6). Such women may have signs of impending life-threatening transtentorial herniation. Postmortem investigation reveals fibrinoid arterial wall necrosis, perivascular microinfarcts and brain edema as well as widespread hypoxic ischemic neuronal damage [Richards 1988].

The development of frank hemorrhage into previous areas of ischemic cerebral infarction in a woman with eclampsia is elegantly described and depicted by Salerni et al [1988].This sequence of events is responsible for a well-established complication in patients with occlusive atherosclerotic cerebrovascular disease [Drislane 1997]. Hypertension and coagulopathy are known to increase the risk of hemorrhagic transformation into previously ischemic areas of the brain in atherosclerotic disease. These comorbid circumstances may also proof to be important in the progression to cerebral hemorrhage in (pre)-eclampsia. The sequential demonstration of CT images in this report raises important issues regarding both the pathogenesis of (pre)-eclampsia related intracranial hemorrhage and its prevention.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is well known for its far more superior soft tissue contrast and multiplanar resolution compared to CT. This technique is therefore extremely effective for the diagnosis of hemorrhage as well as ischemia or edema. Since late 1980's to early 1990's many case reports [Schwaighofer 1989, Raroque 1990, Koyama 1997, Malow 1990, Marano 2003, Vandeplas 1989, Crawford 1987, Frederiksson 1989, Veltkamp 2000] and case series [Schwarts 2000, Morriss 1997, Sanders 1991] describe hyperintense reversible lesions with T2 MR imaging in nearly all women with eclampsia (Figure 7). Where CT is often reported normal in case of cerebral edema, MRI demonstrates transient T2 lesions in the (sub) cortical regions of the parieto-occipital lobes [Dahmus]. Occasional involvement of basal ganglia and/or brainstem is also reported (Figure 8) [Zeeman 2004]. Women with

atypical late eclampsia 6-13 days postpartum have shown low-density areas on CT and positive T2 MRI as well [Raps 1993 and Bartynski 2003] . Women with preeclampsia in the absence of eclamptic convulsions typically do not exhibit such lesions on MRI unless they have neurological symptoms such as visual disturbances or vertigo [Schwartz 2000, Morris 1997, Digre 1993]. Morriss et al found subtle changes on T2 MRI in only 2/10 severely preeclamptic women based on increased signal intensity, compared to markedly abnormal findings of increased T2 signal intensity in a number of locations in all women with eclampsia. The 2 women with preeclampsia had several neurologic symptoms such as headache, vertigo or visual disturbances. These hyperintense lesions are typically thought to resolve without longterm sequelae. Few small case series describe persistent hyperintense T2 lesions that may actually represent permanent brain lesions consistent with infarctions. [Sharshar 1995, Rapps 1993, Sanders 1991, Servillo 2003]

Diffusion Weighted Magnetic Resonance Imaging and Apparent Diffusion Coefficient mapping (DWI/ADC)

Two distinctly different types of cerebal edema, vasogenic and cytotoxic edema, can be distinguished by using certain neuroimaging techniques. Roughly, vasogenic edema is associated with increased hydrostatic pressure and ensuing capillary leak while cytotoxic edema is associated with cell death. Using conventional CT and MRI techniques it is impossible to differentiate between these two forms of cerebral edema. With a series of MR acquisitions including Diffusion-Weighted Imaging sequences (DWI) and Apparent Diffusion Coefficient mapping (ADC) it is now possible to further characterize the hyperintense lesions seen on T2 MR imaging in eclamptic women (Figures 9 -11). The DWI technique is based on the quantification of the diffusion of free water, which is decreased in ischemic brain tissue. It is possible to identify ischemic brain regions within minutes to hours after onset of neurologic symptoms as an area of high signal intensity compared with the signal from normal brain [Burdette 1999, Li 1998, Chien 1992, Warach 1995]. With an ischemic event in evolution a shift of water from the extracellular to the intracellular space results in restricted diffusion and therefore reduced ADC values. This is thought to result from decreased Na^+ K^+- ATP-ase activity in glial cell membranes and consequent

decrease in water molecule transport with ensuing cell death. Such areas appear hyperintense on DWI and represent cytotoxic edema [Burdette 1999]. Quantitatively, the regional ADC values provide a non-invasive tool for monitoring the time evolution and spatial expansion of ischemic lesions. A combination of normal DWI with high T2 signal lesions and increased ADC represents reversible vasogenic edema. Several case reports and case series of eclampsia describe reversible lesions on T2 MR imaging. Studies using additional diffusion-weighted imaging sequences showed that the origin of brain edema in eclampsia is primarily vasogenic, but less commonly, may be associated with ischemic/cytotoxic changes [Friese 2000, Chakravarty 2002]. In such cases DWI hyperintense lesions occur superimposed on the pattern of vasogenic edema with decreased ADC. Of the fifteen single case reports describing neuroimaging features in eclamptic women using these new imaging techniques two women appeared to have infarcts [Schwarts 2000, Koch 2001, Kanki 1999, Jurgensen 2001, Keswani 2000, Schaefer 1997, Schwarz 1998, Mukherjee 2001, Ohno 1999, Chakravarty 2002, Engelter 2000, Friese 2000.] Following these case reports very recently two small [Watanambe 2002, Shah 1999] and two larger case series [Louiero 2003, Zeeman 2004] were reported also taking advantage of these MRI techniques for the evaluation of women with eclampsia. It appears that 20-25 % of women with eclampsia demonstrate lesions consistent with cerebral infarction [Loueiro 2003, Zeeman 2004]. Such lesions were still present on follow up imaging 6-8 weeks later and seem to correspond with the classic neuropathologic data demonstrating evidence of cerebral infarction [Sheehan 1973, Richards 1988]. It has to be mentioned that all these women were normotensive as well as asymptomatic at time of the follow up imaging studies. Unfortuately, detailed neurocognitive studies were not performed in these women to document possible immediate clinical relevance. Nevertheless, it is now well known that subclinical infarcts and white matter lesions in general are related to an increased risk of adverse sequelae including clinical stroke events, physical limitations and cognitive impairment including dementia [Longstreth 1996, Bernick 2001, Vermeer 2003]

Angiography

As discussed earlier many believe that vasospasm is the primary event leading to eclampsia [Trommer 1988, lewis 1988, Will 1987.] This presumption is based on the angiographic appearance of diffuse or multifocal segmental narrowings or vasospasm of the cerebral vasculature. Abnormal findings consistent with vasospasm of large and medium-sized cerebral arteries in the absence of underlying intracranial hermorrhage have been found up to two weeks postpartum in women with severe preeclampsia and eclampsia [Kanayama 1993, Ito 1995, matsuda 1995, Sengar 1997, Rape 1993, Trommer 1988, Call 1988]. Several single case reports employing conventional angiography or magnetic resonance angiography (MRA) [Kanayama 1993, Ito 1995, Hashimoto 1997] and a few case series demonstrate such phenomenon whereas just as many others refute this [Morris 1997, Rutherford 2003, Kobayashi 2001, Matsuda 1995]. Recent experimental data suggest that the appearance of vasospasm on angiography is consistent with a so-called sausage string pattern linked to the development of vascular damage [Jacobsen 2002]. Although it has been known for decades that arteries and arterioles can assume a shape characterised by regular symmetric and alternating areas of constriction and dilatation, the mechanisms underlying this phenomenon have remained an enigma.

Neuroimaging of hemorrhagic complications

In some women with eclampsia sudden death occurs synchronously with a convulsion or follows shortly thereafter, and is a result of massive cerebral hemorrhage. Non-lethal intracranial hemorrhage is also frequently found in (pre)-eclamptic women who undergo neuroimaging due to an abnormality on neurological examination. Cerebral hemorrhage is more common in older women with underlying chronic hypertension [Williams 22nd edition]. The cause of such hemorrhages is known to be due to longstanding hypertension-induced lipohyalinosis, which damages small or medium sized cerebral arteries. The striatocapsular area, thalamus, cerebellum and brain stem are the sites most frequently affected in such hypertensive intracerebral hemorrhage [Imaizumi 2004]. Alternatively, as described by Salerni et al [1988] cerebral infarction may transform into a hemorrhagic infarction. Such intracerebral hemorrhage may be more common in young nulliparae who present with HELLP syndrome and eclampsia although this is speculative. Only rarely, is intracerebral hemorrhage in women with (pre)-eclampsia due to a ruptured aneurysm or arteriovenous malformation [Witlin 1997.]

Occasionally, subarachnoid hemorrhage is reported in (pre) eclampsia [Shah 2003, Gregory 2003, Drislane 1997.] In such cases a small amount of blood is seen over the convexity of the frontal/parietal lobes extending into the sylvian fissure or interhemispheric tissue. Conventional angiography rules out ruptured arterial-venous malformation or intracranial aneurysm, or cortical venous sinus thrombosis. Subarachnoid hemorrhage in (pre)-eclampsia is hypothesized to be the result of rupture of cortical petechiae over the surface of the brain or rupture of small pial veins. This type of subarachnoid hemorrhage seems to carry a benign prognosis since none of the patients described developed permanent neurologic deficits on follow-up exam [Shah 2003, Gregory 2003, Drislane 1997.]

Two additional unique case reports deserve mention in this review. Giannina describes a spontaneous antepartum subdural hematoma associated with preeclampsia /HELLP in conjunction with trombopenia. Uncal herniation resulted in the death of the patient [Giannina 1997.] Biller 1995 describes an eclamptic patient with a right basal ganglia hematoma that subsequently transformed into an abcess. It is hypothesized that the infection occurred through bacterial seeding from an infected episiotomy.

Neuroimaging in the presence of visual disturbances

Visual symptoms may occur in 40 % of preeclamptic women and on rare occasions may be the initial symptom. They include scotomota, amaurosis, blurred vision, diplopia, chromatopsia or homonymous hemianopsia [Weiner 1987.] In the past, blindness was usually attributed to retinal abnormalities to include edema, vascular changes such as retinal arteriolar vasospasm or thrombosis of the central retinal artery or retinal detachment. Now, with the introduction of newer neuroimaging modalities such as MRI, focal cerebral edema including bilateral edema of the lateral geniculate nuclei may be seen [Moseman 2002]. Therefore, the term “cortical blindness” was introduced. Cortical blindness is characterised by intact pupillary light reflexes, intact ocular movements and normal opthalmologic findings thus excluding a peripheral cause of blindness.

Neuroimaging findings in cases where visual distrubances dominate the clinical picture, have ranged from normal to widespread low-density areas on CT [Beck 1981, Beeson 1982, Ozkan 2001, Apollon 2000, Waldron 1985, Schimp 2001, Kesler 1998, Borromeo 2000, Herzog 1990, Waldron 1985, Lau 1987]. The absence of lesions may be due to the limited resolution capacity of CT. Follow up imaging generally demonstrates complete resolution of lesions on CT [Iimaizuzmi 1995, Manfredi 1997.] The majority of (pre)-eclamptic women with cortical blindness recover vision over a period varying from two hours to twenty-one days [Duncan 1989, Cunningham 1995.] Although there are reported cases of persistent deficit [Moseman 2002, Lara, Park 2000,] clinical recovery typically precedes normalization of neuro-imaging findings.

In eclamptic women transient blindness is estimated to occur in about 1-15 % [Cunningam 1995, Torres 1995.] The largest series was reported by Cunningham who describes fifteen such women over a fourteen-year period. These women typically demonstrate low-density areas on CT and T2 hyperintense lesions on MRI. Lesions are seen particularly in the parieto-occipital area and supplied by the posterior circulation, and are reversible on follow up imaging [Do 2002, Chambers 2004, Apollon 2000, Torres 1995, Duncan 1989, Herzog 1990.] The presence of transiently increased velocity using transcranial Doppler ultrasound [Torres 1995] and the presence of vasogenic edema in the absence of restricted diffusion (i.e. no evidence of ischemic lesions) using diffusion MRI seems to confirm this finding [Jurgensen 2001, Chambers 2004].

So far, only three women have been described in the literature demonstrating permanent blindness. Two of them had a combination of both abnormal retinal findings consistent with Purtschers retinopathy and MR evidence of brain infarcts located in the lateral geniculate nuclei [Blodi 1990, Moseman 2002].The third patient with persistent blindness did not undergo MR imaging and therefore no conclusions can be drawn [Lara 2002.] Two additional case reports deserve mention. Delefosse describes a case of transient cortical blindness in a woman who was 26 days postpartum. The authors concluded that retained placental fragments may be associated [Delefosse 2003].

Finsterer describes a preeclamptic patient who suffered transient cortical blindness after nitroglycerin administration. MR imaging with diffusion sequences demonstrated a typical picture of vasogenic edema. The authors conclude that nitroglycerin may aggravate the development of vasogenic edema secondary to enhancement of cerebrovascular vasodilation and may result in cortical blindness by this mechanism.

Cerebral autoregulation

Cerebral autoregulation is the process by which cererbal blood flow remains constant in the face of alterations in cerebral perfusion pressure [Strandgaard 1984, Paulson 1990.] Cerebral autoregulatory mechanisms protect the brain from acute hemodynamic pertubations. Cerebral blood flow in a nonpregnant healthy individual is generally maintained constant over a mean arterial pressure range of 60-150 mm Hg [Paulson 1990]. Whether pregnancy evokes an adaptation of this range is unknown, although alterations due to chronic hyperventilation are proposed [van Hook 1999]. Likewise, it is tempting to hypothesize a shift of this autoregulatory range in the presence of pregnancy complications such as preeclampsia. Again, whether this occurs is unknown but a substantial disturbance of certain features pertaining to cerebral autoregulation in eclampsia is reported [Oehm 2003.]

Cerebral autoregulatory mechanisms consist of both myogenic and neurogenic components, such as the sympathetic tone. Counteraction of increased systemic blood pressure is achieved primarily by varying arteriolar resistance through

changing the vessel diameter [Paulson 1990]. The area supplied by the posterior circulation is most vulnerable to a possible failure of autoregulatory mechanisms since this area has less sympathetic innervation and may have the least ability for neurogenic response to increased blood pressure [Lassen 1973]. The cerebral white matter is composed of myelinated fiber tracts in a cellular matrix of glial cells, arterioles and capillaries. This composition causes susceptibility to the accumulation of fluid, vasogenic edema, in the extracellular spaces [Beausan 1981, Schwartz 1998, Port 1998].

The clinical, pathological, and neuroimaging findings in eclampsia have led to two major theories centered around the phenomenon of cerebral autoregulation. According to the first, extreme vasospasm of the cerebral vasculature occurs as a response to acute hypertension [Ito 1995, Trommer 1988]. Subsequently, cerebral blood flow is thought to decrease, and when extreme, is hypothesized to result in ischemia, cytotoxic edema and, eventually, tissue infarction. According to the alternate concept, sudden elevations in systemic blood pressure may exceed the cerebrovascular autoregulatory capacity. When autoregulation fails, regions of passive vasodilation and vasoconstriction develop, especially in arterial boundary zones. At the capillary level disruption of the end-capillary pressure occurs with subsequent increase in hydrostatic pressure. This may result in hyperperfusion and extravasation of plasma and red cells through opening of the endothelial tight junctions, which may lead to the accumulation of vasogenic edema [Schwartz 2000, Hauser 1988, Strandgaard 1984, Paulsen 2002]. This latter theory has gained much attention recently, also in the non-obstetric literature. This phenomenon is coined reversible posterior leucoencephalopathy syndrome (RPLS) and includes the, more familiar, clinical diagnosis of hypertensive encephalopathy [Hackett 1998].

The next paragraph elaborates on the similarity of the cerebrovascular mechanisms in eclampsia with RPLS. In adddition, implications of this theory for the clinical management of hypertensive disorders of pregnancy are explored.

Is eclampsia a form of reversible posterior leuco-encephalopathy syndrome (RPLS) ?

The role of vasospasm as the primary mechanism for convulsions in women with preeclampsia is challenged by the neuroimaging data presented in this review. Impaired cerebral autoregulation is now increasingly thought to be the major determinant for the development of eclamptic encephalopathy. Reversible Posterior Leucoencephalopathy Syndrome (RPLS) is hypothesized to be the primary injury based on its clinical, pathological, as well as neuroimaging features [Hinchey 1996 , Schwartz 1998, Pavlakis 1999, Williams 1996, Easton 1998, Hatashita 1986, Kontos 1981]. In non-pregnant patients RPLS may occur after a subacute elevation of blood pressure. Areas of cerebrovascular vasodilation and vasoconstriction may both coexist in the acute phase of hypertension [Edvinsson 2002]. The clinical presentation is variable and may include headaches, seizures, visual changes, altered mental status, and occasionally focal neurologic signs. Endothelial cell dysfunction is thought to play a prominent role in the etiopathogenesis of RPLS. Endothelial injury leads to altered regulation of the vascular response to systemic vasoactive metabolites such as angiotensin-II, as well as to intrinsic release of endothelial vasoactive substances, resulting in blood vessel hyperactivity and labile blood pressure [Roberts 1989, Taylor in Chesley 1999, Harder 1987, Redman 1999]. Endothelial cell dysfunction resulting in increased barrier permeability is also thought to play a major role in preeclampsia [Roberts 1989, Taylor 1999, Redman 1999]. In the transplant population RPLS is a well-known complication of immunosuppressive therapy [Schwarz 1995], possibly based on the same mechanisms of endothelial cell dysfunction. It may also be seen in the setting of uremia, hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) [Kinshita 2003]. RPLS is reported with the use of chemotherapeutic agents such as cisplatin, interferon A, intrathecally administered methotrexate as well as in patients with acute intermittent porphyria and cryoglobinuria [Covarrubioas 2002, Port 1998, Schwarz 1998].

Why do some women with a relatively mild hypertension develop eclamptic convulsions ? It is tempting to hypothesize that the upper limit of cerebral autoregulation is reduced in women (pre)-eclampsia but evidence for this is lacking. From clinical observation it seems that failure of cerebrovascular autoregulatory mechanisms may occur in response to either a rapid and/or relatively large blood pressure increase. Subsequently, forced overdistension of the cerebral vasculature

poses risk for vessel damage and barotrauma. This is illustrated in women with preeclampsia by finding increased cerebral blood flow using velocity-encoded phase contrast MRI [Zeeman 2004] and increased cerebral perfusion pressure using transcranial Doppler ultrasound [Riskin 1999, Williams 1998]

Implications for practice

The rational approach to Reversible Posterior Leucoencephalopathy Syndrome in pregnancy

The effect of normal pregnancy, let alone, preeclampsia, on the upper limit of mean arterial pressure at which autoregulation operates is unknown. Almost a fifth of eclamptic women reportedly have maximum systolic blood pressures of < 140 mmHg prior to the event [Sibai 1990, Mattar 2000.] Although the risk of convulsions seems certainly greater in clinically severe compared to mild preeclampsia, reliance on the level of blood pressure for grading severity of disease can be disastrous. This was recently shown by Martin et al [2005] who scrutinized the peripartum course of 28 preeclamptic women who experienced a hemorrhagic stroke. Severe diastolic hypertension (>110 mmHg) did not necessarily develop prior to the event. Indeed, the great majority of the patients in this case series never exhibited a single or sustained diastolic blood pressure of 105-110 mmHg.

Furthermore, blood pressure treatment alone does not necessarily seem to prevent the development of RPLS nor hemorrhagic stroke. Autoregulation is abnormal in these patients and, as said, prediction of the degree of dysfunction and in whom it will occur is difficult. In general, blood pressure needs to be reduced to a safe range to avoid loss of cerebral autoregulation. As discussed in the prior paragraph, likely because of endothelial dysfunction, preeclampsia is capable of regionally affecting vascular smooth muscle function. Alterations in the cerebral circulation in (pre)-eclamptic women may occur despite minimal elevation in blood pressure. Eclamptic women with such borderline hypertension are often young primigravidas whose blood pressures have risen markedly from low levels. The

critical threshold could be related to the patients customary blood pressure prior the development of hypertension. Furthermore, the relative rapidity of changes may be of primary importance although this is difficult to study.

Accurate evidence based recommendations for the use of antihypertensive treatment in women with severe (pre)-eclampsia do not exist, however. The final recommendation of the NICHD Working Group Report, and as such endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP), is to treat acute severe hypertension in (pre)-eclampsia when systolic blood pressure is > 160 mmHg and/or diastolic blood pressure is sustained > 105 mmHg [NICHD 2000].

Most seizures occur during the intrapartum and postpartum periods. None of the clinical signs and symptoms considered to be prognostic of seizures are absolutely reliable. [Sibai 1981] Symptoms may occur before or after the onset of convulsions, and they include persistent occipital or frontal headaches, blurred vision, photophobia, epigastric or right upper quadrant pain, and altered mental status. Patients will have at least one of these symptoms before the onset of eclamptic convulsions in 60-75 % of the cases [Sibai 2005]. Headache may herald the loss of autoregulation and clinically this makes sense.

The lack of a full understanding of the etiology of eclamptic convulsions has mounted in considerable disagreement considering the best anticonvulsant for the prevention and control of such seizures. Without going into much detail, which is the focus of other excellent reviews [Sibai 2004, 2005, Katz 2004], the use of magnesium sulfate for the prevention and treatment of eclamptic seizures has been well supported despite the fact that we know very little of its mechanisms and actions [Magpie 2002, Witlin 1999,Sibai 2004]

Do all women with eclampsia need neuroimaging studies ?

One can question the indication for neuroimaging studies in eclampsia or when (pre)-eclampsia is complicated by transient blindness, especially if the clinical course is typical, with prompt response to therapy. Most reported cases of blindness in pregnancy have been secondary to cortical cerebral edema and thus are often labelled as cortical blindness. These women typically have normal fundoscopic examinations and lesions consistent with cerebral edema on MRI. Cortical blindness is almost always transient as are the neuroimaging findings associated with it.

Recurrent eclamptic seizures refractory to magnesium sulfate, however, may be associated with structural central nervous system abnormalities such as sinus thrombosis [Dunn 1986.] Whilst epilepsy and eclampsia will account for most peripartum seizures all cases where atypical signs exist require thorough neurological examination [Keay, Konstantinopoulos 2004.] Neuroimaging studies could generally be limited to those women who have additional focal neurological signs, prolonged coma, atypical convulsions and those who have a prolonged return to complete recovery following delivery. In such women hemorrhage or other serious abnormalities requiring specialised interventions must be promptly excluded. MRI is much more often contributory compared with CT in patiens with hypertensive disorders of pregnancy [Dahmus 1992, Manfredi 1997]. The use of MRI diffusion and ADC mapping allows an earlier and clearer differentiation of cytotoxic and vasogenic edema. Even though the clinical Consequences of making this distinction are still limited at time of this review, employing this type of imaging may have important prognostic implications for eclamptic women in the future [Zeeman 2004, Loureiro 2003.]

Conclusions

Eclampsia is almost exclusively a disorder of human pregnancy, the pathogenesis of which remains unknown. For ethical reasons experimental studies precisely evaluating the cerebrovascular condition are far and few between. Based on similarities both radiologically and clinically as well as pathologically, attention is directed towards Reversible Posterior Leucoencephalopathy Syndrome (RPLS) as a comparable model. Specialised MR findings sugggest a continuum of pathology that is proportionally associated with the severity of the clinical findings including hydrostatic edema. If severe enough, such edema may result in cellular ischemia and irreversible cell death [Tamaki 1984]. It is now demonstrated that up to one fourth of eclamptic women may have evidence of cerebral tissue loss 6 weeks postpartum. There are no reliable predictors no signs or symptoms to forecast the development of eclampsia in women with hypertensive disorders of pregnancy. Eclampsia is rarely associated with persistent, clinically recognizable, neurologic morbidity and epilepsy is not a recognized longterm complication [Sibai 1985.] However, intra-cerebral hemorrhage is a well-known cerebrovascular complications of eclampsia frequently leading to maternal death or major permanent disability. The proposed progression from ischemic to hemorrhagic infarction in eclamptic patients may have important therapeutic implications. In general, therapy should be directed toward lowering blood pressure so as to limit the further development of vasogenic edema and subsequent ischemia. Therapy should also include treatment with Magnesium sulfate, and maintaining adequate platelet levels to avoid hemorrhage.

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