Eclampsia & preeclampsia

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Preeclampsia and the risk of cerebral white matter lesions

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Submitted

Abstract

INTRODUCTION

Several years after pregnancy women with a history of eclampsia have cerebral white matter lesions more often compared to parous controls. The presence of these lesions is hypothesized to be the long-term result of the posterior reversible encephalopathy syndrome (PRES). Preeclamptic women may also experience PRES in the absence of eclamptic seizures. The aim of this study was to assess presence and severity of white matter lesions in formerly preeclamptic women.

METHODS

Cerebral MR imaging was performed on 73 formerly preeclamptic women and 75 healthy parous controls. Presence and severity of white matter lesion were determined by a neuroradiologist blinded for patient category.

RESULTS

Formerly preeclamptic women had white matter lesions significantly more often (37%) and more severely (mean 0.11, median 0.00, range 0-2.34ml) compared to controls (21%, p=0.04, mean 0.015, median 0.00, range 0-0.13ml, p=0.02). Average age (37±6 years) and elapsed time since index pregnancy (5.1±3.7 years) were similar in both groups. Within the formerly preeclamptic women current hypertension and a history of early-onset preeclampsia (<37 weeks) were independently associated with presence of white matter lesions.

CONCLUSIONS

Cerebral white matter lesions were present more often and more severely in formerly preeclamptic women compared to age-matched controls. Although, the predisposition of formerly preeclamptic women to cardiovascular disease, especially those with early-onset preeclampsia, may be an important cause of cerebral white matter lesions, a history of PRES is possibly an additive risk factor for the development of these lesions. Our findings indicate that preeclampsia might be a risk factor for early cerebrovascular damage.

Introduction

Women who had a pregnancy complicated by eclampsia, have cerebral white matter lesions (WML) several years later more often compared to women with normotensive pregnancies.[1] In addition, women with a history of preeclampsia have an increased risk of cardiovascular disease including stroke.[2,3] It has been suggested that the WML in formerly eclamptic women are a long term result of the posterior reversible encephalopathy syndrome (PRES)[1]. PRES is characterized by neurologic symptoms such as headache, altered mental functioning, seizures and loss of vision, together with bilateral vasogenic subcortical edema mainly in occipital and parietal lobes on cerebral computed tomography (CT) or magnetic resonance (MR) imaging.[4] It has been hypothesized that severe vasogenic edema can cause compression of cerebral tissue leading to reduced perfusion followed by ischemia, hypoxia and cell death.[5] Although its pathophysiology is still unclear, PRES has been recognized in eclampsia as well as in a variety of other disorders including several of iatrogenic or neurotoxic etiology.[6,7] These disorders are associated with endothelial dysfunction and hypertension in most cases.[5,6] Tonic-clonic seizures are not mandatory for the diagnosis of PRES and preeclamptic women may demonstrate signs, symptoms and imaging features of PRES in the absence of an eclamptic seizure.[8-10] The incidence and possible sequelae of PRES in women with preeclampsia are unknown, because cerebral imaging in such women is not standard practice. The aim of this study was to assess the presence and severity of WML in formerly preeclamptic women.

Materials and Methods

Study participants

The project was approved by the University Medical Center Groningen (UMCG) Institutional Review Board and all participants signed informed consent. The UMCG is a tertiary referral and academic teaching hospital in The Netherlands that serves as a perinatal referral center for high-risk pregnancies. A small percentage of healthy women without complicated pregnancies chooses to deliver in the UMCG as well. The annual delivery rate averages 1,600. The population in the northern part of the Netherlands is predominantly Caucasian. The department works with an electronic admission and delivery database since 1988. Women who were admitted with preeclampsia between 1988 and 2005 were selected and matched for age and year of index pregnancy to women

who experienced eclampsia of whom we reported in previous studies.[1,11] These formerly preeclamptic women were invited to participate in the current study by mail. In addition to this group, all women admitted to the obstetric high care with severe preeclampsia and/or HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) over a 2-year period (January 1, 2005 and December 31, 2006) were invited by mail to participate. Five formerly preeclamptic women who delivered in other hospitals than the UMCG had heard about this study and requested to participate in our study, which was allowed. Preeclampsia and gestational hypertension were defined according to internationally agreed standards.[12,13]

Only those women who were without contraindications for MR imaging (i.e. presence of metallic objects, tattoos, current pregnancy or claustrophobia) were eligible. When eligible, medical records were reviewed for accuracy and severity of diagnosis of preeclampsia and for the presence of neurological symptoms (visual disturbances, headache, increased tendon reflexes, myoclonia, nausea and vomiting) and HELLP syndrome during their admission. Exclusion criteria, besides mentioned MRI contraindications, included preexistent epilepsy, demyelinating disorders, a known cerebrovascular accident, intracranial infections or a history of any neurosurgical procedure. Formerly preeclamptic women were subsequently matched for age (within 2 years) and year of index pregnancy (within 2 years) with parous control women whose pregnancies had been uncomplicated and normotensive. These controls were recruited either through the department's electronic delivery database or recruited amongst hospital/department employees and their family members. Their records were evaluated to confirm that the pregnancy was indeed uneventful and normotensive.

Physical examination

On the day of MR imaging, body weight and blood pressure were measured. Blood pressure was measured manually with an aneroid sphygmomanometer. Participants were in sitting position with their arm resting on the chair-arm. Blood pressure was measured after a resting period of > 5 minutes and repeated after one hour if blood pressure was high. Blood pressure of ≥ 140/90 mmHg, or known hypertension with current antihypertensive medication use was used for the diagnosis of current hypertension in this group of women. The lowest measured blood pressure was used for analysis. Measurements were done by well-trained final year medical students and physicians.

MRI protocol

All studies were performed on a 3 Tesla MRI system (Philips Intera) at the Neuroimaging Center of the School for Behavioural and Cognitive Neurosciences in Groningen using 5 mm slices with a 20% gap and a matrix: 256 x 256. Used sequences include T1 (repetition time [TR] 700 ms, echo time [TE] 8.4 ms, α=65°, number of averages = 1), Proton Density (TR 3000 ms, TE 26.7 ms, α=90°), T2 (TR 3000 ms, TE 120 ms, α=90°) and fluid attenuation inversion recovery (FLAIR) (TR 11000 ms, TE 100 ms, TI 2800 ms, α=90°, number of averages = 2). For all women that underwent imaging in the second half of the study additional venous BOLD scans were preformed in order to detect microbleeds (volume scan with a voxel size of 0.45 x 0.45 x 1.00 mm. TR 34.9, TE 49.9, α=15°, matrix: 512 x 512). These were performed in 36 formerly preeclamptic women and 46 control women. An experienced neuroradiologist, blinded to participant's category and clinical data, rated the presence, size and number of white matter lesions. White matter lesions were considered present if hyperintense on FLAIR, proton density-weighted and T2-weighted image and not hypointense on a T1-weighted image. A WML severity score was used to asses the severity of WML for the subcortical area as described previously.[14,15] Briefly, the size of subcortical WML were rated according to their largest diameter in categories of small (< 3 mm), medium (3-10 mm), or large (> 10 mm). Considering them spherical with a fixed diameter per size category, a total volume-index of subcortical WML was calculated (range 0 – 0.4 mL). Having less than 3 possible small lesions and no confluent lesions was considered as no lesions to adjust for possible misclassifications. WML were considered periventricular lesions if the largest diameter was adjacent to the ventricular lining.

Data analysis

Demographic data were compared using Chi-square or Student t-test where appropriate. The presence of WML was compared between groups using Chi-square. The severity of WML between the groups was analyzed by using the Mann-Whitney (2 groups) or Kruskal-Wallis (3 groups) test. When the Kruskal-Wallis test was used, the Mann-Whitney was used as a post-hoc test. Univariate and multivariate binary logistic regression analysis were used for identify variables related to the presence of WML. Univariate regression analysis was used to identify variables related to WML severity. Considered covariables for the preeclampsia and control groups are listed in Table 1, estimated gestational age and birth weight were not included. Covariables for the preeclampsia subgroups are listed in Table 2. A P-value of < 0.05 was considered statistically significant. SPSS version 16.0 was used for data analysis.

Results

Three control participants were excluded because they had been diagnosed with gestational hypertension during the index pregnancy and a fourth control participant because she suffered epilepsy. One of the controls was excluded because of the incidental finding of a brain tumor during the MRI scan and one control was excluded because she demonstrated brain WML suggestive of a demyelinating disorder. One formerly preeclamptic woman was excluded because the diagnosis of preeclampsia could not be confirmed. The remaining number of participating women was 73 in the formerly preeclamptic group and 75 in the control group. In the formerly preeclamptic group 3 women had hypertension without proteinuria but with HELLP syndrome during the index pregnancy. One of the control women was of Asian origin, all other participants were Caucasian.

The participant's characteristics are shown in Table 1. As may be expected, the estimated gestational age and birth weight were significantly different between the groups. Current age and elapsed time since the index pregnancy were similar for both groups. Current systolic and diastolic blood pressure as well as current body weight was significantly higher in the formerly preeclamptic group. In the preeclamptic group 8 (11%) women had pre-existent hypertension prior to the index pregnancy and 10 (14%) women had suffered preeclampsia in more than one pregnancy.

Table 1 Participant's characteristics. Values are ± standard deviation.

	Controls (n = 73)	**Preeclampsia** (n = 75)	**P-value**
Age (years)	36.9 ± 6.0	36.6 ± 6.2	0.76
Elapsed Time since Index Pregnancy (years)	5.0 ± 3.3	5.3 ± 4.1	0.61
Birth Weight of Child (grams)	3464 ± 462	1842 ± 1176	0.00
Estimated Gestational Age at Delivery (weeks)	39.9 ± 1.2	33.0 ± 5.1	0.00
Current Systolic BP (mmHg)	116 ± 12	127 ± 12	0.00
Current Diastolic BP (mmHg)	74 ± 9	82 ± 11	0.00
Current Weight (kg)	71.0 ± 11.7	76.1 ± 18	0.03
Currently Hypertensive	4 (5%)	18 (25%)	0.00
Currently Smoking	14 (19%)	13 (18%)	0.88
History of Migraine	16 (21%)	24 (33%)	0.09

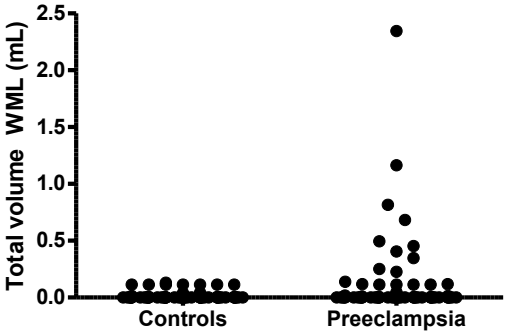

Figure 1 The total volume of white matter lesions in the formerly preeclamptic group and the control group. Mann-Whitney test, p = 0.02.

Significantly more women in the formerly preeclamptic group had WML compared to women in the control group (p=0.04, table 2). In addition, WML were more severe in the formerly preeclamptic women compared to the controls (p = 0.02, Figure 1, Table 2). In the formerly preeclamptic group, age (β = 0.09, P = 0.04) and current hypertension (β = 1.34, p = 0.02) were associated with the presence of WML. Adjusting for age revealed that current hypertension was independently associated with the presence of WML (β = 1.18, P = 0.04) in the formerly preeclamptic women. Current hypertension was not associated with severity of WML and none of the other women's characteristics (Table 1) were independently associated with neither presence nor severity of WML. In the control group no associations were found with the presence of WML.

The subgroup analyses within the preeclamptic group are shown in Table 2. The presence of HELLP syndrome or neurological symptoms during the index pregnancy in formerly preeclamptic women was not related to the presence or severity of WML. However, women who delivered prior to a gestational age of 37 weeks (early-onset preeclampsia) had significantly more often WML in comparison to those with late-onset preeclampsia. Also, the WML were significantly more severe in the formerly early-onset preeclamptic women compared to late-onset preeclampsia (Table 2) and controls (p<0.01, Figure 2). Formerly preeclamptic women had WML more often when they were currently hypertensive (11/18, 61%) compared to non-hypertensive formerly preeclamptic women (16/55, 29%, p = 0.02). The WLM were more severe in the currently hypertensive women, however, this did not reach significance (p = 0.07). There was no difference in presence or severity of WML between preeclamptic women with or without preexistent hypertension, preeclampsia during subsequent pregnancies, use of magnesiumsulphate and diastolic blood pressure above 110 mmHg during preeclampsia (an indicator for severe preeclampsia, Table 2). Of these factors, only early-onset preeclampsia was associated with the presence of WML (β = 1.73, p = 0.01).

Table 2 Presence and volume of white matter lesions (WML) in formerly preeclamptic women, control women and preeclampsia subgroups.

	Preeclampsia and Control groups		**P-value**
	Controls (n=75)	***Preeclampsia (n=73)***	
WML present	16 (21%)	27 (37%)	0.04
Mean volume	0.015 (0.00 – 0.13)	0.11 (0.00 – 2.34)	0.02
	Preeclampsia subgroups		
	Late-onset PE (>37 weeks, n=22)	***Early-onset PE (<37 weeks, n=51)***	
WML present	3 (14%)	24 (47%)	0.01
Mean volume	0.01 (0.00 – 0.11)	0.15 (0.00 – 2.34)	0.01
	Mild or no diastolic hypertension (n=47)	***Severe diastolic hypertension (n=25)***	
WML present	10 (14%)	16 (64%)	0.62
Mean volume	0.22 (0.00 – 2.34)	0.06 (0.00 –0.49)	0.42
	No neurologic symptoms (n=25)	***Neurologic symptoms (n=48)***	
WML present	10 (40%)	17 (35%)	0.70
Mean volume	0.14 (0.00 – 1.16)	0.97 (0.00 – 2.34)	0.59
	No HELLP syndrome (n=34)	***HELLP syndrome (n=39)***	
WML present	14 (41%)	13 (33%)	0.49
Mean volume	0.09 (0.00 -1.16)	0.13 (0.00 – 2.34)	0.80
	No $MgSO_4$ (n=49)	***$MgSO_4$ (n=24)***	
WML present	20 (41%)	7 (29%)	0.33
Mean volume	0.10 (0.00 - 1.16)	0.13 (0.00 – 2.34)	0.40

Volume is in ml with the range in parenthesis. The median was 0.00 ml in all (sub)groups. Severe diastolic hypertension is defined as ≥ 110 mmHg.

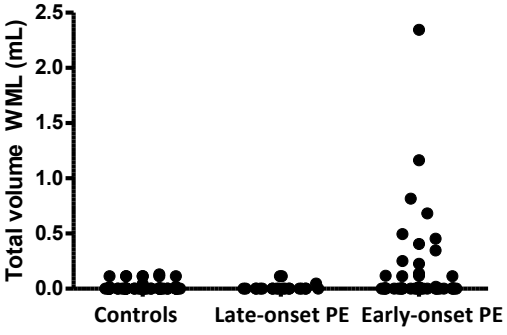

Figure 2 Total volume of white matter lesions in the control group, late-onset preeclamptic group and early-onset preeclamptic group. Kruskal-Wallis test over all: $p < 0.01$. Post-hoc: early-onset PE vs. late-onset PE: $p = 0.01$ and vs. controls: $p < 0.01$. PE = preeclampsia.

In the formerly preeclamptic group 2 women had a lacunar infarct and 1 woman had a cortical infarct. None of the control women had cerebral infarcts. All of the three women who had infarcts had several WML in addition. One had recurrent preeclampsia in three pregnancies and diabetes mellitus type 2, another had hereditary renal dysfunction, two had early-onset preeclampsia, two were currently hypertensive, and two had hypothyroidism.

Five formerly preeclamptic women had periventricular WML versus none of the controls (p=0.02). These five women also had subcortical WML in addition and all had early-onset preeclampsia. Microbleeds were seen in one control woman and in one formerly preeclamptic woman.

Comment

In this study we found that several years after the index pregnancy formerly preeclamptic women had cerebral WML more often and more severe compared to control women with normotensive pregnancies. This appeared predominantly in women with early-onset preeclampsia. In addition, the current blood pressure of formerly preeclamptic women was significantly higher compared to controls and in the formerly preeclamptic women current hypertension was independently associated with the presence of WML. Since a relationship with neurologic symptoms at the time of preeclampsia could not be demonstrated in our study, PRES may not be the single factor associated with these WML.

The current concept of the development of PRES is related to breakthrough of the brain's well developed autoregulatory capacity.[16] From clinical observations it seems that in the presence of endothelial dysfunction, sudden, even minute, elevations in systemic blood pressure may result in failure of cerebral autoregulation.[17] It has been hypothesized that in this syndrome forced vasodilatation, increased hydrostatic pressure and hyperperfusion result in disruption of the blood-brain barrier.[18] Subsequent extravasation of plasma and opening of the endothelial tight junctions (blood-brain barrier) is followed by formation of vasogenic edema and results in manifestation of the clinical syndrome with accompanying neuroimaging findings.[4,7,16]

Eclamptic women demonstrate vasogenic edema on CT and MRI at the acute moment.[4,9,10] Using diffusion weighted imaging (DWI) in a subset of women areas with cytotoxic edema can also be demonstrated.[5,19] It has been suggested that vasogenic edema in PRES/eclampsia can progress to such an extent that regional perfusion pressure

and blood flow decrease causing ischemia and cytotoxic edema.[5,20] Vasogenic edema resolves as the blood pressure normalizes [4], however, at two months follow-up approximately one fourth of eclamptic women demonstrate areas of gliosis or infarction within and around the area of previously restricted diffusion as seen on DWI.[5,19] In addition, several years after the index pregnancy formerly eclamptic women have WML more often and more severe compared to parous controls, in a linear relationship with the number of tonic-clonic seizures.[1] These findings suggest a causal relationship between severe cerebral vasogenic edema during the acute phase of PRES and the subsequent development of infarction and WML.

Preeclamptic women do not usually demonstrate cerebral abnormalities on radiologic imaging during the acute moment, although some women with severe preeclampsia have cerebral edema consistent with PRES.[8-10,21,22] We found that the presence of neurologic symptoms during the index pregnancy was not associated with the presence of WML several years after the index pregnancy which may suggest that PRES is not solely responsible for WML in the long term. Because of the reported inconsistency in presence of imaging abnormalities during the acute phase in women with preeclampsia[21,22], it is possible that some of our participants did suffer PRES during the index pregnancy. Whether or not they had subtle signs or symptoms of PRES may have been missed in our study due to its retrospective nature.

An additional explanation for the high percentage of women with WML in our group of formerly preeclamptic women, is the high prevalence of current hypertension in this group. In general, cardiovascular risk factors, especially hypertension, are related to the presence and progression of WML. The presence of hypertension is a risk factor for the development of WML in elderly populations[23,24] and younger cohorts.[25] Age is the predominant determinant for the presence of WML, however, this is a less important risk factor in younger (<55 yrs) populations.[25] The exact clinical importance of the presence of WML in a young cohort as in our study, is not clear. However, in the elderly there is evidence that the presence and particularly the severity of WML are important risk factors for the development of cognitive impairment, vascular dementia, Alzheimer's disease and stroke.[26]

A recent meta-analysis revealed that formerly preeclamptic women, especially those with early-onset preeclampsia, have an increased risk of ischemic and hemorrhagic stroke, both fatal and non-fatal, in later life.[3] Women who suffered preeclampsia appear to be at increased risk of hypertension, ischemic heart disease, stroke and venous thromboembolism later in life.[3] The results from our study are in line with these epidemiologic findings. In formerly preeclamptic women we found a high percentage of current hypertension and WML and in women with early-onset preeclampsia also more

often and more severe WML. A current concept is that pregnancy is a vascular and metabolic 'stress test' for a woman's health later in life.[27] If a woman develops preeclampsia – especially early-onset preeclampsia – she 'fails' to adapt to the cardiovascular and metabolic challenges of pregnancy. She has a higher risk to develop cardiovascular disease later in life. The exact underlying mechanism of the increased risk for cardiovascular disease following a pregnancy complicated with preeclampsia remains unknown but risk factors for atherosclerosis such as chronic hypertension, dislipidemia, obesity and glucose intolerance are likely to play a role.[28] This stresses the importance of decreasing the number of risk factors by changing life style and checking blood pressure regularly post partum in these young women.

Several methodological limitations to this study deserve attention. First, this study is a retrospective study and there are no imaging data of our participants prior to their index pregnancy. Whether WML were present prior to the index pregnancy, is therefore unknown, but considered unlikely. Second, cerebral imaging was not performed during the index pregnancy. This makes it impossible to identify those women who may have had cerebral edema due to PRES and to relate this to the current presence of WML. Third, we retrieved information on neurological symptoms retrospectively from medical records. This may be unreliable if used to determine retrospectively which women may have had signs and symptoms of PRES at the acute moment during the index pregnancy.

Perspectives

To our knowledge this study is the first to report cerebral imaging and cerebral white matter lesions in the long term in a considerable group of women with a history of preeclampsia. The exact cause of WML as well as the clinical implications of our findings are so far unknown, but seem ominous considering the higher incidence of stroke in later life in women who suffered preeclampsia. In older populations an association between WML and cognitive impairment has been found.[24,29] However, self-reported cognitive impairment was not obvious in a younger cohort with a history of preeclampsia.[11,30] Presence of WML is associated with the development of vascular dementia and Alzheimer's disease later in life. In addition to cognitive impairment and dementia, the baseline severity of WML is associated with the risk of stroke.[31,32] Therefore, the finding of WML in formerly preeclamptic women could indicate a precursor of cerebrovascular disease later in life. Future research should determine the clinical importance and development throughout the years of these WML in this young group of women.

Source of Funding

This project has financially been supported by ZonMW (90700235), the Netherlands organization for health research and development.

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Part II

Er is
nog nooit
een mens geweest
die een korrel aarde
heeft bezeten

(Jan Arends)