Original Research

Regional Distribution of Cerebral White Matter Lesions Years After Preeclampsia and Eclampsia

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OBJECTIVE: To assess the distribution of cerebral white matter lesions in women who had eclampsia, preeclampsia, or normotensive pregnancies. The pathophysiology of these lesions, more often seen in formerly eclamptic and preeclamptic women, is unclear but may be related to a predisposition for vascular disease, the occurrence of the posterior reversible encephalopathy syndrome, or both while pregnant. Assessing the distribution of such lesions may give insight into their pathophysiology and possible consequences.

METHODS: This retrospective cohort study determined the presence, severity, and location of white matter lesions on cerebral magnetic resonance imaging scans of 64 formerly eclamptic, 74 formerly preeclamptic, and 75 parous control women.

RESULTS: Formerly preeclamptic and eclamptic women have white matter lesions more often (34.4% [n=47] compared with 21.3% [n=16]; $P<.05$) and more severely (0.07 compared with 0.02 mL; $P<.05$) than parous women in a control group. In all women, the majority of lesions was located in the frontal lobes followed by the parietal, insular, and temporal lobes.

CONCLUSION: White matter lesions are more common in women with prior pregnancies complicated by preeclampsia or eclampsia compared with parous women in a control group. In no group does regional white matter lesion distribution correspond to the occipitoparietal edema distribution seen in posterior reversible encephalopathy syndrome.

(Obstet Gynecol 2014;123:790–5)
DOI: 10.1097/AOG.0000000000000162

LEVEL OF EVIDENCE: II

In previous studies an increased prevalence of cerebral white matter lesions was found in formerly eclamptic and preeclamptic women compared with women after normotensive pregnancies.[1,2] Although the pathogenesis of white matter lesions remains to be elucidated, the increased propensity for cerebrovascular and cardiovascular disease in formerly preeclamptic women[3] may be an associated factor. We hypothesize that an episode of posterior reversible encephalopathy syndrome, which is considered the underlying cause of the neurologic symptoms in eclamptic as well as some preeclamptic patients, may play an additional role.[4] In posterior reversible encephalopathy syndrome, severe vasogenic edema has been suggested to potentially progress to such an extent that regional cerebral perfusion decreases, leading to areas of cytotoxic edema, infarction, and development of white matter lesions in the long term.[5,6]

In elderly individuals, white matter lesions are associated with cognitive decline and dementia[7] and are mainly located in the frontal and parietal lobe.[8–10] Although impaired subjective cognitive functioning in formerly eclamptic women has been reported,[11,12] no significant differences were found for objective measures of sustained attention and executive functioning

after eclampsia.[13] Moreover, in former patients with posterior reversible encephalopathy syndrome, permanent clinical symptoms have been found including impaired self-perceived as well as objective neurocognitive functioning and visual disturbances,[11,12,14–16] partly thought to be related to permanent cerebral lesions. However, the clinical implications of white matter lesions in formerly preeclamptic and eclamptic women remain so far unclear.

To get insight into the pathophysiology and possible consequences of white matter lesions, this study assessed the distribution of such lesions in women who had eclampsia or preeclampsia compared with women who had normotensive pregnancies several years prior.

MATERIALS AND METHODS

Participants were enrolled in this retrospective cohort study as part of ongoing follow-up studies assessing cerebral long-term consequences of preeclampsia and eclampsia such as white matter lesions and neurocognitive functioning.[1] Three groups of women were recruited for these studies, ie, formerly eclamptic, formerly preeclamptic, and parous control women.

Women with a diagnosis of eclampsia in their medical history between 1988 and 2005 were identified from the electronic admission, diagnosis, and delivery databases of the University Medical Center Groningen. Recruitment and selection criteria have been published previously.[1,2] In the meantime, additional formerly eclamptic women have been recruited to participate in our follow-up studies through collaboration with two other tertiary referral centers: the VU University Medical Center Amsterdam and Isala Clinics Zwolle. In addition, six formerly eclamptic women who delivered in other hospitals and who had heard about this study requested to participate in the current study, which was allowed. Recruitment and selection criteria of participating women with a diagnosis of preeclampsia or normotensive pregnancies in their medical history were reported previously.[2] Briefly, medical records of formerly eclamptic and preeclamptic women were reviewed for accurateness of diagnosis and to extract clinical and demographic characteristics. Both eclampsia and preeclampsia were defined according to the definition of the International Society for the Study of Hypertension in Pregnancy.[17] Parous women in the control group were recruited through either the department's electronic delivery database or among hospital employees and their family members. Their records were evaluated to confirm that the pregnancy was indeed uneventful and normotensive. Exclusion criteria included contraindication for magnetic resonance image (MRI) scanning, a history of epilepsy, cerebrovascular accident, demyelinating disorders, intra-cranial infections or any cranial neurosurgical procedure, or the inability to understand Dutch. Only women who did not meet any of the exclusion criteria were invited to participate in the current study by mail.

After the MRI procedure and after a period of rest, blood pressure was measured manually using a aneroid sphygmomanometer. Patients with a systolic blood pressure of 140 mmHg or greater, diastolic blood pressure 90 mmHg or greater, or both or currently using antihypertensive medication or both were designated as currently hypertensive.[18]

Approval for this project was obtained from the Medical Ethics Committee of the University Medical Center Groningen and all participants signed informed consent.

Detailed MRI study protocols have been previously described.[1] Briefly, participants underwent MRI on a 3-T MRI system using the following sequences: T1, proton density, T2, and fluid-attenuated inversion recovery using parameters as described previously.[1] Transverse slice thickness was 5 mm with a 20% interslice gap. The presence, size, and number of white matter lesions were rated by an experienced neuroradiologist, who was blinded for patient category as previously described.[1,19] White matter lesions were considered present if hyperintense on fluid-attenuated inversion recovery, T2- and proton density-weighted images and not hypointense on T1-weighted images. Subcortical white matter lesions were categorized according to their largest diameter as small (less than 3 mm), medium (3–10 mm), or large (greater than 10 mm). The number of lesions was evaluated per size category for the following locations: frontal, parietal, temporal, occipital, insular, brainstem, and cerebellum. Considering them spherical with a fixed diameter per size category, a total approximated volume for subcortical white matter lesions was determined.

For evaluation of prevalence and mean volume of lesions in each group, correction for inclusion of partial volume was performed as previously described.[2] Briefly, for each participant, an arbitrary two small lesions were subtracted from the total number of small lesions. This means that women with only two small lesions or less were considered as white matter lesion–negative. Correction for partial volume was not possible for evaluation of regional distribution because it is not feasible to determine from which brain region(s) the partial volume correction (ie, two small lesions) should be subtracted if a woman demonstrates small lesions in more than one region. Therefore, prevalence of white matter lesions according to brain region was evaluated in lesion-positive women only with inclusion of all lesions, ie, without correction of partial volume.

Descriptive statistics such as demographic information are presented as means±standard deviations for continuous variables and percentages for dichotomous variables.

Demographic data were compared among formerly eclamptic, preeclamptic, and control women using analysis of variance for normally distributed data, or Kruskal-Wallis test for data that were not normally distributed. Dichotomous variables, ie, presence of white matter lesions, current hypertension, current smoking, and nulliparity, were compared between the groups using χ^2 with pair wise χ^2 as the post hoc test. Lesion volume between formerly (pre)eclamptic and control women was compared using the Mann-Whitney test. To evaluate differences in presence of white matter lesions between brain regions, the proportion of women with lesions in the frontal lobe was compared with the proportion of women with lesions in the other brain regions using McNemar's test.

Differences were considered statistically significant at $P \leq .05$. For evaluating differences in presence of white matter lesions between brain regions, a Bonferroni correction was applied to this α level. Data analyses were performed using SPSS statistical package for Windows 8.

RESULTS

The recruitment and inclusion process of the formerly preeclamptic women (n=74) and the women who had normotensive pregnancies (n=75) has recently been described in a report on presence and lesion load of white matter lesions.[2] The group of formerly eclamptic women has been expanded since our last report,[1] in which neuroimaging data of 39 formerly eclamptic women were presented. Therefore, we now provide detailed description of the recruitment of the entire group of women who had eclampsia. In total, 137 formerly eclamptic women were identified. Six of these women were excluded, one because diagnosis of eclampsia could not be confirmed, another because of a history of a cerebrovascular accident, and a third as a result of inability to understand Dutch. In addition, three women had died in the interim, two of whom were the result of cerebral complications resulting from eclampsia and one as a result of gynecologic cancer. Of the remaining 131 formerly eclamptic patients, 69 could be reached and were willing to participate. Six of them were subsequently excluded as a result of contraindications for MRI scanning. Three of the 63 women who were included in the formerly eclamptic group had not experienced tonic–clonic seizures. These three, however, had experienced generalized myoclonic twitches while conscious, suggesting cerebral involvement.

Therefore, for this study, we describe the MRI findings of a total of 63 formerly eclamptic, 74 formerly preeclamptic, and 75 parous control participants.

Table 1 shows baseline characteristics of the study participants. Mean age at the time of participation was similar for all groups; all groups were in their late 30s. However, elapsed time since the index pregnancy was longer for the formerly eclamptic women (7.6±4.7 years) compared with both formerly preeclamptic women (5.2±4.1 years) and parous women in the control group (5.0±3.3 years). Furthermore, the percentage of women who were nulliparous at the time of the index pregnancy differed between the groups with most nulliparous women in the formerly eclamptic group (82.5%) followed by formerly preeclamptic (67.6%) and control women (46.7%). Estimated gestational age at delivery was more than 6 weeks shorter in formerly eclamptic and preeclamptic women compared with parous women in the control group. In addition, as expected, birth weight of the neonate was approximately 45% lower in the formerly eclamptic and preeclamptic group than the control group.

Current weight and the percentage of women who currently smoke were comparable among the three groups. Systolic and diastolic blood pressures were higher and hypertension occurred four times more often in formerly eclamptic and preeclamptic women than in parous women in the control group.

Although formerly eclamptic (n=20 [31.7%]) and preeclamptic women (n=27 [36.5%]) appeared to have subcortical white matter lesions more often than parous women in the control group (n=16 [21.3%]), these differences did not reach significance (P=.11). However, when grouped together, the (pre)eclamptic group had lesions significantly more often than parous women in the control group (34.4% compared with 21.3%; P<.05). In addition, lesion load was more than threefold in formerly preeclamptic and eclamptic women (mean volume 0.07 mL, range 0.00–2.35 mL) compared with women in the control group (mean volume 0.02 mL, range 0.00–0.13 mL, P<.05).

The cerebral regional distribution of lesions in white matter lesion–positive women was comparable for all groups (Fig. 1). In all three groups, the majority of lesions was located in the frontal lobes (P<.005; frontal lobe compared with any other brain region). In the formerly preeclamptic group, all women with lesions (n=27) demonstrated these in the frontal lobes. Eighty-five percent (n=17) of the formerly eclamptic women with lesions had these lesions in the frontal lobe; for control participants, this was 87.5% (n=14). The parietal lobe was the second most affected region by white matter lesions, that is, in 35%

Table 1. Participant Characteristics

Characteristic	Women in the Control Group (n=75)	Preeclampsia (n=74)	Eclampsia (n=63)
Current age (y)	36.9±6.1	36.6±6.2	38.2±6.3
Elapsed time (y)	5.0±3.3	5.2±4.1	7.6±4.7*
Estimated gestational age at delivery (wk)	40.1±1.1[†]	33.2±5.1	33.5±4.5
Neonatal birth weight (g)	3,464±462[†]	1,848±1,169	1,923±1,008
Nulliparous (n)	46.7% (35)[‡]	67.6% (50)[§]	82.5% (52)
Current systolic BP (mmHg)	116±12[†]	127±12	126±14
Current diastolic BP (mmHg)	74±9[‖]	82±11	79±10
Current hypertension (n)	5.6% (4)[‖]	24.3% (18)	20.8% (10)
Current weight (kg)	70.8±10.5	76.1±17.7	73.9±14.9
Current smoking (n)	18.7% (14)	18.8% (13)	16.4% (9)
White matter lesions present (n)	21.3% (16)	36.5% (27)	31.7% (20)

BP, blood pressure.
Data are mean±standard deviation or % (n of women).
* $P<.01$ compared with those in the control group and preeclampsia.
[†] $P<.001$ compared with preeclampsia and eclampsia.
[‡] $P<.01$ compared with preeclampsia and $P<.001$ compared with eclampsia.
[§] $P<.05$ compared with eclampsia.
[‖] $P<.01$ compared with preeclampsia and $P<.05$ compared with eclampsia.

of formerly eclamptic (n=7), 29.6% of formerly pre-eclamptic (n=8), and 25% of control women (n=4). In addition, three formerly preeclamptic women (11.1%) and one control woman (6.3%) demonstrated lesions in the temporal lobes. The insular lobes were affected by white matter lesions in four formerly eclamptic women (20.0%) and two women in the control group (12.5%). One formerly eclamptic woman (5.0%) had a lesion located within the cerebellum.
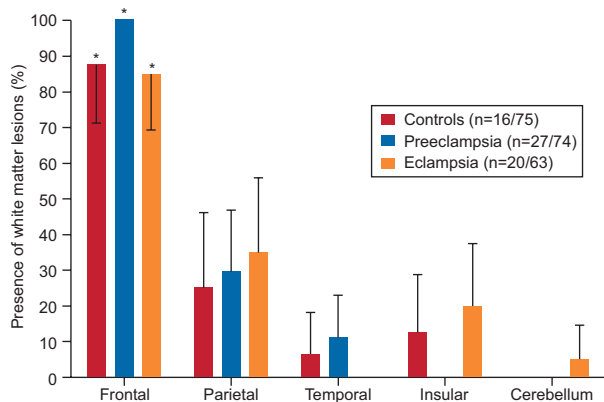
Fig. 1. Regional distribution of cerebral white matter lesions in white matter lesion–positive women. Presence of white matter lesions (with 95% confidence interval) per brain region for white matter lesion–positive women in the parous control group, formerly preeclamptic group, and formerly eclamptic group. Women who did not demonstrate white matter lesions are not included in this figure. No white matter lesions were observed in the occipital lobe and brainstem in any of the groups. *$P<.005$ compared with any other brain region of the same group.

Wiegman. Cerebral Lesions After Preeclampsia and Eclampsia. Obstet Gynecol 2014.

White matter lesions in more than one brain region were observed in 40.0% of the formerly eclamptic (n=5), 33.3% of formerly preeclamptic (n=9), and only in 25.0% of control women (n=4). In all participants, except for three formerly eclamptic and two women in the control group, lesions in the parietal, temporal, or insular lobe and cerebellum were accompanied by lesions in the frontal lobes. None of the participants showed involvement of the occipital lobe or brainstem.

Periventricular white matter lesions were present in only one formerly eclamptic woman. She did not demonstrate any subcortical white matter lesions. In five formerly preeclamptic women, periventricular lesions were observed. These women all demonstrated subcortical lesions in addition. None of the control women had periventricular white matter lesions. In all women demonstrating periventricular white matter lesions, these lesions considered mild, a pencil thin lining surrounding only part of the ventricles.

In the formerly eclamptic group, one woman demonstrated a lacunar infarct and two women had cortical infarcts. Two of these women also demonstrated subcortical white matter lesions. In the formerly preeclamptic group, two women had lacunar infarcts and one woman demonstrated a cortical infarct. These three women all had subcortical white matter lesions in addition to the infarcts. None of the control women had cerebral infarcts.

DISCUSSION

The pathophysiology of white matter lesions in formerly preeclamptic and eclamptic women remains speculative and by assessing their distribution, we

aimed to provide insight into their development. Previously, we have hypothesized that such white matter lesions may be related to posterior reversible encephalopathy syndrome.[1,2] In posterior reversible encephalopathy syndrome, an acute increase in blood pressure may cause loss of cerebral autoregulation, resulting in blood–brain barrier disruption, vasogenic edema formation, and neurologic symptoms.[20–22] Severe vasogenic edema in the acute phase of posterior reversible encephalopathy syndrome may reduce blood flow to ischemic levels, resulting in cytotoxic edema.[5] This may later appear as infarction or white matter lesions on MRI.[5,6] We expected a similar white matter lesion distribution to that of cerebral edema in posterior reversible encephalopathy syndrome. However, although the edema in posterior reversible encephalopathy syndrome is typically located in the occipitoparietal lobes,[23] this study demonstrates only few women with lesions in the posterior brain regions. In fact, the majority of lesions were located in the frontal lobes. Moreover, this distribution was similar between women who had posterior reversible encephalopathy syndrome, ie, the formerly eclamptic women, and women without posterior reversible encephalopathy syndrome, ie, the parous women in the control group. Therefore, a direct causal relationship between the cerebral edema of posterior reversible encephalopathy syndrome and white matter lesions in formerly preeclamptic and eclamptic women seems unlikely.

Alternatively, in the general population, the presence of hypertension is associated with cerebral white matter lesions,[24–26] which may also explain the higher prevalence of such lesions in our preeclamptic and eclamptic women. Preeclampsia is associated with an increased risk for vascular disease later in life, including hypertension, ischemic and hemorrhagic stroke, and ischemic heart disease.[3] In this context, the cardiovascular and metabolic demands of normal pregnancy are considered a physiologic "stress test."[27] Predisposed women fail this test and develop preeclampsia during pregnancy, thereby revealing their increased lifetime risk for cerebrovascular and cardiovascular disease. In this scheme, an underlying predisposition for cardiovascular disease may result in development of both white matter lesions and preeclampsia without a direct causal relationship between the two. The higher prevalence of current hypertension in formerly preeclamptic and eclamptic women is in line with this "stress test" theory and epidemiologic data. Moreover, the regional distribution of white matter lesions in these women is similar to what has been found in other conditions that are associated with vascular disease such as dementia and migraine.[8,9,28]

In the elderly, white matter lesions are associated with stroke, cognitive decline, and dementia.[7] The clinical implications of such lesions in our relatively young cohort of preeclamptic and eclamptic women are currently unknown. Whether cognitive functioning may sooner or later also be affected is currently under investigation. Because a role for posterior reversible encephalopathy syndrome in the development of white matter lesions cannot be completely ruled out, also clinical follow-up of former patients with posterior reversible encephalopathy syndrome is of interest. In a rather small percentage of such patients, persistent neurocognitive complaints and neuroimaging abnormalities have been described. Self-perceived cognitive functioning is impaired in formerly eclamptic women.[11,12] Furthermore, diminished objective neurocognitive functioning, visual disturbances, and epilepsy have been described after both eclampsia-related as well as nonobstetric posterior reversible encephalopathy syndrome.[14–16,29] However, comprehensive longitudinal studies concerning neurocognitive functioning after posterior reversible encephalopathy syndrome are lacking.

A few limitations of the current study should be noted. First, because neuroimaging is not a standard procedure during preeclampsia and eclampsia, the location of cerebral edema in the acute phase of posterior reversible encephalopathy syndrome cannot be individually related to the distribution of lesions years later. Furthermore, which preeclamptic women potentially had posterior reversible encephalopathy syndrome is not known. Second, white matter lesions may have been present before the index pregnancy, but this information is obviously not available. Third, we might have slightly overestimated the prevalence of lesions per brain region because it is technically not feasible to correct for inclusion of partial volume.

This study describes the regional distribution of white matter lesions in formerly preeclamptic and eclamptic women as well as parous women who never exhibited pregnancy-related hypertension. The regional distribution of white matter lesions, mostly in the frontal lobe, may be a reflection of the predisposition for vascular disease in formerly eclamptic and preeclamptic women. The difference in chronic hypertension incidence between women in the control group and study patients may explain a major part of the difference in the presence of subcortical lesions and future study should explore the role of chronic hypertension and brain white matter lesions in individuals in the reproductive age group. Whether a history of posterior reversible encephalopathy syndrome plays an additional role remains speculative but is less likely. These findings may add to the existing literature concerning the importance of evaluation of

vascular risk factors in formerly preeclamptic and eclamptic women.

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