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Eclampsia & preeclampsia

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Brain lesions several years after eclampsia



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Abstract

OBJECTIVE

Eclampsia is thought to have no long-term neurological consequences. We aimed to delineate the neurostructural sequelae of eclampsia, in particular brain white matter lesions, utilizing high-resolution 3-tesla MRI.

STUDY DESIGN

Formerly eclamptic women were matched for age and year of index pregnancy with normotensive parous controls. The presence and volume of brain white matter lesions were compared between the groups.

RESULTS

MRI scans of 39 formerly eclamptic and 29 control women were performed on average 6.4 ± 5.6 years following the index pregnancy at a mean age of 38 years. Eclamptic women demonstrated subcortical white matter lesions more than twice as often compared to controls (41 % versus 17 %, OR 3.3, CI 1.05 – 10.61, $p = 0.04$).

CONCLUSIONS

Cerebral white matter lesions occur more often in formerly eclamptic women compared to women with normotensive pregnancies. The exact pathophysiology underlying these imaging changes and their clinical relevance remains to be elucidated.

Introduction

Eclampsia, a specific neurologic complication of pregnancy, is associated with hypertension and endothelial cell dysfunction.^{1,2} Because of its neuroimaging findings and clinical features eclampsia is considered a form of the posterior reversible encephalopathy syndrome (PRES).³ Besides eclampsia, this syndrome has been recognized in a variety of other disorders which are associated with endothelial dysfunction and some degree of hypertension, including several of iatrogenic or neurotoxic etiology.^{4,5} Its pathophysiology is still unclear, but as its name suggests, the syndrome is thought to be reversible. To our knowledge there have been no studies of long-term outcomes in patients with this syndrome. Similarly, eclampsia is considered by most to be a monophasic event with no long-term neurological sequelae. At least two recent studies have documented cytotoxic cerebral edema in up to 25% of women suffering from eclamptic seizures. In these women neuroimaging findings consistent with cerebral infarctions were demonstrated when studied several months following delivery.^{6,7} Moreover, there is now evidence that women who suffered eclampsia may develop some degree of neurocognitive dysfunction.⁸ This prompted us to investigate whether brain white matter lesions (WML) were more frequently present in formerly eclamptic women compared with women who experienced uneventful pregnancies.

Materials and Methods

Study participants

The University Medical Center Groningen (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. From 1988 until 2005, 73 women were diagnosed with eclampsia. Eclampsia was defined as new onset of seizures after 20 weeks gestational age and within 1 week postpartum in women with preeclampsia. Preeclampsia was defined according to internationally agreed standards.^{9,10}

Of these 73 women the medical records were reviewed for accuracy of diagnosis of eclampsia. Upon reviewing the medical records, one formerly eclamptic participant was excluded because the diagnosis eclampsia could not be confirmed. Two had died from cerebral complications (both due to hypoxic encephalopathy secondary to severe cerebral edema) as a result of eclampsia and one woman died of cervical cancer several years after pregnancy. The remaining 69 women were invited by mail to participate in this MRI study. Forty-six (67%) formerly eclamptic women were reached and willing to participate. Exclusion criteria included preexistent epilepsy or other neurological disorders including a known cerebrovascular accident, intracranial infections, a history of any neurosurgical procedure, current pregnancy or claustrophobia. Furthermore, because of the use of a 3 Tesla magnet women with metallic implants including some dental inlays as well as heavy metallic tattoos were excluded as well. Of the formerly eclamptic participants 4 appeared to have general contra-indications for MRI scanning. Each of the remaining formerly eclamptic women was matched for age (within 1 year) and year of index pregnancy (within 2 years) with a parous control whose pregnancy 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. Forty such women were willing to participate. Their records were evaluated to confirm that the pregnancy was indeed uneventful.

One control participant was subsequently excluded because she was diagnosed with gestational hypertension during the index pregnancy and a second control participant because she suffered epilepsy. Three of the normotensive controls had general contra-indications for MRI.

Blood pressure was measured manually with aneroid sphygmomanometer in sitting position after a resting period. Blood pressure of $\geq 140/90$ mmHg was used for the diagnosis of hypertension in this group of women. The project was approved by the UMCG Institutional Review Board and all women signed informed consent.

MRI protocol

All studies were performed on a 3 Tesla MRI system (Philips Intera) at the Neuroimaging Center of the School for Behavioral and Cognitive Neurosciences in Groningen using 5 mm slices with a 20% gap. Used sequences include T1 (repetition time [TR] 700 ms, echo time [TE] 4.7 ms, $\alpha=65^\circ$), Proton Density (TR 3000 ms, TE 26.7 ms, $\alpha=90^\circ$), T2 (TR 3000 ms, TE 120 ms, $\alpha=90^\circ$), and FLAIR (TR 11000 ms, TE 100 ms, $\alpha=90^\circ$). 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 proton density-weighted and T2-weighted image (Figure 1) and not hypointense on a T1-weighted image. A WML severity score was used to assess the extent of increased white matter signal intensity on FLAIR images for the subcortical area as described previously^{11,12}. Briefly, for subcortical WML an index for their total volume was approximated (based on number and size of all subcortical lesions (range 0 - 0.4 mL). The size of subcortical WML were rated according to their largest diameter in categories of small (< 3 mm), medium (3-10 mm), or large lesions (> 10 mm). Considering them spherical with a fixed diameter per size category, a total approximated volume of subcortical WML was calculated. No periventricular WML were demonstrated except for one patient who demonstrated lesions suggestive of demyelinating disease and who was excluded from the analysis.

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 test. The relation between the number of seizures and the presence of WML was analyzed using regression analyses methods. For the test for trend the variables were entered as continuous measures in the regression model. The relation between the number of seizures and the severity of WML was analyzed using the Kruskal-Wallis test. A P value of < 0.05 was considered statistically significant. SPSS version 14.0 (SPSS Inc, Chigaco, IL) was used for data analysis.

Results

For this study we evaluated the MRI data of 41 formerly eclamptic women and 31 healthy parous control women with a history of normotensive pregnancies. Two MRI scans of formerly eclamptic women were not useable due to extensive movement artifacts. One of the controls was excluded because of the incidental finding of a brain tumor during the MRI scan. A second control was excluded because she demonstrated brain WML suggestive of a demyelinating disorder. This resulted in 39 eligible MRI scans in the formerly eclamptic group and 29 in the control group. All women were Caucasian except for two formerly eclamptic participants who were of African-American and Indonesian descent. Of the eclamptic participants 29 of 39 (74%) were nulliparous versus 15 (52%) of

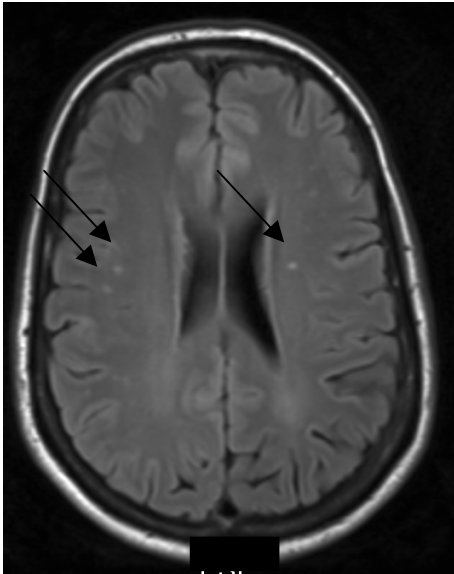


Figure 1 Magnetic Resonance Image (FLAIR) of a formerly eclamptic woman, demonstrating several white matter lesions (arrows).

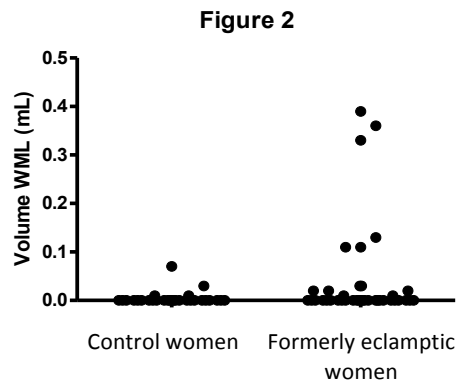


Figure 2 White matter lesion volume load in healthy control women compared to formerly eclamptic women. Mann-Whitney test $p = 0.025$.

controls. Nineteen participants had experienced a single seizure, 10 women had 2 seizures, 8 experienced 3 seizures and 2 women had 4 seizures. One formerly eclamptic woman was known with insulin-dependent diabetes mellitus and one with systemic lupus erythematosus. None of the other formerly eclamptic women nor any of the controls had a known underlying medical disorder at time of pregnancy nor at follow-up. Six of the formerly eclamptic participants (15%) as well as 4 women in the control group (14%) were currently hypertensive and/or using antihypertensive medication. Current age, elapsed time since index pregnancy, current blood pressure as well as the gestational age at delivery and birth weight of the index pregnancy 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 in the two groups.

Of the formerly eclamptic women cerebral WML were found in 16 of 39 (41%), compared with 5 of 29 (17%) women in the control group ($p = 0.03$). As shown in figure 2, there was a large variation of WML volume within the eclampsia group. Mean WML volume in the formerly eclamptic participants was 0.041 mL (SE 0.016) vs. 0.004 mL (SE 0.002) in the control group. However, there was a significant difference in WML lesion volume between the groups (mean rank 29.4 and 38.3, respectively, $p = 0.025$). Five of

the 6 (83%) women with the largest WML volume had experienced multiple seizures compared with 16 of 33 (48%) eclamptic women with lesser WML volume ($p = 0.11$). Four of the 6 (67%) women with the largest WML volume also had HELLP syndrome compared with 16 of 33 (48%) eclamptic women with lesser WML lesion load ($p = 0.41$). $MgSO_4$ was administered in 26 of 39 (67%) of women, of which 5 received it prior to the first seizure. Of these 26 women 12 (46%) had WML on MRI. This is not significantly different from the group that did not receive $MgSO_4$ ($p=0.36$) and the number of seizures was not different between the group and the group without $MgSO_4$ administration.

The maximum blood pressure at the time of seizures was not different between the formerly eclamptic women with or without WML (188 ± 7 vs. 199 ± 7 mmHg diastolic respectively, p -value 0.29 and 109 ± 4 vs. 116 ± 3 mmHg systolic, p -value 0.123). The presence of HELLP and the parity at the time of seizures were not associated with the presence of white matter lesions in the formerly eclamptic group (p -values 0.24 and 0.50 respectively).

As shown in Figure 3, there was a positive correlation between the number of seizures and the presence of WML (test for trend, $p = 0.009$). Women who had experienced 3 or more seizures ($n = 10$) demonstrated WML more than 3 times as often as compared to controls ($p = 0.01$). The Kruskal-Wallis test showed a significant p -value of 0.042 when applied for the WML volume in these groups. The mean rank for the control group was 29.4, for formerly eclamptic women with 1 seizure ($n = 19$) 34.2, 2 seizures ($n = 10$) 39.1 and 3 or more seizures ($n = 10$) 45.4. These numbers, together with Figure 4, suggest that there is a significant relation between the number of experienced seizures and the severity of WML.

In the formerly eclamptic group two participants demonstrated evidence of cortical infarction and one woman demonstrated lacunar infarcts. None of the healthy control participants demonstrated such lesions.

Table 1 Relevant characteristics of participants.

	Controls (n = 29)	Eclampsia (n = 39)	P-value
Current age (years)	38 ± 6.9	38 ± 6.2	0.79
Current SBP (mmHg)	119 ± 14	126 ± 13	0.10
Current DBP (mmHg)	75 ± 9.5	76 ± 17	0.96
Elapsed time since index pregnancy (years)	5.3 ± 4.3	7.1 ± 4.7	0.88
EGA at delivery (weeks)	39.7 ± 1.3	33.6 ± 4.3	< 0.001
Birth weight (grams)	3511 ± 423	1898 ± 915	< 0.001

Results are presented as means ± standard deviations. EGA = Estimated Gestational Age, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure.

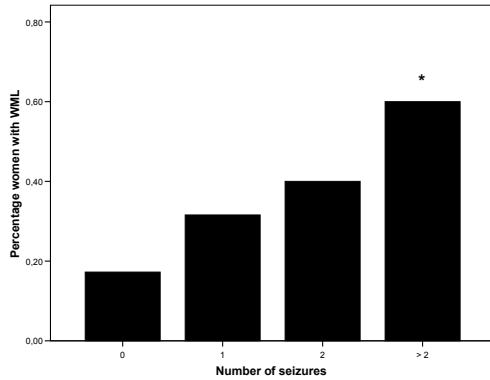


Figure 3 Percentage of women in both groups who demonstrated WML according to number of seizures. *Chi-square test $p = 0.01$, Test for trend $p = 0.01$.

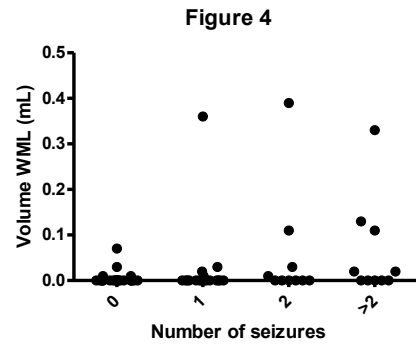


Figure 4 White matter lesion volume load in all subjects according to number of seizures. Kruskal-Wallis test $p = 0.04$, test for trend $p = 0.02$.

Comment

Data now presented are compatible with long-term presence of brain white matter lesions possibly incurred at the time of eclamptic convulsions. Specifically, when studied with magnetic-resonance neuroimaging at a mean of 7.1 years following a pregnancy complicated by eclampsia, 41% of women demonstrated WML compared with only 17 % of control women on average 5.3 years following a contemporaneous non-eclamptic pregnancy. Moreover, the volume of these lesions was significantly larger in the women who had experienced eclampsia, and in addition, the presence and volume of the WML appeared to be associated with the number of seizures. These findings are in concert with recent observations that document MRI evidence of persistent WML in up to 25 % of eclamptic women at short term follow up of 2 months.^{6,7} Another indication that formerly eclamptic women face long-term neurological sequelae comes from Aukes et al.⁸ who describe more self-reported cognitive dysfunction in eclamptic women compared with a non-eclamptic cohort of contemporaneous parous controls. Also in this study an association between the number of seizures and the degree of self-reported cognitive dysfunction seems to be present.⁸ Together these findings may indicate that eclamptic seizures are more harmful than is known at the present time. We, therefore, counter the position by some in the field of high risk obstetrics that the occurrence of eclamptic

seizures is benign and should not be prevented as long as the maternal and fetal condition is being monitored closely during a seizure.¹³

Currently, two concepts regarding the pathophysiology of eclampsia have been presented. According to the `vasculopathy` concept it is suggested that in response to acute severe hypertension cerebral `overregulation` leads to vasospasm.¹⁴ This presumption is based on the angiographic appearance of diffuse or multifocal segmental narrowings suggestive of vasospasm of the cerebral vasculature in women with severe preeclampsia and eclampsia.¹⁵ In that concept, diminished cerebral blood flow is hypothesized to result in ischemia, cytotoxic edema and, eventually, tissue infarction. According to the alternate, and nowadays preferred, concept eclampsia is likely the most common condition described underlying the posterior reversible encephalopathy syndrome (PRES).³ Similar to non-pregnant patients with PRES, MRI demonstrates subcortical cerebral edema in nearly all women with eclampsia when imaged within the first 36 hours after the seizure(s).^{6,7,16} We, therefore assume that also the cohort of formerly eclamptic women now described would have demonstrated this during the acute phase. The current concept of the development of PRES is related to breakthrough of the brain's well-developed autoregulatory capacity.¹⁷ 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 autoregulation.¹⁸⁻²⁰ It is hypothesized that forced vasodilatation, increased hydrostatic pressure and hyperperfusion result in disruption of the blood-brain barrier.^{2,20} Subsequent extravasation of plasma and opening of the endothelial tight junctions (blood-brain barrier) is followed by formation of vasogenic edema and the resulting manifestations of the clinical syndrome and accompanying neuroimaging findings.^{3,4,21} Typical neuroimaging lesions in PRES, which are thought to be transient and indicative of vasogenic edema, predominate in the posterior cerebral white matter and cortex.²¹ However, the name PRES appears to be inappropriate for the imaging findings in eclampsia because upon repeating MRI several weeks after delivery, the cerebral edema had resolved but cerebral WML were visible in almost a fourth of formerly eclamptic women.^{6,7} We suggest that severe vasogenic edema in PRES can reduce tissue perfusion which results in ischemia and the development of cytotoxic edema.^{5,22} In this scheme, such areas of poorly perfused brain may ultimately be at risk for ischemia and even infarction, all of which may give rise to the development of brain WML.²³

Alternatively, some raise the question whether an underlying vascular condition predisposed to both the eclamptic seizures as well as the WML. Obviously, this study was not designed to answer that question. It is now recognized that women with (pre) eclampsia are at increased risk of hypertensive disorders and other cardiovascular and cerebrovascular disorders following pregnancy.^{24,25} It is possible that an underlying

vascular condition gives rise to the development of WML in the years following the eclamptic seizure, rather than WML being a direct consequence of eclampsia. Also, it is possible that the WML preexisted prior to the eclamptic seizures. Nevertheless, our findings that women who experienced multiple seizures more often demonstrated WML and also larger WML volumes are suggestive of a cause and effect relationship between eclamptic seizures and the development of WML. The only way to answer the question whether the WML were preexistent, caused by the eclamptic seizures or by an underlying vascular disease is to perform serial MRI prior to and following eclampsia. Additionally, such women should be considered at risk for development of chronic vascular disorders. Interestingly, there was no difference in the rate of chronic hypertension between formerly eclamptic women and their age-matched controls. This finding is consistent with the work of Chesley²⁶ that primiparous women who experience eclampsia do not demonstrate increased blood pressure years after pregnancy.

The presence of WML in healthy individuals accrues with age. Indeed, more than half of healthy elderly persons demonstrate some degree of WML on MRI.^{27,28} Although the prevalence of WML in younger age categories, such as our study participants, has not been reported, it should not be surprising that in our study 17% of otherwise healthy control women had evidence for such WML late in their fourth decade. The exact pathophysiology underlying these imaging changes and their clinical relevance remain so far unknown.²² Concerning is the relation of WML with several vascular risk factors and the risk for stroke in the general population.²⁹⁻³¹ Epidemiological data suggest that preeclamptic subjects can face long-term cerebrovascular consequences such as the more than 3- to 5-fold increased risk for death from stroke.^{24,25} Together, this suggests a prominent vascular etiology for brain WML.

Besides the tragic cerebrovascular endpoints such as stroke, intriguing information has recently become available regarding the cognitive and affective consequences of brain WML.^{11,32,33} Obviously, aforementioned research pertains to a much older population unlike our much younger formerly eclamptic cohort. However, it is interesting to speculate about the possible clinical consequences of brain WML. Self-reported impaired cognitive function in women years after experiencing eclampsia⁸ resembles the self-reported impaired cognitive function in elderly being related to WML burden.³³ Future research needs to determine whether the appearance, number and location of brain WML in formerly eclamptic women are associated with cognitive dysfunction and structural brain disease.

Taken together with these other studies^{7,8}, our current findings suggest that there may be permanent cerebral sequelae of eclamptic seizures. However, the magnitude of symptomatic neurological disability is yet unknown. These data are also supportive of

prevailing obstetrical practices to give magnesium sulfate for seizure prophylaxis to prevent seizure in women with preeclampsia.

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Rererences

1. Sibai BM, Diagnosis, prevention and management of eclampsia. *Obstet Gynecol* 2005;105:402-10
2. Redman CW, Sargent IL, Latest advances in understanding preeclampsia. *Science* 2005 308:5728;1592-94
3. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996;334:494-500
4. Schwartz RB, Mulkern RV, Gudbjartsson H, Jolesz F. Diffusion-weighted MR imaging in hypertensive encephalopathy: clues to pathogenesis. *AJNR* 1998;19:859-65
5. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion weighted MR images. *AJNR* 2002;23:1038-48
6. Loureiro R, Leite CC, Kahhale S, Freire S, Sousa B, Cardoso EF et al. Diffusion imaging may predict reversible brain lesions in eclampsia and severe preeclampsia: Initial experience. *Am J Obstet Gynecol* 2003;189:1350-5
7. Zeeman GG, Fleckenstein JL, Twickler DM, Cunningham FG. Cerebral infarction in eclampsia. *Am J Obstet Gynecol* 2004;190:714-2
8. Aukes AM, Wessel I, Dubois AM, Aarnoudse JG, Zeeman GG. Self-reported cognitive functioning in formerly eclamptic women. *Am J Obstet Gynecol* 2007;197:365.e1-6
9. Williams' Obstetrics. F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, John C. Hauth, Larry C. Gilstrap, Katharine D. Wenstrom. 22nd edition. McGraw-Hill Companies, Inc. USA , 2005
10. National High Blood Pressure Education Program Working Group report on high blood pressure in pregnancy. *Am J Obstet Gynecol* 2000;183:S1-S22
11. De Groot JC, de Leeuw FE, Oudkerk M, Hofman A, Jolles J, Breteler MM. Cerebral white matter lesions and depressive symptoms in elderly adults. *Arch Gen Psychiatry*. 2000;57:1071-6
12. De Leeuw FE, de Groot JC, Oudkerk M, Witteman JC, Hofman A, van Gijn J et al. A follow-up study of blood pressure and cerebral white matter lesions. *Ann Neurol*. 1999;46:827-33
13. Moran NF. Preventing and treating eclamptic seizures. Will magnesium sulphate for preeclampsia really help? *BMJ*. 2003 4;326(7379):50
14. Trommer BL, Homer D, Mikhael MA. Cerebral vasospasm and eclampsia. *Stroke* 1988;19:326-9
15. Ito I, Sasaki T, Inagawa S, Utsu M, Bun T. MR angiography of cerebral vasospasm in preeclampsia. *Am J Neuroradiol* 1995;16:1344-46
16. Schwartz RB, Feske SK, Polak JF, DeBiolami U, Laia A, Beckner KM, et al. Preeclampsia-eclampsia: clinical and neuroradiographic correlates and insights into the pathogenesis of hypertensive encephalopathy. *Radiology* 2000;217:371-6
17. Cipolla MJ. Cerebrovascular function in pregnancy and eclampsia. *Hypertension* 2007;50:14-24
18. Port JD, Beauchamp NJ. Reversible intracerebral pathologic entities mediated by vascular autoregulatory dysfunction. *Radiographics* 1998;18:353-67
19. Mattar F, Sibai BM. Eclampsia VIII. Risk factors for maternal morbidity. *Am J Obstet Gynecol* 2000;182:307-12
20. Mukherjee P, McKinstry RC. Reversible Posterior Leukoencephalopathy Syndrome: Evaluation with Diffusion-Tensor MR Imaging *Radiology*. 2001;219:756-765

21. Schwartz RB, Jones KM, Kalina P, Bajakian RL, Mantello MT, Garada B et al. Hypertensive encephalopathy: findings on CT, MR imaging and SPECT imaging in 14 cases. *AJR* 1992;159:379-83
22. Stott VL, Hurrell MA, Anderson TJ. Reversible posterior leukoencephalopathy syndrome: a misnomer reviewed. *Int Med J* 2005;35:83-90
23. Pantoni L. Pathophysiology of age-related cerebral white matter changes. *Cerebrovasc Dis* 2002;13:7-10
24. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ* 2003;326:845
25. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ* 2001;323:1213-7
26. Chesley LC. Recognition of the long-term sequelae of eclampsia. *Am J Obstet Gynecol* 2000;182:249-50.
27. De Leeuw FE, Groot de JC, Achten E, Oudkerk M, Ramos LMP, Heijboer R et al. Prevalence of cerebral white matter lesions in elderly people: a population-based magnetic resonance imaging study. The Rotterdam Scan Study. *J Neurol Neurosurg Psychiatry* 2001;70:9-14
28. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP et al. Incidental findings on brain MRI in the general population. *N Engl J Med*. 2007;357:1821-8
29. De Leeuw FE, de Groot JC, Oudkerk M, Witteman JCM, Hofman A, van Gijn J et al. Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain* 2002;125:765-72
30. Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, et al. Stroke risk profile predicts white matter hyperintensity volume: the Framingham study. *Stroke* 2004;35:1857-61
31. Kuller LH, Longstreth Jr WT, Arnold AM, Bernick C, Bryan RN, Beauchamp Jr NJ et al. White matter hyperintensity on cranial magnetic resonance imaging. A predictor of stroke. *Stroke* 2004;35:1821-5
32. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MMB. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003;348:1215-22
33. De Groot JC, de Leeuw FE, Oudkerk M, Hofman A, Jolles J, Breteler MMB. Cerebral white matter lesions and subjective cognitive dysfunction. The Rotterdam Scan Study. *Neurology* 2001;56:1539-45

