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Published in:
Obstetrics and Gynecology

DOI:
10.1097/AOG.0b013e31824da5a8

Publication date:
2012

Long-Term Visual Functioning After Eclampsia

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OBJECTIVE: Complete neurocognitive recovery after eclampsia has been questioned with the expression of neurocognitive deficits by affected women and demonstration of cerebral white matter lesions on magnetic resonance imaging years after eclampsia. We hypothesized that formerly eclamptic women may experience impaired vision-related quality of life (QOL) and visual field loss as a result of the presence of such lesions in the cerebral visual areas.

METHODS: Using the National Eye Institute Visual Function Questionnaire-39/Nederlands questionnaire, vision-related QOL was compared between formerly eclamptic women and control participants after normotensive pregnancies. Furthermore, in formerly eclamptic women, visual fields were assessed using automated perimetry, and presence of white matter lesions was evaluated using cerebral magnetic resonance imaging. Presence of a relationship between these lesions and National Eye Institute Visual Function Questionnaire-39/Nederlands scores was estimated.

RESULTS: Forty-seven formerly eclamptic women and 47 control participants participated 10.1±5.2 and 11.5±7.8 years after their index pregnancy, respectively. Composite scores and 4 out of 12 National Eye Institute Visual Function Questionnaire-39/Nederlands subscale scores were significantly lower in formerly eclamptic women than in control participants ($P<.01$ for composite scores). This could not be explained by visual field loss, because all formerly eclamptic women who underwent perimetry (n=43) demonstrated intact visual fields. White matter lesions were present in 35.7% of formerly eclamptic women who underwent magnetic resonance imaging (n=42) and were associated with lower vision-related QOL scores ($P<.05$ for composite scores).

CONCLUSION: Formerly eclamptic women express lower vision-related QOL than control participants, which seemed at least partly related to the presence of white matter lesions. However, such women do not have unconscious visual field loss. Vision-related QOL impairment expressed by formerly eclamptic women may therefore be related to problems with higher-order visual functions.

(Obstet Gynecol 2012;119:959–66)
DOI: 10.1097/AOG.0b013e31824da5a8

LEVEL OF EVIDENCE: II

Visual disturbances are relatively common during the acute phase of eclampsia, including transient cortical blindness, scotomata, visual neglect, and blurred vision, and can often be attributed to the presence of cerebral edema.[1] Although the exact pathophysiology of eclampsia remains to be elucidated, it is considered to be an expression of the posterior reversible encephalopathy syndrome.[2] As its name suggests, this syndrome is thought to be a completely reversible condition. However, the reversibility of this syndrome, and eclampsia in particular, has been questioned lately.[3] In previous studies, one-fourth of eclamptic women showed persistent cerebral white matter lesions and brain tissue loss on magnetic resonance imaging (MRI) 6 weeks postpar-

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The authors thank Anne Marijn van der Graaf and Nina Roos for assistance with gathering data of visual field assessments and vision-related QoL questionnaires; and Annemieke Bolte and Jim van Eyck for identifying formerly eclamptic women in the database of the VU Medical Center and Isala Clinics, respectively, and facilitating the extraction of data from the medical records of these women.

Presented as a poster at the XVII ISSHP World Congress, October 3–6, 2010, Melbourne, Australia, and as an oral presentation at the EuroISSHP Congress, October 5–7, 2011, Rome, Italy.

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Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/12

tum.[4,5] Furthermore, several years after eclampsia, such lesions are more prevalent in formerly eclamptic women compared with women with normotensive pregnancies.[6]

In general, visual disturbances expressed by patients with posterior reversible encephalopathy syndrome or eclampsia are known to be transient. However, permanent visual field abnormalities, in particular hemianopia, but also permanent blindness, have been described and are thought to be related to persistent lesions in the visual cortex.[3,7] Moreover, in a Scandinavian follow-up study, 11% of formerly eclamptic women reported persistent visual disturbances.[8] However, median follow-up time of these studies was relatively short, being less than 1 year.

When located in the visual pathway from the optic nerve to optic radiation, white matter lesions may cause (un)conscious visual field defects or impairment of higher-order visual functions such as visual perception and spatial orientation. Visual disturbances might be a contributing factor related to persistent complaints described by some formerly eclamptic women such as poor concentration and limited attention span.[8,9] We hypothesized that years after eclampsia decreased vision-related quality of life (QOL) and visual field loss may be experienced as a result of the presence of white matter lesions in the cerebral visual areas. We choose to use a validated vision-related QOL questionnaire to evaluate these women's own perception of daily functioning in relation to vision. The questionnaire determines the influence of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning in addition to task-oriented domains related to daily visual functioning. Subsequently, the relationship of this self-perceived vision-related QOL with the prevalence of visual field defects and cerebral white matter lesions was assessed.

MATERIALS AND METHODS

Women with a diagnosis of eclampsia in their medical history between 1988 and 2008 were identified in the University Medical Center Groningen, VU University Medical Center Amsterdam and Isala Clinics Zwolle. These hospitals are teaching hospitals that serve as tertiary perinatal referral hospitals in The Netherlands. Eclampsia was defined according to the definition of the International Society for the Study of Hypertension in Pregnancy.[10] Exclusion criteria included pre-existing glaucoma or other conditions known to be related to visual field defects, epilepsy or other neurological disorders including a known cerebrovascular accident, intracranial infections, or a history of any cranial neurosurgical procedure. Also, current pregnancy and an age of younger than 18 years were used as exclusion criteria.

In the three participating hospitals, electronic admission, diagnosis, and delivery databases are kept up to date, which were used to identify eligible study participants (Fig. 1). In total, 133 women were diagnosed with eclampsia in these three hospitals between 1988 and 2008. In addition, six women who delivered in other hospitals than the participating clinics and who had heard about this study requested to participate in the current study, which was allowed.

Medical records were reviewed for accuracy of diagnosis of eclampsia and to extract clinical and demographic characteristics. On review, one woman was excluded because a diagnosis of eclampsia could not be confirmed. Three women were described as having had generalized myoclonic twitches while remaining conscious. Because these twitches suggest cerebral involvement, these women were not excluded from the study although they had not experienced tonic–clonic seizures. Four women had died in the interim, two of whom as a result of cerebral complications resulting from eclampsia, one resulting from breast cancer, and one attributable to cervical cancer years after her pregnancy. Four other women were excluded, two women as a result of a current pregnancy, one because of a cerebrovascular accident, and one because she did not speak Dutch.

This resulted in 130 formerly eclamptic women who were eligible to participate. These women received a written invitation for participation in this study. Of these women, 47 women could be reached and were willing to participate. Several women, who decided not to take part in the study, mentioned travel distance and time commitment as the main reason for nonparticipation. Some other women did not want to be confronted with their medical history.

In addition to these formerly eclamptic women, 47 parous control women who had normotensive pregnancies participated in this study (Fig. 1). These women were recruited among hospital personnel of the University Medical Center Groningen. In total, 80 such women were randomly selected and invited to participate, of which 50 decided to take part in the study. One of them was excluded as a result of a history of hypertension in pregnancy. An additional two had to be excluded as a result of ophthalmologic conditions known to be associated with visual field impairment.

Both formerly eclamptic and control participants filled out a questionnaire related to their obstetric and current and past medical history. Approval for this project was obtained from the Medical Ethics Commit-

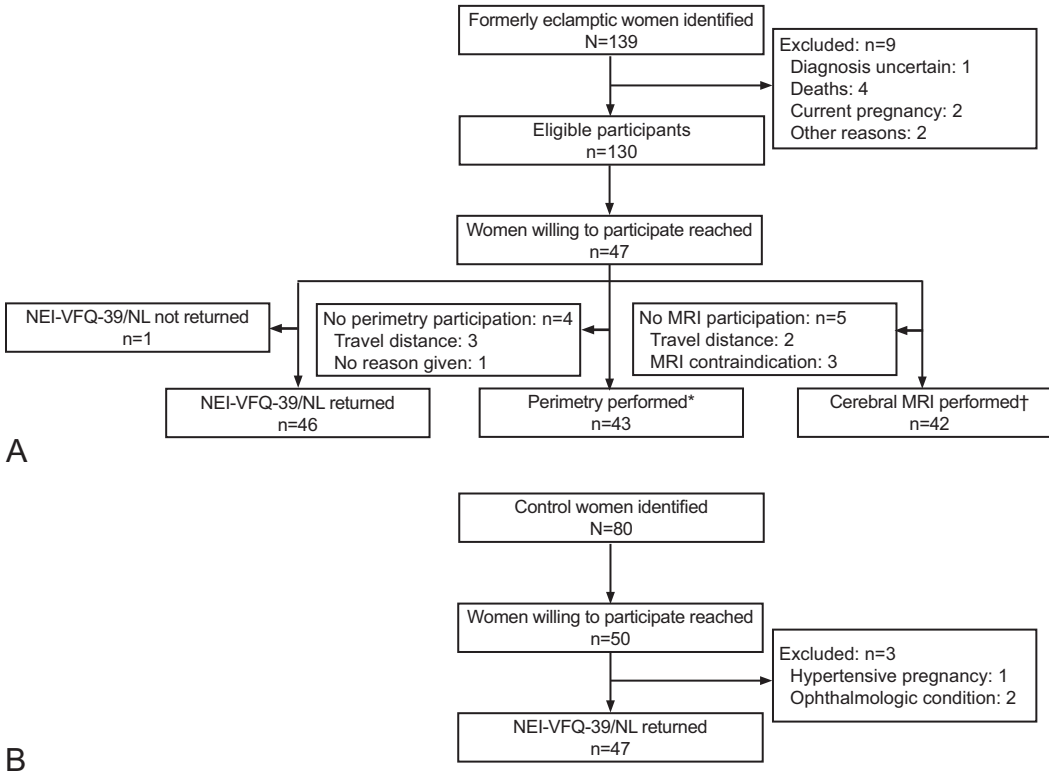

Fig. 1. Flow diagram illustrating the inclusion and exclusion process of study participants. **A.** The selection of formerly eclamptic women. **B.** The selection of control participants. *Forty-two of these women returned the National Eye Institute Visual Function Questionnaire-39 (NEI-VFQ-39/NL). †Forty-one of these women returned the NEI-VFQ-39/NL.
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tee of the University Medical Center Groningen, and informed consent was obtained from the participants.

Vision-specific health-related QOL was compared between formerly eclamptic and parous control participants using the validated Dutch translation of the National Eye Institute Visual Function Questionnaire-39/Nederlands.[11] The English version of this questionnaire was developed at RAND Health under the sponsorship of the National Eye Institute and was designed to measure the dimensions of self-reported vision targeted health status.

The National Eye Institute Visual Function Questionnaire-39/Nederlands consists of a base set of 25 questions and 14 additional questions generating the following vision-targeted subscales: general health, general vision, near and distance activities, driving difficulties, peripheral vision, color vision, ocular pain, vision-related role function, vision-related dependency, vision-related social functioning, and vision-related mental health. Each question was scored on a 0 to 100 scale with 0 being the worst and 100 being the best possible score. Each subscale score was calculated by averaging the scores of the questions that constitute that particular subscale. The composite score was calculated by averaging all vision-targeted subscale scores, excluding the general health subscore.

The National Eye Institute Visual Function Questionnaire-39/Nederlands was filled out by 46 formerly eclamptic women, of which 42 had participated in visual field testing. One of the women, who had undergone perimetry and MRI, did not return the questionnaire. Three women filled out the questionnaire but did not participate in visual field testing as a result of travel distances. Results were compared with scores from 47 parous control women, who participated in vision-related QOL assessment only.

The prevalence of visual field defects was assessed in 43 formerly eclamptic women at the Department of Ophthalmology of the University Medical Center Groningen using automated perimetry. The control group did not undergo visual field testing as a result of an expected very low prevalence of visual field defects in these participants. This presumption was based on data from the Rotterdam Study, which showed a prevalence of visual field loss of 3% in the

general elderly population (55–64 years).[12] In our group of healthy women of on average 40 years old, the prevalence of visual field defects would likely be less than 3% and probably even closer to 1%. Based on literature indicating approximately a 50% prevalence of visual field defects in patients with former stroke,[13] we anticipated that at least 25% of formerly eclamptic women who demonstrate cerebral white matter lesions would experience some degree of visual field loss. Although a formal power calculation could not be performed as a result of lack of available data in the literature, we considered the number of 43 formerly eclamptic women to evaluate whether the prevalence of visual field loss in such women is clinically relevant.

An assistant of the Department of Obstetrics and Gynecology was trained by a certified technician in conducting automated perimetry using the Humphrey Field Analyzer. The visual field was tested with a 52-point suprathreshold test that covered the central visual field with a radius of 24°, a test identical to the test used in the Rotterdam Study.[14] Visual field loss was defined as nonresponse to a light stimulus of 6 dB above a threshold-related estimate of the hill of vision in at least three contiguous test points or four including the blind spot.

Visual field testing was performed on one eye at a time with the contralateral eye covered. The patient was asked to look straight ahead while lights were projected at different places in the perimeter. Participants were instructed to click a button every time they noticed a projected light.

Test reliability was evaluated using the reliability indices for false-positive and false-negative answers; fixation stability was observed by the perimetrist. In case of visual field loss or an unreliable test result (more than 33% false-positive or false-negative catch trials or poor fixation as observed by the perimetrist), the test was repeated in the same session after a break. Visual field loss on an initial test is, as a result of a learning effect, quite common and should always be confirmed or falsified.[15]

Cerebral MRI was performed in 42 of the 47 formerly eclamptic participants as part of an ongoing follow-up study assessing white matter lesions after eclampsia.[6] These MRI scans were made on a 3-Tesla MRI system using the following sequences: T1, T2, proton density, and fluid-attenuated inversion recovery. The presence of white matter lesions was rated by an experienced neuroradiologist as previously described.[6,16] Briefly, such lesions were considered present if hyperintense on T2- and proton density-weighted images and not hypointense on T1-weighted images. The presence of subcortical white matter lesions was evaluated for the following locations: frontal, parietal, temporal, occipital and insular lobe, brain stem, and cerebellum. To correct for inclusion of partial volume, women with two small white matter lesions or less were considered as negative. Descriptive statistics such as demographic information and scores on the National Eye Institute Visual Function Questionnaire-39/Nederlands were presented as means±standard deviations for continuous variables and percentages for dichotomous variables.

Demographic data and National Eye Institute Visual Function Questionnaire-39/Nederlands subscale and composite scores were compared between formerly eclamptic and control women using Fisher's exact test, independent Student's *t* test, or Mann-Whitney *U* tests, where appropriate. The relation between National Eye Institute Visual Function Questionnaire-39/Nederlands scores and presence of white matter lesions was assessed using Mann-Whitney *U* tests. Differences were considered statistically significant at $P \leq .05$. Data analyses were performed using SPSS for Windows 18.

RESULTS

In this study, 47 formerly eclamptic women participated. Of these women, 46 completed the National Eye Institute Visual Function Questionnaire-39/Nederlands, 43 underwent perimetry, and 42 underwent cerebral MRI. In total, 47 parous control women who did not experience a hypertensive pregnancy filled out the National Eye Institute Visual Function Questionnaire-39/Nederlands.

Table 1 shows baseline characteristics of the study participants. Mean age and elapsed time since

Table 1. Characteristics of Formerly Eclamptic and Parous Control Participants

	Eclampsia (n=47)	Control (n=47)	*P*
Age (y)	40.3±7.0	41.7±8.1	.362
White	91.5 (83.5–99.5)	100.0 (100.0–100.0)	.117
Elapsed time since index pregnancy (y)	10.1±5.2	11.5±7.8	.631
Nulliparous	87.2 (77.7–96.8)	80.9 (69.7–92.1)	.574
Estimated gestational age at delivery (wk)	33.9±4.7	39.8±1.9	<.001
Birth weight of child (g)	2,022±1,054	3,522±544	<.001

Data are mean±standard deviation or % (95% confidence interval) unless otherwise specified.

index pregnancy at the time of participation were similar for both groups. Also, the percentage of white women and nulliparity at the time of index pregnancy were comparable between the groups. However, as may be expected, birth weight and estimated gestational age at delivery were significantly lower in formerly eclamptic women compared with parous control participants.

Vision-related QOL may be influenced by visual field defects and impairment of higher-order visual functions and therefore was assessed in formerly eclamptic women and parous control participants. Compared with parous control participants, formerly eclamptic women had significantly lower composite scores as well as lower scores on all subscales. This difference was significant for the composite of the National Eye Institute Visual Function Questionnaire-39/Nederlands and for four of 12 subscales, specifically, general health, vision-related social functioning, driving, and peripheral vision (Table 2). For the subscales general vision, ocular pain, near and distance activities, vision-related mental health, vision-related role function, vision-related dependency, and color vision, the differences did not reach significance (Table 2).

Automated perimetry was performed in 43 formerly eclamptic women. At the first examination, nine of these women showed abnormal test results in at least one eye and one had an unreliable test result. On the repeat test, all had a reliable test result and none showed visual field defects.

In total, 42 formerly eclamptic participants underwent MRI, of which 15 (35.7%, 95% confidence interval [CI] 21.2–50.2%) demonstrated white matter lesions. All but two of these women (86.7%, 95% CI 69.5–100.0%) had these lesions in the frontal lobe and some in the parietal lobe (n=4; 26.6%, 95% CI 4.2–49.0%), insular lobe (n=3; 20.0%, 95% CI 0.0–40.2%), or cerebellum (n=1; 6.7%, 95% CI 0.0–19.4%). No lesions were observed in the occipital, temporal lobe, or brain stem. Five formerly eclamptic women demonstrated white matter lesions in multiple brain regions (33.3%, 95% CI 9.5–57.2%).

Magnetic resonance imaging scans were available for 41 of the formerly eclamptic participants who also filled out the National Eye Institute Visual Function Questionnaire-39/Nederlands. For three women, no scans were available as a result of general contraindications for MR scanning and another two participants waived participation in MRI scanning as a result of travel distance. Fourteen (34.1%, 95% CI 19.6–48.6%) formerly eclamptic women who participated in the National Eye Institute Visual Function Questionnaire-39/Nederlands demonstrated white matter lesions. These women had lower subscale scores compared with formerly eclamptic women without lesions, except for the subscale color vision (Table 3). This difference was significant for the subscales general vision, near activities, vision-related role function, and peripheral vision. In addition, formerly eclamptic women with white matter lesions had a significantly

Table 2. National Eye Institute Visual Function Questionnaire-39 Subscale and Composite Scores of Formerly Eclamptic and Parous Control Participants

	Eclampsia (n=46)	Control (n=47)	*P*
General health	67.3±15.8	74.7±14.0	.027
General vision	80.5±11.2	83.3±9.3	.175
Ocular pain	86.1±17.1	90.2±12.8	.380
Near activities	93.2±9.4	94.9±6.1	.508
Distance activities	92.9±10.4	96.5±4.1	.362
Social functioning	98.3±5.1	100.0±0.0	.006
Mental health	90.2±12.1	93.5±7.5	.181
Role function	92.4±12.8	95.9±7.1	.327
Dependency	98.9±3.0	99.5±2.9	.142
Driving	75.6±14.8	85.9±11.1	.001
Color vision	98.4±8.2	100.0±0.0	.151
Peripheral vision	90.8±17.0	98.4±8.1	.002
Composite score	90.9±7.8	94.5±3.5	.005

Data are mean±standard deviation unless otherwise specified.

Table 3. National Eye Institute Visual Function Questionnaire-39 Subscale and Composite Scores of Formerly Eclamptic Women With and Without White Matter Lesions

	Eclampsia With White Matter Lesions (n=14)	Eclampsia Without White Matter Lesions (n=27)	*P*
General health	62.5 (32.5–100.0)	65.0 (32.5–100.0)	.173
General vision	75.0 (60.0–85.0)	85.0 (60.0–100.0)	.010
Ocular pain	87.5 (37.5–100.0)	87.5 (50.0–100.0)	.530
Near activities	91.7 (70.8–100.0)	95.8 (50.0–100.0)	.037
Distance activities	91.7 (66.7–100.0)	100.0 (58.3–100.0)	.115
Social functioning	100.0 (91.7–100.0)	100.0 (70.0–100.0)	.192
Mental health	90.0 (70.0–100.0)	95.0. (45.0–100.0)	.175
Role function	90.6 (56.3–100.0)	100.0 (50.0–100.0)	.028
Dependency	100.0 (93.8–100.0)	100.0 (87.5–100.0)	.460
Driving	66.7 (58.3–91.7)	75.0 (50.0–100.0)	.377
Color vision	100.0 (75.0–100.0)	100.0 (50.0–100.0)	.659
Peripheral vision	87.5 (50.0–100.0)	100.0 (25.0–100.0)	.045
Composite score	86.3 (72.7–97.5)	95.3 (62.0–100.0)	.035

Data are median (range) unless otherwise specified.

lower composite score compared with those without lesions.

DISCUSSION

Women who have experienced eclampsia report lower vision-related QOL on average 10 years after the index pregnancy compared with parous control participants who had normotensive pregnancies. In formerly eclamptic women, lower vision-related QOL was associated with the presence of cerebral white matter lesions. Because visual fields of these women were intact when examined by perimetry, this suggests that lower vision-related QOL was not the result of (un)conscious visual field loss related to white matter lesions.

Visual disturbances are relatively common during the acute phase of eclampsia, attributed to the presence of reversible cerebral vasogenic edema, mainly in the (sub)cortical parieto-occipital and temporal regions.[17,18] The fact that a substantial percentage of formerly eclamptic women expresses persistent neurocognitive deficits and demonstrates white matter lesions[6] stimulated us to examine the possibility that these lesions could be associated with (un)conscious visual field loss.

Unawareness of visual field loss is a commonly described phenomenon[19,20] and can be attributed to occurrence of perceptual filling-in, in which missing information of a visual field defect is inferred from the surrounding intact visual field.[21] In addition, several animal studies have shown a marked potential for brain plasticity in response to both retinal and cortical lesions.[22,23] Interestingly, also human studies show evidence for (partly) functional recovery of visual field loss after cerebral scotomata.[24–26] Therefore, although formerly eclamptic women in our study did not demonstrate visual field loss on perimetry, one could hypothesize that small visual field defects might have been present in the period directly after the acute phase of eclampsia. We assessed visual fields years after eclampsia, a timeframe that might have allowed for rearrangement of visual pathways affected by white matter lesions. Hence, especially small visual field defects may have shrunken to undetectable abnormalities.[27]

Absence of identifiable lesions in the visual pathway from the optic nerve to optic radiation of our participants can obviously also explain a true absence of visual field defects after eclampsia. It seems plausible that white matter lesions after eclampsia are mainly located in the parieto-occipital region because vasogenic edema during the acute phase of eclampsia is most commonly observed here.[2] This edema, when severe enough, has been suggested to decrease regional cerebral perfusion pressure and blood flow to ischemic levels leading to areas of cytotoxic edema and infarction.[28] However, this study demonstrated only a few women with parietal white matter lesions and absence of such lesions in both the occipital and temporal lobe. Interestingly, white matter lesions were located in the frontal lobe in the majority of women with lesions. Because the primary visual cortex is located within the occipital lobe, these results can well explain the absence of visual field loss in formerly eclamptic women. Furthermore, the location of white matter lesions suggests a different or additional etiology of these lesions other than ischemia resulting from vasogenic edema. As a result of the relatively small group of lesion-positive women, further research addressing lesion location and its etiology after eclampsia is required.

Vision-related QOL was assessed using the National Eye Institute Visual Function Questionnaire-39/Nederlands, a commonly used questionnaire in the field of ophthalmology. A broad spectrum of ocular conditions has been shown to potentially alter vision-related QOL as measured by the National Eye Institute Visual Function Questionnaire-39/Nederlands, including glaucomatous and poststroke visual field loss,[29,30] congenital cataract,[31] and diabetic retinopathy.[32] In contrast with the objective visual field assessment as a measure of visual function, the National Eye Institute Visual Function Questionnaire-39/Nederlands comprises aspects of daily functioning in relation to vision strictly from a participant's perspective. In addition to lower National Eye Institute Visual Function Questionnaire-39/Nederlands composite scores in formerly eclamptic women, subscale scores related to general health, driving, peripheral vision, and vision-related social functioning were lower as well. This lower vision-related QOL appeared to be at least partly related to the presence of white matter lesions in formerly eclamptic women because women who demonstrated such lesions had a lower composite score as well as lower scores on one-third of the subscales compared with those without lesions. It should be noted that additional smaller, but still relevant, differences in subscale scores between the groups may have been missed as a result of insufficient power. However, although the number of women evaluated in this project may appear limited, in the context of the rare incidence of eclampsia, this study is considered sizeable.

The underlying mechanism by which white matter lesions might lead to lower vision-related QOL is still speculative at this moment because visual fields

were intact. A possible explanation is that these lesions may interfere with neurocognitive functioning pertaining to higher-order visual functions, which might subsequently result in lower vision-related QOL and commonly reported complaints of formerly eclamptic women such as difficulties with reading texts. The majority of lesions in formerly eclamptic women appeared to be located in the frontal and parietal lobe, which are involved in higher-order visual functions, including visual memory and visuospatial processing.[33–35] Future research is needed to objectively assess such higher-order functions in formerly eclamptic and control women using a detailed neurocognitive test battery.

A few limitations of the current study should be noted. First, as a result of the retrospective nature of this study, no data are available on visual functioning before the index pregnancy. However, a prospective study design seems unfeasible in view of the rare incidence of eclampsia. Second, management and outcome of eclamptic women may have changed in the period during which our participants had eclampsia. However, this long period was required to obtain a sizeable study population, especially because the participation rate of eclamptic women was relatively low.

In conclusion, formerly eclamptic women have lower vision-related QOL, which seemed associated with the presence of cerebral white matter lesions. Because these lesions did not appear to induce visual field loss, further research is needed to unravel the underlying mechanism of lower vision-related QOL and its relationship with white matter lesions. However, our results are in line with the current doubts about the complete reversibility of eclampsia. In addition to earlier proposed long-term sequelae pertaining to self-perceived neurocognitive functioning, eclampsia may also affect visual functioning years after the complicated pregnancy.

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