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### Eclampsia & preeclampsia

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# Self-reported cognitive functioning in formerly eclamptic women

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## **Abstract**

### **OBJECTIVE**

Recently, persistent brain white matter lesions were demonstrated in eclamptic women when imaged 6 weeks postpartum. Moreover, many of these women complain about cognitive limitations years after the eclamptic pregnancy. Therefore, in a cohort of such women we assessed cognitive failures in daily life.

### **STUDY DESIGN**

Thirty formerly eclamptic women completed the Cognitive Failures Questionnaire. Scores were compared with those of formerly preeclamptic (n=31) and healthy parous control participants (n=30) using a priori Student t-tests. Groups were matched in terms of current age and years elapsed since index pregnancy.

### **RESULTS**

Formerly eclamptic women scored significantly higher compared with healthy parous controls (43.5 vs. 36.1 respectively,  $p < 0.05$ ).

### **CONCLUSION**

Formerly eclamptic women reported significantly more cognitive failures many years after the index pregnancy. It is hypothesized that this might be due to some degree of cerebral white matter damage. This subjective assessment of cognitive function needs to be confirmed with objective neurocognitive testing and related to neuroimaging findings.

## Introduction

The exact pathophysiology of eclampsia has not been elucidated. One of the main theories is that eclampsia is an expression of hypertensive encephalopathy<sup>1</sup>, which more recently has been named Posterior Reversible Encephalopathy Syndrome (PRES).<sup>2-4</sup> PRES is also recognized as a complication in various other, nonpregnancy-related disorders, including several of iatrogenic or neurotoxic origin, connective tissue disease, acute glomerulonephritis in children and more.<sup>5</sup> Clinically, PRES is characterized by specific symptoms such as headache, seizures, altered mental status and visual disturbances.<sup>2,6</sup> In PRES, it is thought that in the presence of endothelial dysfunction an acute increase in blood pressure exceeds the upper limit of cerebral autoregulation.<sup>2</sup> In this scheme, forced dilatation of cerebral arteries is followed by blood-brain barrier disruption and formation of vasogenic cerebral edema. The syndrome of PRES is clinically reversible by lowering of blood pressure and/or discontinuation of the offending drug, or in pregnancy, by termination of the pregnancy. Nevertheless, it is hypothesized that when vasogenic edema becomes severe enough, it can result in reduced tissue perfusion and cytotoxic edema due to irreversible ischemic changes leading to brain white matter lesions.<sup>7</sup> Indeed, there is evidence to sustain this concept. Previous studies<sup>2,7,8</sup> using magnetic resonance imaging within days of seizures in eclamptic women showed vasogenic edema mainly in the subcortical white matter of the parieto-occipital lobes and adjacent grey matter. In almost one-fourth of eclamptic patients, persistent white matter lesions, consistent with the appearance of cerebral tissue loss (i.e. gliosis), have been demonstrated with follow-up MRI 6 weeks postpartum.<sup>7,9</sup> Together, these findings contradict the predominant concept that eclampsia is a condition in which women can expect full clinical recovery. Cerebral white matter lesions in the general, mostly aging, population have been associated with a decline in cognitive functioning and dementia.<sup>10,11</sup> To our knowledge, cognitive functioning of previously eclamptic women as well as non-obstetric subjects who experienced PRES has never been investigated. Information about the cognitive abilities in this particular patient population of much younger age is important to either confirm or reject possible harmful effects of persistent white matter lesions due to cytotoxic edema.

In the current study we sought to evaluate subjective cognitive functioning in formerly eclamptic, formerly preeclamptic and healthy parous women by using a validated Cognitive Failures Questionnaire (CFQ).<sup>12,13</sup> We hypothesized that the self-reported cognitive function of formerly eclamptic women is impaired compared with formerly preeclamptic and healthy parous control subjects.

## Materials and Methods

### *Participants*

The University Medical Center Groningen (UMCG) Obstetrics department is part of one of the 8 university teaching hospitals in The Netherlands, serving as a tertiary referral center. The annual delivery rate at the UMCG varied from 1600 to 1900 in the last 5 years. The department has used an electronic delivery database since 1988. This database was utilized to identify participants. Seventy-three women diagnosed with eclampsia were admitted to the UMCG between 1988 and 2005. Three women died in the interim, two of which died because of the complications of eclampsia (hepatic rupture with bleeding for several days followed by multiple organ failure and severe cerebral edema which resulted in infratentorial herniation). The third woman died from cervical carcinoma several years after pregnancy. We were unable to contact 28 of these women, resulting in 42 women who were eligible to participate. Each formerly eclamptic woman was matched for age and year of index pregnancy with a formerly preeclamptic woman and a healthy parous control. Controls with epilepsy or other neurological or psychiatric disorders known to influence cognitive functioning were excluded, as were those with a history of alcohol or substance abuse. (Pre)eclampsia was defined according to the definition by the International Society for the Study of Hypertension in Pregnancy.<sup>14</sup> Thus, a total of 126 women were invited to participate in the study and were mailed a questionnaire package. Women in all 3 groups were sent a Dutch translation of the CFQ together with a questionnaire concerning demographic characteristics including employment, education and marital status as well as former and current psychosocial functioning. Participants were also asked about traumatic brain injury and brain surgery in the past, and current use of medication. A total of 92 women returned the questionnaires, resulting in a response rate of 73%. Of the group of formerly eclamptic women 31 completed the questionnaire, as did 31 of the formerly preeclamptic group and 30 of the healthy control group. A few of the formerly eclamptic women declined to participate because they considered the questions too confrontational. All medical records were reviewed to confirm the diagnosis of (pre)eclampsia and to extract clinical information. Through reviewing the medical records, documentation of one woman was insufficient to confirm the diagnosis of eclampsia and therefore she was excluded from the study. This resulted in a total number of 30 formerly eclamptic women participating in this study. The study was approved by the local investigational review board and informed consent for this study was signed by all participants.

### *Cognitive Failures Questionnaire (CFQ)*

The CFQ<sup>12</sup> is a questionnaire assessing the likelihood of committing errors in completing daily tasks, which the participant should be capable of doing, i.e. the routines of every day life. Participants were instructed to complete the items with specific reference to the past six months. The CFQ consisted of 25 items that were scored on a five-point scale (range: 0 = *never* to 4 = *very often*). Thus, the total score ranged from 0 – 100, with higher scores indicating more frequently occurring cognitive failures. A recent factor analytic study<sup>13</sup> confirmed the usefulness of the total score as an index of general cognitive failures as well as four subscales pertaining to more specific areas of cognitive failures. These subscales were Memory (7 items, range 0 - 28) assessing participants' forgetfulness (e.g. "Do you find you forget appointments?"), Distractibility (9 items, range 0 - 36) to assess disturbance of internally focused attention (e.g. "Do you daydream when you ought to be listening to something?"), Blunders (7 items, range 0 - 28) reflecting social blunders and motor control (e.g. "Do you say something and realize afterwards that it might be taken as insulting?", "Do you bump into people?") and Names (2 items, range 0 – 8), (e.g. "Do you find you forget people's names?").

### *Statistical Analysis*

Because of our expectation that cognitive failures would occur specifically in the eclamptic group, planned comparisons (t-tests) were carried out to analyse total CFQ scores as well as scores on the subscales. Demographic characteristics and parameters relevant to psychosocial functioning were analyzed using t-tests or chi-square analyses where appropriate. All tests were two-tailed with alpha set at 0.05.

## **Results**

Relevant characteristics at the time of the index pregnancy are shown in Table I. In the formerly eclamptic groups, no differences were found between participating and non-participating women (Table 1). Formerly eclamptic women scored significantly higher on the CFQ compared with healthy parous controls (Table 2). The difference in total CFQ scores between formerly eclamptic and preeclamptic women showed a nonsignificant trend ( $p=0.08$ ).

**Table 1** Gestational characteristics of index pregnancy.

Group	Eclampsia (n = 30)	Preeclampsia (n = 31)	Controls (n = 30)	Non-participating formerly eclampsia (n = 39)
Percentage primiparous	80	57	52	64
Gestational age (weeks)*	33.2 ± 4.5	34.6 ± 5.0	39.8 ± 1.3	32.3 ± 4.1
Birth weight (grams)*	1849 ± 961	2132 ± 1226	3551 ± 477	1628 ± 818
Percentage Caesarean Section	71	61	8	79
Number of seizures (%):				
- 1	16 (53)			20 (51)
- 2	10 (33)			8 (21)
- 3	4 (13)			7 (18)
- 4	-			3 (8)
- Unknown	-			1 (3)

\*Results are given as means ± standard deviations.

Eclamptic women who experienced three seizures had significantly higher CFQ total scores compared with those who only had one seizure (Table 2), suggesting that each seizure had cumulative harmful effects that resulted in increased CFQ scores. As for the CFQ subscales, formerly eclamptic women had higher scores compared with both formerly preeclamptic women and healthy parous controls, however no significant differences were found. Table 3 shows relevant demographic and psychosocial characteristics for all three groups. Current age of the participants in all groups was similar. There was no difference in elapsed time since the index pregnancy between any of the groups.

**Table 2** CFQ scores.

Group	Eclampsia (n = 30)	Preeclampsia (n = 31)	Controls (n = 30)
CFQ total score (0-100)	43.5 ± 14.6*	36.9 ± 13.9	36.1 ± 13.9
Memory (0-28)	10.8 ± 5.1	9.0 ± 3.9	9.2 ± 4.7
Distractibility (0-36)	16.6 ± 5.6	14.4 ± 5.3	13.5 ± 5.6
Blunders (0-28)	11.2 ± 4.3	9.4 ± 4.5	8.9 ± 3.6
Names (0-8)	4.8 ± 2.2	4.1 ± 2.3	4.6 ± 1.8
CFQ total score (0-100):			
1 seizure (n = 16)	39.1 ± 10.9		
2 seizures (n = 10)	43.8 ± 16.3		
3 seizures (n = 4)	60.0 ± 14.5 <sup>†</sup>		

Results are given as means ± with standard deviations.

\*p = 0.049, t(58) = 2.0 vs. Controls, <sup>†</sup>p = 0.005, t(18) = -3.2 vs. Eclampsia with 1 seizure

**Table 3** Relevant current demographic, medical and former psychological characteristics

Group	Eclampsia (n = 31)	Preeclampsia (n = 31)	Controls (n = 30)
Current age (years)	38.7 ± 6.6	40.3 ± 5.2	38.7 ± 7.0
Elapsed time since index pregnancy (years)	7.6 ± 5.0	6.8 ± 4.5	5.8 ± 4.1
Education **	8.7 ± 1.5	7.9 ± 1.9	8.6 ± 2.1
Married or cohabited	25 (83)	26 (84)	25 (83)
No work outside of home:	8 (27)	5 (16)	6 (20)
- Of whom receive disability/sickness benefits	4 (50)*	0	2 (33)
Tobacco use	5 (17)	9 (29)	6 (20)
Alcohol use	15 (50)	19 (61)	18 (60)
Antihypertensive medication	2 (7)	8 (26) <sup>†‡</sup>	0
Migraine	9 (30)	14 (45) <sup>§</sup>	5 (17)
Episodes of feeling down and/or lack of interest:			
- Of which related to pregnancy or postpartum period	17 (57)	15 (48)	17 (57)
	9 (53) <sup>‡</sup>	9 (60) <sup>‡</sup>	2 (12)
Psychological therapy because of pregnancy related problems	8 (27) <sup>‡</sup>	3 (10)	0

Number of women with percentages in parenthesis. Current age, elapsed time since index pregnancy and education are presented as means ± standard deviations. \*\*Education was measured by an increasing scale (1-11) depending on the highest level of completed education. \*p ≤ 0.05 vs. Preeclampsia, <sup>†</sup>p ≤ 0.05 vs. Eclampsia, <sup>‡</sup>p ≤ 0.01 vs. Controls, <sup>§</sup>p ≤ 0.05 vs. Controls.

There was no difference in the number of women who were currently not working outside the home. However, 4 out of the 8 (50%) formerly eclamptic women reported to be unable to work because of their current health status. Moreover, these women received sickness or disability benefits in contrast to none of the formerly preeclamptic women. In this latter group, 5 women who reported not to be working outside the home stated that this was their personal choice. Significantly more women of the preeclamptic group reported a history of migraine compared with the control subjects ( $p = 0.02$ ). No participant reported a history of epilepsy, nor any other relevant intercurrent medical condition. Two women in the control group reported a cerebral contusion without any permanent sequelae in the past. There was no difference in level of education between the groups. Use of tobacco and alcohol was similar in all three groups. The current use of antihypertensive medication was significantly higher in the formerly preeclamptic group compared with the formerly eclamptic and control groups ( $p = 0.040$ ).



and  $p = 0.003$ , respectively). A similar number of women in each group reported to have experienced past episodes of lack of interest and/or phases of feeling down. Compared with the control subjects, significantly more women in the formerly eclamptic and preeclamptic groups reported that these episodes were specifically related to the index pregnancy or delivery ( $p = 0.010$  and  $p = 0.004$ , respectively). Eight of the formerly eclamptic women had received psychological treatment because of these problems, which was significantly greater compared to the control women ( $p = 0.002$ ). There was no difference between any of the groups in number of women receiving current psychological therapy.

## Comment

The main finding of this study is that several years after a pregnancy complicated by eclampsia, women reported impaired cognitive functioning compared with healthy parous women. In addition, women who experienced multiple eclamptic seizures reported greater cognitive impairment compared with those who experienced one seizure. This is a remarkable finding since the predominant view holds that eclampsia concerns a one-time event without any known long-term consequences, provided that intracranial haemorrhage does not precede or follow the acute moment.

The difference in CFQ outcomes may indicate that eclamptic seizures are more harmful than has previously been thought. The concept that the occurrence of eclamptic seizures does not affect maternal outcome as long as the maternal and fetal condition is being monitored closely during a seizure are no longer acceptable.<sup>15,16</sup> The significant difference in CFQ outcomes between formerly eclamptic women and healthy controls likely indicates that formerly eclamptic women function worse in daily life. The CFQ outcomes suggest that this is expressed by more slips of memory, memory for names, more slips of attention and psychomotor function in daily life. Yet, this impaired functioning should be acknowledged as an *indication* of how these women function and more (objective) neurocognitive testing should be conducted. The difference in outcome between the formerly eclamptic and preeclamptic groups, did not reach significance. Yet, the trend towards significant difference together with inspection of Table II, suggests that scores in the preeclamptic group closely resembled those of the healthy parous controls. This lack of significant difference is likely due to a type II error. Future studies with larger groups should better determine differences in functioning between formerly eclamptic and preeclamptic women.

Virtually nothing is known about long-term consequences of PRES in either obstetric or non-obstetric patients regarding their neurocognitive and social functioning. However, there is some evidence that preeclampsia may increase the risk of psychiatric conditions such as depression or Post Traumatic Stress Disorder (PTSD) relative to women with uncomplicated pregnancies.<sup>17,18</sup> The present study employed questions about episodes in the past that were characterised by a loss of interest and/or depressed mood as a crude index of past depression. The finding that formerly eclamptic and preeclamptic women indicated that they had experienced more of such episodes that were specifically tied to the index pregnancy or delivery is consistent with this previous literature on psychiatric sequelae of (pre-) eclampsia.<sup>17,18</sup>

Interestingly, the prevalence of migraine was found to be higher in both formerly preeclamptic and eclamptic women in our study. The association between (pre)eclampsia and migraine has been reported before.<sup>19,20</sup> Both conditions are thought to be characterized by hyperperfusion of the brain<sup>21,22</sup>, are related to changes in female sex steroid hormones<sup>23</sup> and have similar symptoms (headache, visual disturbances and nausea).<sup>6</sup> However, the exact pathophysiology of, as well as the association between, migraine and (pre)eclampsia remains unknown. In addition, white matter lesions in the cerebral posterior circulation territory are more frequently demonstrated in the general population in people who suffer migraine, especially in women.<sup>24</sup> This may also be of particular relevance to women with eclampsia.

It should be noted that CFQ scores reflect self-reported difficulties pertaining to everyday slips of attention and action. Although the CFQ has demonstrated satisfactory internal consistency, retest reliability and cross-cultural validity<sup>25,26</sup>, additional measures are needed to illuminate the origins of elevated scores. For example, a previous study<sup>27</sup> found elevated CFQ scores in organic (predominantly dementia) and functional (i.e., depression or anxiety) patients. Yet, the authors were unable to identify specific CFQ profiles that discriminated between those organic and functional groups. Thus, although the present findings are potentially consistent with an interpretation in terms of brain white matter lesions, alternative explanations cannot be ruled out. For example, it remains possible that cognitive failures in the eclampsia group were due to non-organic variables such as increased levels of anxiety or depression. Furthermore, it is also possible that higher cognitive failures scores reflect the specific conviction of eclamptic women that they suffer memory and concentration difficulties. That is, it may be that objectively, eclamptic women are comparable to healthy controls, yet interpret the occurrence of cognitive failures as evidence for the negative sequelae of their eclamptic seizures. It is possible that some women attribute a more negative meaning to cognitive lapses than others, resulting in higher estimates of their occurrence over the index period of the prior

6 months as identified in the CFQ instructions. However, the increase of cognitive dysfunction with increased number of seizures and the finding that more women in the eclamptic group were unable to work and received disability benefits may be taken as support for the notion that differences in reported cognitive failures reflected genuine dysfunctions in daily life rather than a self-report bias.

Several additional methodological limitations to this study deserve attention. First, the retrospective nature of the study may have resulted in selection bias. For example, if formerly eclamptic women with more cognitive dysfunction were eager to participate, seeking for recognition of self-perceived cognitive limitations, the cognitive impairment might be overestimated. In addition, the CFQ is a retrospective instrument subject to the limitations of human memory. Secondly, as the CFQ is a subjective measure of cognitive function, neurocognitive examination will be needed to demonstrate objectively cognitive abilities and limitations. A third limitation to this study is that the investigated groups are small. However, in the context of the rare incidence of eclampsia this represents a sizeable study, the results of which may be clinically important.

In conclusion, formerly eclamptic women report some degree of cognitive impairment many years after the index pregnancy. Whether the cognitive impairment found in this study cohort of formerly eclamptic subjects might be due to some degree of permanent cerebral white matter disturbance remains to be seen. Further research is now ongoing in order to confirm our findings, employing objective neurocognitive testing such as functional MRI and neuroimaging to assess the relationship with brain white matter lesions in formerly eclamptic women. The potential for identification (and eventually prevention and treatment) of chronic cognitive and psychosocial impairment in this particular group of young mothers is of important societal relevance and will also draw attention to possible longterm sequelae following PRES in other, nonpregnancy-related patient categories. The paradigm that eclampsia is a condition of which the women can expect full clinical recovery, may need to be revised and the importance of preventing eclamptic seizures should be emphasized.

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