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Correlation between cognitive assessment scores and circulating cerebral biomarkers in women with pre-eclampsia and eclampsia

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ABSTRACT

Objectives: The cerebral injury biomarkers neurofilament light chain (NfL) and tau and the glial activation biomarker glial fibrillary acidic protein (GFAP) may reflect neurological injury in pre-eclampsia. We assessed if there was a correlation between cognitive function assessment scores and plasma concentrations of these biomarkers in pre-eclampsia.

Study design: Women with eclampsia, pre-eclampsia and normotensive pregnancies from the South African PROVE biobank were included. Blood samples were taken at inclusion. The Montreal Cognitive Assessment was performed after delivery at the time of discharge. The correlation between cognitive assessment scores and plasma concentrations of cerebral biomarkers was analysed using Spearman correlation adjusted for time from eclamptic seizure.

Main outcome measures: We included 49 women with eclampsia, 16 women with pre-eclampsia complicated by pulmonary oedema, 22 women with pre-eclampsia without pulmonary oedema, HELLP or neurological complications and 18 women with normotensive pregnancies.

Results: There was a correlation between impaired cognitive function and increased plasma concentrations of NfL in women with eclampsia and women with pre-eclampsia and pulmonary oedema ($r = -0.37$, $p = 0.009$ and $r = -0.56$, $p = 0.025$ respectively). No correlation between impaired cognitive function and NfL in pre-eclampsia cases without pulmonary oedema, HELLP or neurological complications or normotensive pregnancies was found. No correlation with cognitive impairment was found in any groups for tau or GFAP.

Conclusions: We found a correlation between impaired cognitive function assessment and plasma NfL concentrations in women with eclampsia and pre-eclampsia complicated by pulmonary oedema. These findings suggest that acute neuroaxonal injury may cause or contribute to cognitive impairment in these women.

Abbreviations: BMI, body mass index; EDTA, ethylenediaminetetraacetic acid; GFAP, glial fibrillary acidic protein; HELLP, Haemolysis elevated liver enzymes and low platelets; HIV, human immunodeficiency virus; IQR, interquartile range; ISSHP, International Society for the Study of Hypertension in Pregnancy; IUFD, intrauterine fetal demise; MoCA, Montreal Cognitive Assessment; NC, neurological complications; NfL, neurofilament light chain; PROVE, Pre-eclampsia Obstetric Adverse Events; QC, quality control; rs, rank correlation coefficients; SD, standard deviations; Simoa, Single molecule array.

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1. Introduction

Pre-eclampsia is a pregnancy-specific disease, defined by the onset of hypertension and end-organ engagement after gestational week 20 [1]. It affects 3–5 % of all pregnancies and is a leading contributor to maternal morbidity and mortality, especially in low- and middle-income countries [2]. Acute cerebral complications of pre-eclampsia include eclampsia, cerebral oedema and intracranial haemorrhage [3]. The long-term neurological consequences for these women include increased life-time risks of vascular and Alzheimer's dementia, stroke and epilepsy [4–6]. It is not known if the increased risk for long-term neurological consequences associated with pre-eclampsia is due to pre-existing risk factors where pre-eclampsia acts as a stress-test, or if pre-eclampsia and its complications lead to irreversible endothelial and consequently neuronal injury [7]. Studies have shown that women with prior pre-eclampsia have more temporal and frontal white matter lesions [8–10], reduced cortical grey matter volume and total smaller brain volume [11], when compared to women with previous normotensive pregnancies.

Several studies have investigated cognitive impairment in women with previous pre-eclampsia months to years after pregnancy, but the results are conflicting. A systematic review and *meta*-analysis from 2018 showed no clear evidence of cognitive impairment on standard objective tests, but a higher incidence of subjective cognitive failure in women with prior pre-eclampsia though they excluded women with eclampsia [12]. Our group has previously shown that women with pre-eclampsia complicated by pulmonary oedema and eclampsia demonstrate an acute impairment in cognitive function after delivery at the time of discharge, compared to normotensive women [13].

Cerebral biomarkers may be useful in predicting and diagnosing neurological complications in pre-eclampsia. Tau and neurofilament light chain (NfL), which are axonal proteins, and glial fibrillary acidic protein (GFAP), which is a filament protein in astrocytes, are useful predictive and diagnostic tools in neurodegenerative disorders [14]. We and others have investigated the role of cerebral biomarkers in pre-eclampsia and have shown that plasma concentrations are increased in women with pre-eclampsia complicated by haemolysis, elevated liver enzymes and low platelets (HELLP) or neurological complications [15–18]. But there is still a paucity of data regarding the correlation of cerebral biomarkers to cognitive function in pre-eclampsia. In this study, we compared plasma concentrations of cerebral biomarkers NfL, tau and GFAP among women with pre-eclampsia of different severity and women with normotensive pregnancies to their performance on objective cognitive assessments at time of discharge after delivery.

2. Materials and methods

2.1. Population

Women with pre-eclampsia and normotensive pregnancies were recruited to the PROVE (Pre-eclampsia Obstetric Adverse Events) biobank and database (ISCRTN registration number ISRCTN10623443) at Tygerberg Hospital in Cape Town, South Africa. Tygerberg hospital is a referral academic centre and delivers >8,000 high risk pregnancies yearly. Detailed information about PROVE can be found in the published protocol [19].

2.2. Exposure

Pre-eclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) but also required significant proteinuria to make the diagnosis [20]. Eclampsia was confirmed when pre-eclampsia was complicated by generalized tonic-clonic seizures in the absence of another aetiology. Pulmonary oedema was diagnosed when there was an oxygen saturation <92 %, bibasal fine inspiratory crackles on auscultation and compatible radiological features on chest X-ray in a woman with confirmed pre-eclampsia.

Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome was defined as a platelet count $<100 \times 10^9$/L, aspartate aminotransferase >70 μ/L, and haemolysis as demonstrated by lactate dehydrogenase > 600 μ/L or haemolysis on a peripheral blood smear. Renal impairment was defined as creatinine > 120 μmol/L. Severe hypertension was defined as systolic blood pressure greater than or equal to 160 mmHg and/or diastolic blood pressure greater than or equal to 110 mmHg.

We included women with singleton pregnancies and ability to speak and understand Xhosa, Afrikaans or English. Exclusion criteria were known neurological or cardiac disease. For women with normotensive pregnancies, additional exclusion criteria were chronic hypertension and diabetes mellitus.

2.3. Variables obtained from the medical charts

Maternal age (years), parity (parous or nulliparous), human immunodeficiency virus (HIV) status (positive or negative), diabetes (type 1, 2 or gestational), chronic hypertension, anaemia, depression, gestational age at delivery (weeks), mode of delivery (vaginal delivery, planned caesarean section or emergency caesarean section), post-partum haemorrhage (>500 ml for vaginal delivery and >1000 ml for caesarean section), HELLP syndrome and neonatal outcome (discharged home, transferred to neonatal unit, termination of pregnancy, i.e. that women were advised not to proceed with their pregnancy due to high risk of maternal complications in very early onset preeclampsia, or IUFD (intrauterine demise)/stillborn).

2.4. Variables obtained by interview

Marital status (cohabiting or single), education (years), job situation (working, student or unemployed), living conditions (house, apartment or informal settlement), smoker (current smoker), alcohol use (current user) and methamphetamine use (current user).

2.5. Cognitive function test

Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA) [21]. MoCA is an objective test composed of a variety of cognitive domains consisting of attention, concentration, executive function, memory, language, visio-spatial abilities, abstract thinking, mathematical calculations and orientation. The highest possible score is 30 points and a score of 26 points or more indicates normal function. An additional point was added to the total score of the test if the woman being tested had a total school education consisting of 12 year or less according to the test instructions [13]. The tests were performed as close to discharge as possible to avoid the women being too ill or too tired to perform adequately.

2.6. Plasma samples

Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes for plasma extraction at the time of inclusion in the study, after a diagnosis of pre-eclampsia or at the time of admission for delivery (normotensive controls). All samples were centrifuged, aliquoted and then frozen at −80 degrees Celsius until analysis.

2.7. Cerebral biomarker assays

The concentrations of tau, NfL and GFAP in plasma were measured using the Single molecule array (Simoa) Neuro 4-plex kit on an HD-X Analyzer, as described by the kit manufacturer (Quanterix, Billerica, MA) [22]. Calibrators were run in duplicates, while samples were run in singlicates with a 4-fold dilution. Two quality control (QC) samples from

plasma were run in duplicates in the beginning and the end of each run. For GFAP, a QC sample with a concentration of 49.6 pg/mL resulted in a repeatability of 11.9 % and an intermediate precision of 11.9 %. For a GFAP QC sample with a concentration of 403 pg/mL, repeatability was 7.2 % and intermediate precision was 10.1 %. For NfL, a QC sample with a concentration of 11.1 pg/mL gave a repeatability of 6.8 % and an intermediate precision of 10.7 %. For NfL QC sample with a concentration of 429 pg/mL, repeatability was 15.4 % and intermediate precision was 15.4 %. For *T*-tau, a QC sample with a concentration of 2.4 pg/mL gave a repeatability of 13.3 % and an intermediate precision of 13.3 %. For a *T*-tau QC sample with a concentration of 11.2 pg/mL, repeatability was 4.3 % and intermediate precision was 10.3 %. Laboratory technicians were blinded to groups and other clinical data.

2.8. Statistical methods

Demographic and clinical characteristics were presented as means with standard deviations (SD) and percentages. MoCA scores and cerebral biomarkers (NfL, tau and GFAP) were presented as medians with interquartile range (IQR). Non-parametric comparisons between groups were performed using Kruskal-Wallis test, followed by pairwise comparisons versus normotensive pregnancy using Mann-Whitney *U* test with Bonferroni correction.

Correlations between MoCA scores and cerebral biomarkers were analysed using non-parametric Spearman rank correlation coefficients (r_s). For illustrative purposes, MoCA scores were plotted versus log(NfL), log(tau) and log(GFAP) along with fitted regression lines. For women with eclampsia, the results were adjusted for time elapsed from blood sampling to eclamptic seizure. Results were also adjusted to potential confounders maternal age and parity. When adjusting for the potential confounders gestational age at plasma sampling and use of magnesium sulphate, the results remained similar (Table S1).

Outliers were removed from graphical presentation in figures for illustrative purpose, but all observations were included in the statistical analyses. All statistical tests were performed at the 5 % significance level. Statistical analyses were performed using SPSS version 26.0 (SPSS; PASW statistics) for MAC software package and SAS/STAT software, Version 9.4 of the SAS System for Windows (SAS Institute, Cary, NC, USA).

3. Results

A total of 171 women were included consecutively during the study period and of those, 153 women underwent subjective and/or objective tests for cognitive function. Eleven women were excluded due to language barriers. The cognitive assessment results have been published [13].

105 women had plasma analysed for the cerebral biomarkers NfL, tau and GFAP and these women were included in the study population as shown in Fig. 1. Of these, 49 had eclampsia, 16 had pre-eclampsia with pulmonary oedema, 22 had pre-eclampsia without pulmonary oedema, HELLP or neurological complications and 18 had a normotensive pregnancy. These women have been included in a larger study of biomarkers previously [18].

3.1. Background characteristics

Maternal characteristics and pregnancy outcomes are presented in Table 1. Women with eclampsia were younger, more often registered as students, more commonly nulliparous and more often smokers. Thirteen women (26 %) with eclampsia developed HELLP syndrome and eight (16 %) had renal impairment. Seventeen women (35 %) were diagnosed with severe hypertension.

Women with pre-eclampsia complicated by pulmonary oedema had higher BMI (body mass index), a shorter gestational age at delivery, delivered an infant of lower birthweight and more often experienced termination of pregnancy. Four (25 %) had HELLP syndrome and/or renal impairment, and sixteen (81 %) developed severe hypertension.

3.2. MoCA scores

Women with eclampsia and pre-eclampsia with pulmonary oedema had lower MoCA scores (median, IQR), compared to women with normotensive pregnancies (21.0, IQR 19.0–26.0 and 23.0, IQR

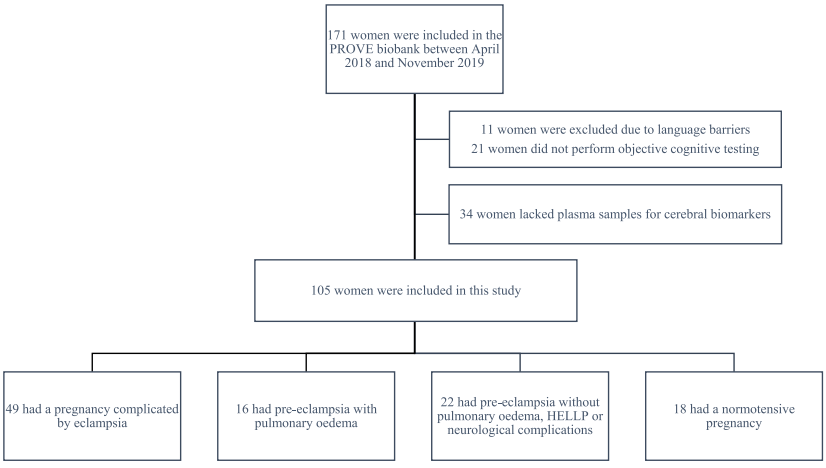

Fig. 1. Flow chart over the study population.

Table 1
Maternal characteristics and pregnancy outcomes of the study population.

	Normotensive pregnancy	Pre-eclampsia without pulmonary oedema, HELLP or neurological complications	Pre-eclampsia with pulmonary oedema	Eclampsia
n	**18**	**22**	**16**	**49**
Maternal age, years (SD)	29.3 (6)	24.9 (5)	28.4 (8)	22.0 (6)
BMI (SD)	27.9 (6)	27.8 (8)	31.0 (7)	25.1 (5)
Missing data (n)	1	3	3	12
Marital status, n (%)				
Single	8 (44)	12 (55)	2 (12)	25 (51)
Cohabiting	10 (56)	10 (45)	14 (88)	24 (49)
Education				
years (SD)	10.7 (2)	10.9 (2)	11.2 (1)	10.6 (2)
>10 years education, n (%)	14 (78)	19 (86)	12 (75)	38 (78)
Job situation, n (%)				
Working	5 (28)	7 (32)	6 (38)	11 (22)
Student	2 (11)	4 (18)	1 (6)	17 (35)
Unemployed	11 (61)	11 (50)	9 (56)	21 (43)
Living conditions, n (%)				
House or apartment	13 (72)	12 (55)	9 (56)	28 (57)
Informal settlement	5 (28)	10 (45)	7 (44)	21 (43)
Nulliparous, n (%)	4 (22)	12 (55)	7 (44)	36 (73)
HIV positive, n (%)	4 (22)	4 (18)	1 (6)	3 (6)
Smoker, n (%)	1 (6)	0 (0)	2 (13)	10 (20)
Alcohol use, n (%)	0 (0)	1 (4)	0 (0)	6 (12)
Metamphetamine use, n (%)	0 (0)	0 (0)	0 (0)	2 (4)
Diabetes, n (%)	0 (0)	1 (5)	0 (0)	0 (0)
Chronic hypertension, n (%)	0 (0)	4 (18)	1 (6)	4 (8)
Anaemia, n (%)	4 (22)	3 (14)	0 (0)	0 (0)
Depression, n (%)	1 (6)	1 (4)	0 (0)	0 (0)
GA at delivery, weeks (SD)	37.0 (3.0)	33.6 (3.8)	30.1 (4.6)	33.1 (4.6)
Mode of delivery, n (%)				
Vaginal delivery	3 (17)	7 (32)	5 (31)	21 (43)
Planned caesarian section	15 (83)	1 (4)	0 (0)	0 (0)
Emergency caesarian section	0 (0)	14 (64)	11 (69)	28 (57)
Postpartum haemorrhage, n (%)	0 (0)	1 (4)	1 (6)	6 (12)
Coagulation disorder (%)	0 (0)	0 (0)	2 (13)	9 (18)
Delivery-discharge, days (SD)	3.9 (6.3)	5.1 (2.7)	9.9 (5.4)	8.0 (4.7)
Admission to OCCU, n (%)	2 (11)	3 (14)	16 (100)	41 (84)
Admission to ICU, n (%)	0 (0)	0 (0)	2 (13)	6 (12)
Administration of $MgSO_4$	0 (0)	17 (77)	16 (100)	39 (80)
Maternal complications, n (%)				
HELLP	0 (0)	0 (0)	4 (25)	13 (26)
Renal impairment	0 (0)	0 (0)	4 (25)	8 (16)
Severe hypertension	0 (0)	6 (27)	16 (81)	17 (35)
Neonatal outcome, n (%)				
Discharged home	16 (89)	9 (41)	3 (19)	15 (31)
Transferred to neonatal unit	2 (11)	9 (41)	8 (50)	22 (45)
Termination of pregnancy	0 (0)	3 (14)	4 (25)	5 (10)
IUFD/stillborn	0 (0)	1 (4)	1 (6)	7 (14)
Birthweight, g (SD)	3013 (739)	2029 (950)	1498 (832)	2027 (960)

Values are presented as means (standard deviation) and numbers (percentage).
BMI; body mass index, GA; gestational age, HELLP; Haemolysis, elevated liver enzymes and low platelets, HIV; Human Immunodeficiency Virus, ICU; intensive care unit, IUFD; intrauterine demise, IQR; interquartile range, $MgSO_4$; magnesium sulphate, OCCU; obstetrical critical care unit, SD; standard deviatio.

Table 2
MoCA-scores and cerebral biomarkers related to groups.

Group	n=	MoCA-scores	p-value	NfL (pg/mL)	p-value	tau (pg/mL)	p-value	GFAP (pg/mL)	p-value
Normotensive pregnancy	18	27.5 (24.0–29.0)	–	8.23 (4.08–10.4)	–	2.61 (1.47–4.40)	–	27.6 (17.4–41.9)	–
Pre-eclampsia without pulmonary oedema, HELLP or neurological complications	22	26.5 (24.8–28.3)	ns	14.8 (9.89–22.3)	<0.001	3.64 (2.47–5.25)	ns	48.1 (31.2–58.6)	<0.05
Pre-eclampsia with pulmonary oedema	16	23.0 (19.0–26.8)	<0.001	17.9 (14.1–29.5)	<0.001	3.63 (1.99–7.16)	ns	71.7 (46.7–129)	<0.001
Eclampsia	49	21.0 (19.0–26.0)	<0.001	18.0 (10.0–30.4)	<0.001	6.30 (3.90–10.7)	<0.001	115 (62.1–199)	<0.001

Values are presented as medians (interquartile range). Mann Whitney *U* test.
MoCa, Montreal Cognitive Assessment; NfL, neurofilament light chain; ns, non-significant; GFAP, glial fibrillary acidic protein.
Please note that these results have been published previously [13,18].

19.0–26.8 *vs* 27.5 IQR 24.0–29.0, p < 0.001) (Table 2). These results have been published previously, but the population differs due to availability of blood samples and thus is also presented in this article [13].

3.3. Cerebral biomarkers

Plasma concentrations of cerebral biomarkers NfL, tau and GFAP are presented in Table 2. Women with eclampsia, pre-eclampsia with pulmonary oedema and pre-eclampsia without pulmonary oedema, HELLP or neurological complications demonstrated increased plasma concentrations of NfL compared to women with normotensive pregnancies (18.0 pg/mL, IQR 10.0–30.4; 17.9 pg/mL, IQR 14.1–29.5; 14.8 pg/mL, IQR 9.89–22.3 *vs* 8.23 pg/mL, IQR 4.08–10.4, p < 0.001). Women with eclampsia had increased plasma concentrations of tau compared to women with normotensive pregnancies (6.30 pg/mL, IQR 3.90–10.7 *vs* 2.61 pg/mL, IQR 1.47–4.40, p < 0.001). Women with eclampsia, women with pre-eclampsia with pulmonary oedema and pre-eclampsia without pulmonary oedema, HELLP or neurological complications demonstrated increased plasma concentrations of GFAP compared to women with normotensive pregnancies (115 pg/mL, IQR 62.1–199; 71.7 pg/mL, IQR 46.7–129; 48.1 pg/mL, IQR 31.2–58.6 *vs* 27.6 pg/mL, IQR 17.4–41.9, p < 0.05). These women were also included in a larger population where results of cerebral biomarkers have been presented [18].

3.4. Correlation between MoCA scores and cerebral biomarkers

The correlations between cognitive function measured by MoCA scores and plasma concentrations of cerebral biomarkers are presented in Figs. 2-4.

There was a moderate negative correlation between MoCA scores and concentrations of NfL in women with pre-eclampsia with pulmonary oedema, presented in Fig. 2 (r_s = -0.56, p = 0.025). There was a slightly weaker correlation for NfL and MoCA scores in women with eclampsia (rs = −0.37, p = 0.009). No correlations were found among women with pre-eclampsia without pulmonary oedema, HELLP or neurological complications and women with normotensive pregnancies. There were no correlations between MoCA scores and tau or GFAP in any of the groups (Figs. 3-4). The results remained similar after adjusting for the potential confounders maternal age and parity (data not shown).

4. Discussion

4.1. Main findings

There was a correlation between impaired objective cognitive function measured with the MoCA assessment and increased circulating concentrations of NfL in women with pre-eclampsia with pulmonary oedema and eclampsia. The correlation was strongest in women presenting with pulmonary oedema. There was no such correlation in

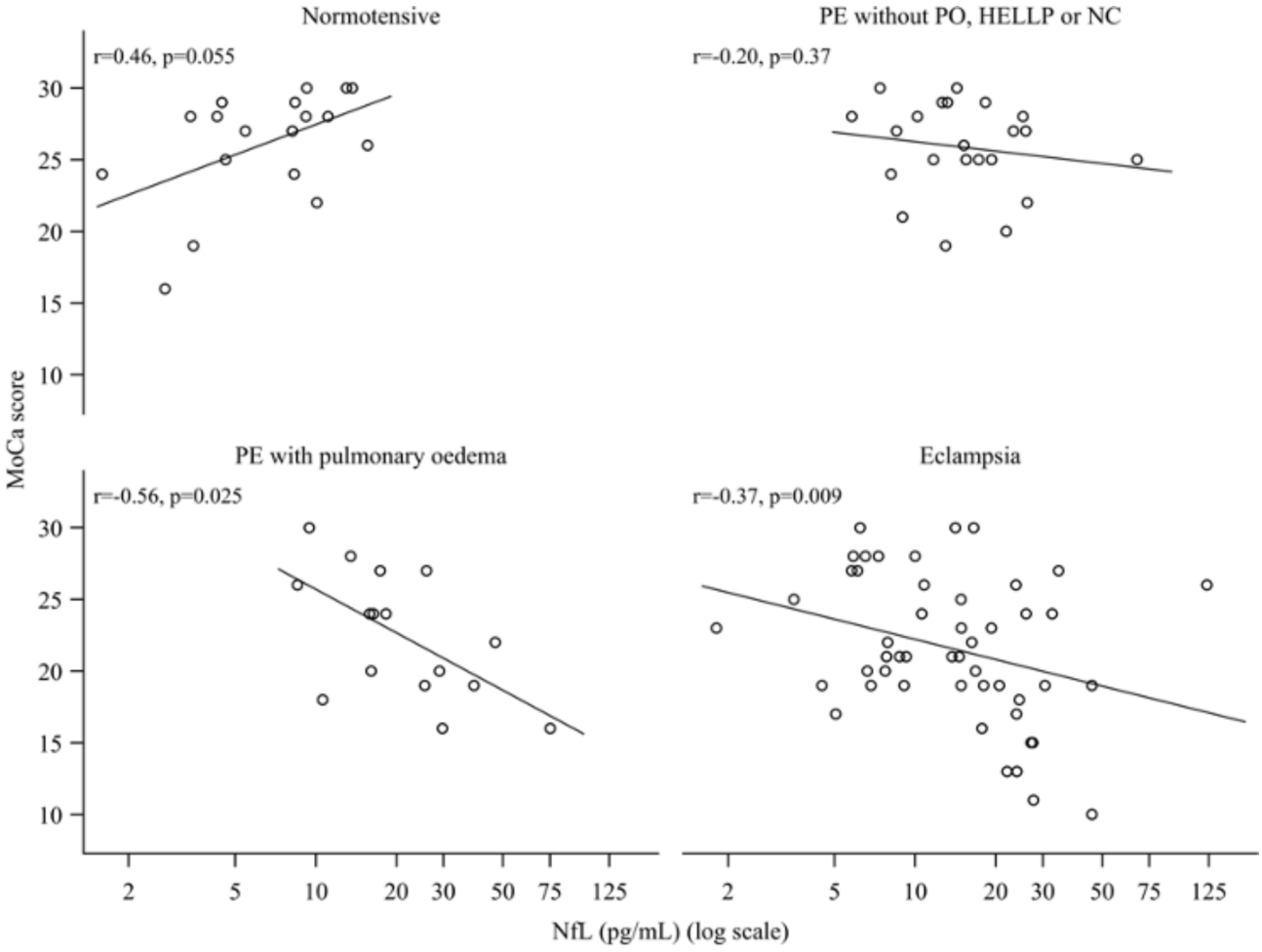

Fig. 2. Correlation between Montreal cognitive assessment scores (MoCA) and log-versions of plasma concentrations of cerebral biomarkers neurofilament light chain (NfL), tau and glial fibrillary acidic protein (GFAP) in relation to groups. Analyses were made using a non-parametric Spearman correlation test. The results were adjusted for time from eclamptic seizure. HELLP; Haemolysis elevated liver enzymes and low platelets, MoCA; Montreal cognitive assessment, NC; neurological complications, PE; pre-eclampsia, PO; pulmonary oedema,

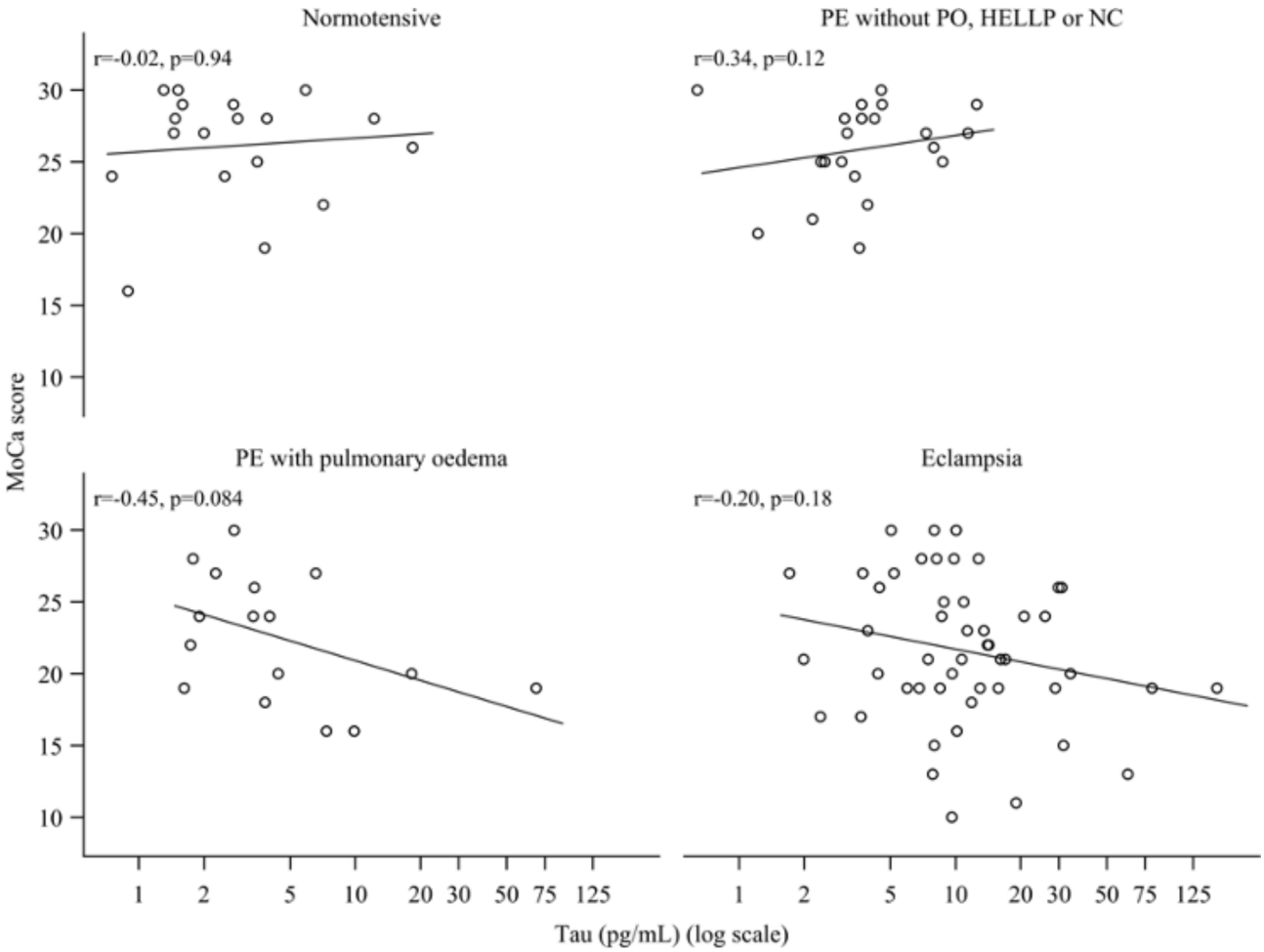

Fig. 3. Correlation between Montreal cognitive assessment scores (MoCA) and log-versions of plasma concentrations of cerebral biomarkers neurofilament light chain (NfL), tau and glial fibrillary acidic protein (GFAP) in relation to groups. Analyses were made using a non-parametric Spearman correlation test. The results were adjusted for time from eclamptic seizure. HELLP; Haemolysis elevated liver enzymes and low platelets, MoCA; Montreal cognitive assessment, NC; neurological complications, PE; pre-eclampsia, PO; pulmonary oedema,

women with pre-eclampsia without pulmonary oedema, HELLP or neurological complications or women with normotensive pregnancies. There was no correlation observed between MoCA scores and tau or GFAP in any of the groups.

4.2. Results in context

We have previously shown that women with eclampsia and pulmonary oedema demonstrate lower scores on objective cognitive function tests in close proximity to disease compared to women with normotensive pregnancies and women with pre-eclampsia without pulmonary oedema, HELLP or neurological complications [13]. When we adjusted for confounding factors, the results only remained true for women with eclampsia. We also demonstrated that subjective cognitive function rated before onset of disease was similar between groups [13].

Our group has shown that the cerebral biomarkers NfL, tau and GFAP are increased in plasma in women with pre-eclampsia complicated by HELLP or neurological complications [18]. Cerebral biomarkers may have potential for diagnosing or predicting pre-eclampsia with neurological complications. We postulate that the degree of cognitive impairment at the time of insult may correlate to the severity of pre-eclampsia and the circulating concentrations of cerebral biomarkers. This study supports this hypothesis by demonstrating a negative correlation between plasma NfL concentrations and MoCA scores in women with severe pre-eclampsia. However, we could not show such a correlation for tau or GFAP.

To our knowledge, there are no studies assessing a correlation between circulating cerebral biomarkers and cognitive assessment in pregnancy. Others have shown a negative correlation between increased concentrations of plasma NfL and cognition in patients with Alzheimer's and Parkinson's disease [22] and higher baseline plasma concentrations of NfL have shown to be associated with worsening of global cognition in elderly patients [23]. The same group also showed that changes in plasma concentrations of NfL correlated with short-term cognitive change, suggesting that plasma NfL is a promising marker for the short-term prognosis of nonspecific neurodegenerative and cognitive impairment [24]. In addition, a negative correlation between increased serum concentrations of GFAP and cognitive function decline measured using the Mini-Mental State Examination in patients with neurodegenerative diseases has been shown [24]. Yet another study found a negative association between serum concentrations of tau days after traumatic brain injury and cognitive dysfunction measured by the MoCA test six months later [26]. We only found a moderate negative correlation between NfL and cognitive outcome and no correlation between the other cerebral biomarkers tau and GFAP. Further studies are needed to confirm these findings.

4.3. Research implications

A leading theory behind the pathogenesis of cerebral complications

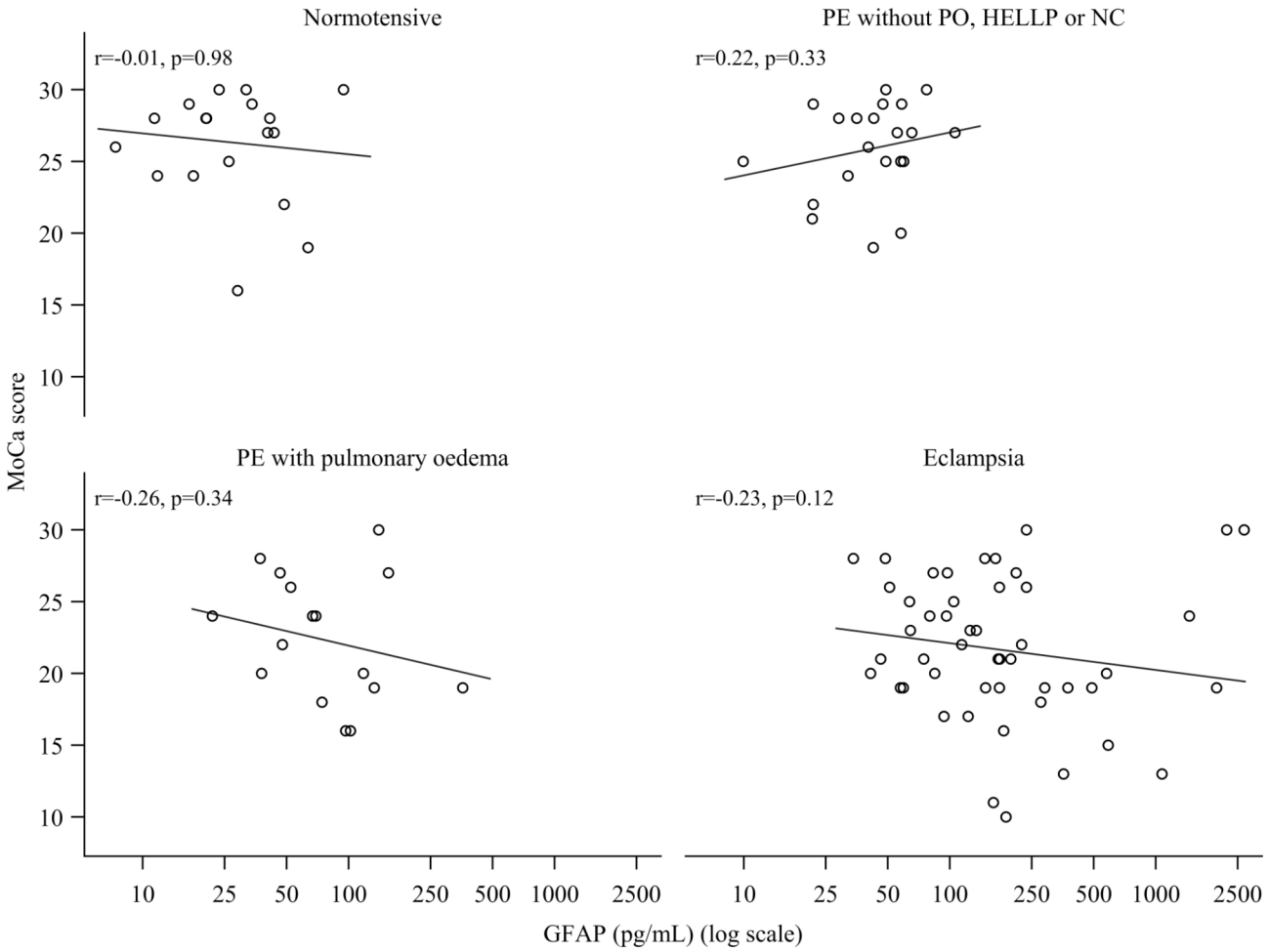

Fig. 4. Correlation between Montreal cognitive assessment scores (MoCA) and log-versions of plasma concentrations of cerebral biomarkers neurofilament light chain (NfL), tau and glial fibrillary acidic protein (GFAP) in relation to groups. Analyses were made using a non-parametric Spearman correlation test. The results were adjusted for time from eclamptic seizure. HELLP; Haemolysis elevated liver enzymes and low platelets, MoCA; Montreal cognitive assessment, NC; neurological complications, PE; pre-eclampsia, PO; pulmonary oedema,

seen in pre-eclampsia is altered dynamic autoregulation of the cerebral blood flow and impaired function of the blood–brain-barrier resulting in neuroinflammation [25–27]. This study supports this theory by demonstrating a correlation between increased concentrations of NfL in plasma and impaired cognition measured by MoCA in women with pre-eclampsia with severe features. The correlation proved strongest in women with pulmonary oedema, who are reported to also present with cerebral oedema in up to 20 % of cases [28].

There is a need of larger, prospective studies to investigate if cognitive impairment seen in the acute setting persists and how these findings relate to neuroimaging and circulating biomarkers.

4.4. Clinical implications

This study shows that circulating cerebral biomarkers, in particular NfL, might have a role in diagnosing cognitive impairment in the acute phase of pre-eclampsia with severe features, such as eclampsia and pulmonary oedema. Potentially, cerebral biomarkers could be of use in predicting long-term neurological consequences at discharge after delivery and thus identifying women at risk. These women could be offered early interventions in terms of closer monitoring of blood pressure and cognitive function.

4.5. Strengths and limitations

One of the strengths within this study is that it presents a unique cohort of women with pre-eclampsia with severe complications, including eclampsia and pulmonary oedema. Due to the low incidence of these complications in high-income countries, identifying a similar population in these settings would likely be unfeasible. The analyses of cerebral biomarkers are validated, robust and show high accuracy. The study is also the first in its kind to compare outcome of cerebral biomarkers and cognitive function in this group of women.

There are several limitations with this study. The number of admission days in the hospital varied, hence there was a difference in time elapsed from plasma sampling to test of cognitive function. The MoCA test used to assess cognitive function has not been validated in a South African population, which has been discussed in our previous publication [13]. Lastly, we do not have follow-up examinations of cognitive function or repeated analyses of cerebral biomarkers.

5. Conclusions

Here, we demonstrate a correlation between impaired cognitive function assessment and increased plasma concentrations of NfL in women with eclampsia and pre-eclampsia complicated by pulmonary oedema. This study supports the theory that there is an acute neuroaxonal injury in pre-eclampsia with severe features, and that this may

cause or contribute to a direct impairment in cognitive function measured objectively. Cerebral biomarkers might have the potential to serve as diagnostic tools as well as prediction for acute neurological complications in pre-eclampsia and may also predict long-term cerebral outcome.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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