Cerebral biomarkers in neurologic complications of preeclampsia

OBSTETRICS

Cerebral biomarkers in neurologic complications of preeclampsia

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BACKGROUND: There is no tool to accurately predict who is at risk of developing neurologic complications of preeclampsia, and there is no objective method to determine disease severity.

OBJECTIVE: We assessed whether plasma concentrations of the cerebral biomarkers neurofilament light, tau, and glial fibrillary acidic protein could reflect disease severity in several phenotypes of preeclampsia. Furthermore, we compared the cerebral biomarkers with the angiogenic biomarkers soluble fms-like tyrosine kinase 1, placental growth factor, and soluble endoglin.

STUDY DESIGN: In this observational study, we included women from the South African Preeclampsia Obstetric Adverse Events biobank. Plasma samples taken at diagnosis (preeclampsia cases) or admission for delivery (normotensive controls) were analyzed for concentrations of neurofilament light, tau, glial fibrillary acidic protein, placental growth factor, soluble fms-like tyrosine kinase 1, and soluble endoglin. The cerebrospinal fluid concentrations of inflammatory markers and albumin were analyzed in a subgroup of 15 women. Analyses were adjusted for gestational age, time from seizures and delivery to sampling, maternal age, and parity.

RESULTS: Compared with 28 women with normotensive pregnancies, 146 women with preeclampsia demonstrated 2.18-fold higher plasma concentrations of neurofilament light (95% confidence interval, 1.64—2.88), 2.17-fold higher tau (95% confidence interval, 1.49—3.16), and 2.77-fold higher glial fibrillary acidic protein (95% confidence interval, 2.06—3.72). Overall, 72 women with neurologic complications (eclampsia, cortical blindness, and stroke) demonstrated increased plasma concentrations of tau (2.99-fold higher; 95% confidence interval, 1.92—4.65) and glial fibrillary acidic protein (3.22-fold higher; 95% confidence interval, 2.06—5.02) compared with women with preeclampsia without pulmonary edema; hemolysis, elevated liver enzymes, and low platelet count; or neurologic complications (n=31). Moreover, angiogenic markers were higher, but to a lesser extent. Women with hemolysis, elevated liver enzymes, and low platelet count (n=20) demonstrated increased plasma concentrations of neurofilament light (1.64-fold higher; 95% confidence interval, 1.06—2.55), tau (4.44-fold higher; 95% confidence interval, 1.85—10.66), and glial fibrillary acidic protein (1.82-fold higher; 95% confidence interval, 1.32—2.50) compared with women with preeclampsia without pulmonary edema; hemolysis, elevated liver enzymes, and low platelet count; or neurologic complications. There was no difference shown in the angiogenic biomarkers. There was no difference between 23 women with preeclampsia complicated by pulmonary edema and women with preeclampsia without pulmonary edema; hemolysis, elevated liver enzymes, and low platelet count; or neurologic complications for any of the biomarkers. Plasma concentrations of tau and glial fibrillary acidic protein were increased in women with several neurologic complications compared with women with eclampsia only.

CONCLUSION: Plasma neurofilament light, glial fibrillary acidic, and tau were candidate biomarkers for the diagnosis and possibly prediction of cerebral complications of preeclampsia.

Key words: cerebral biomarkers, eclampsia, glial fibrillary acid protein, neurofilament light, prediction, preeclampsia, tau

Introduction

Eclampsia and other cerebral complications of preeclampsia, including cerebral edema, ischemia, and hemorrhage, are leading causes of maternal morbidity and mortality.[1] Preeclampsia and, in particular, eclampsia are associated with long-term maternal neurologic outcomes, including an increased risk of white matter lesions, stroke, seizure disorders, and vascular dementia later in life.[2–4] Despite this, there is no available tool to accurately predict who is at risk of developing these complications, and there is no objective method to determine disease severity apart from imaging and symptom assessment.[5] Symptoms thought to predict eclampsia, such as visual disturbances and severe headache, have poor predictive accuracy with a sensitivity of 35% and specificity of 94% for visual disturbances and a sensitivity of 56% and specificity of 83% for headache.[5] Furthermore, there is no objective way of determining disease severity and who is at risk of developing long-term neurologic sequelae.

The angiogenic biomarkers soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), their ratio (sFlt-1—to—PlGF), and soluble endoglin (sEng) can predict the development of preeclampsia. Revealed PlGF testing can reduce the time to diagnosis of preeclampsia in suspected preeclampsia and reduce maternal adverse outcomes.[6] Similarly, the sFlt-1—to—PlGF ratio has been shown to increase the proportion of women diagnosed with preeclampsia within 7 days of sampling.[7] Case-control studies of angiogenic biomarkers concerning cerebral complications demonstrate that PlGF and sFlt-1 are altered in plasma in severe disease, including eclampsia.[8,9]

Cerebral biomarkers are proteins that are highly specific to the central nervous system and can be measured in cerebrospinal fluid (CSF) or blood (plasma or

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AJOG at a Glance

Why was this study conducted?

Neurologic complications are important contributors to preeclampsia-associated maternal mortality and morbidity. Current diagnostic tools and predictors demonstrate poor sensitivity and specificity. Easily accessible blood biomarkers to identify women at high risk may be useful tools for the prediction of neurologic complications.

Key findings

Cerebral biomarkers have the potential to detect neurologic complications in preeclampsia.

What does this add to what is known?

Plasma concentrations of neurofilament light and tau are increased in preeclampsia but have never been evaluated in women who develop neurologic complications of preeclampsia. Plasma glial fibrillary acidic protein has not been evaluated in preeclampsia. These data contributed to the field by demonstrating the potential usefulness of these biomarkers in neurologic complications in preeclampsia.

serum). Circulating neurofilament light (NfL), tau, and glial fibrillary acidic protein (GFAP) are useful diagnostic and predictive biomarkers for several neurologic disorders, including Alzheimer disease and traumatic brain injury.[10–12] NfL and tau increase when there is axonal injury, and GFAP increases when there is glial cell involvement. NfL and tau are increased in women before a diagnosis of preeclampsia and after, but their ability to diagnose or predict cerebral complications in preeclampsia has not been established.[13–17] GFAP has not been studied in preeclampsia.

First, we assessed whether cerebral biomarkers NfL, GFAP, and tau are increased in maternal plasma in several subtypes of preeclampsia, particularly those with significant neurologic complications, such as eclampsia, stroke, or cortical blindness. Second, we assessed how cerebral biomarkers performed in comparison with the established preeclampsia biomarkers PlGF, sFlt-1, and sEng. Lastly, we correlated concentrations of circulating biomarkers to blood-brain barrier disruption and neuroinflammatory markers in CSF.

Materials and Methods

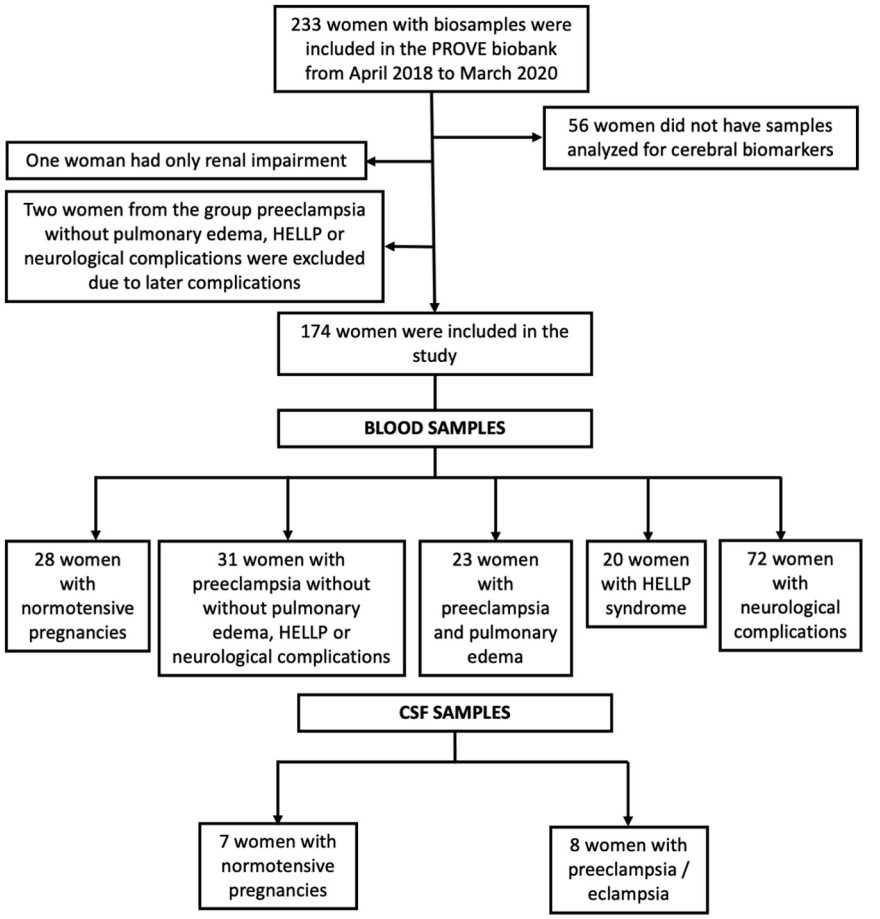
Study cohort

Women with singleton pregnancies recruited to the Preeclampsia Obstetric Adverse Events (PROVE) biobank at Tygerberg Hospital, Cape Town, South Africa, were included.[18] Tygerberg Hospital is the largest referral hospital in the Western Cape Provence of South Africa and delivers more than 8000 high-risk pregnancies yearly and manages many women with complications of preeclampsia.[18] The exclusion criteria were women with known neurologic or cardiac disease. For normotensive women, additional exclusion criteria included chronic hypertension and diabetes mellitus. Preeclampsia was defined according to the recent American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin, but significant proteinuria was also required to diagnose preeclampsia (protein-to-creatinine ratio of $\geq$30 mg/mmol [0.3 mg/mg] or $\geq$0.3 g protein in a 24-hour urine collection or urine dipstick of >1+ in more than 1 occasion).[19] Pulmonary edema was diagnosed when there was worsening dyspnea, fine bibasal inspiratory crackles on auscultation, and features of pulmonary edema on chest x-ray. Hemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome) was defined as a platelet count of $<100 \times 109$/L, aspartate aminotransferase of >70 U/L, and hemolysis as demonstrated by lactate dehydrogenase > 600 U/L or hemolysis on a peripheral blood smear. Eclampsia was diagnosed if generalized tonic-clonic seizures occurred in a woman diagnosed with preeclampsia in the absence of another etiology. Renal impairment was defined as a serum creatinine of >120 umol/L, which is higher than the ACOG definition. Women were followed up from recruitment to discharge. Severe hypertension was defined as a systolic blood pressure of $\geq$160 mm Hg and/or a diastolic blood pressure of $\geq$110 mm Hg.

At inclusion, women with preeclampsia were divided into 4 groups. These groups were preeclampsia with neurologic complications, preeclampsia with HELLP syndrome, preeclampsia complicated by pulmonary edema, and preeclampsia without pulmonary edema, HELLP syndrome, or neurologic complications. All women could have severe hypertension. We used a hierarchical system where women with neurologic complications could also suffer from HELLP syndrome and pulmonary edema at inclusion, women with HELLP syndrome could suffer from pulmonary edema but no neurologic complication, and women with pulmonary edema could not have HELLP syndrome or neurologic complications. After inclusion, any later complications were recorded, but the women remained in their initial groups. If women with preeclampsia without pulmonary edema, HELLP syndrome, or neurologic complications subsequently developed any complications, they were excluded from the study. No pregnant woman with a normotensive pregnancy developed hypertension. We further subdivided preeclampsia with neurologic complications into eclampsia only (1 eclamptic seizure with no other neurologic symptom) or several neurologic complications (women who had multiple seizures, stroke, a Glasgow Coma Scale [GCS] of >13, or eclampsia together with other organ complications).

Baseline data were obtained by interview and extraction from medical records. All data were entered and stored in a Research Electronic Data Capture

FIGURE 1
Flowchart of the study population



CSF, cerebrospinal fluid; *HELLP*, hemolysis, elevated liver enzymes, low platelet count; *PROVE*, Preeclampsia Obstetric Adverse Events.

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database[20] and double-checked for accuracy.

Sample collection

Plasma samples were collected in ethylenediaminetetraacetic acid tubes at inclusion after a diagnosis of preeclampsia or after admission for delivery (normotensive pregnancies). Women could be included before or shortly after delivery. CSF was collected in a subset at the time of spinal anesthesia at delivery. Samples were centrifuged, aliquoted, and frozen at −80°C. Samples were shipped to Melbourne, Australia, for analysis of angiogenic biomarkers and to a neurochemistry laboratory in Gothenburg, Sweden, for analyses of cerebral biomarkers and neuroinflammatory markers.

Biomarker assays

Plasma concentrations of tau, NfL, and GFAP 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).[21] Calibrators were run in duplicates, whereas samples were run in singlicates with a 4-fold dilution. Of note, 2 quality control (QC) samples were run in duplicates at the beginning and end of each run. For GFAP, a QC sample with concentrations of 49.6 pg/mL resulted in a repeatability of 11.9% and an intermediate precision of 11.9. Intra- and interassay coefficients of variation were 4.3% and 15%.

The concentrations of sFlt-1 and PlGF were measured with a commercial electrochemiluminescence immunoassay platform (Roche Diagnostics, Basel, Switzerland). sEng was measured using Endoglin CD/105 DuoSet enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. The samples were run in singlicates, with a 200-fold dilution, and 2 QC samples were run with each plate.

CSF and plasma albumin concentrations were measured by immunonephelometry on a Beckman IMMAGE Immunohistochemistry System (Beckman Instruments, Beckman Coulter Inc, Brea, CA). The CSF-to-plasma albumin ratio was calculated as CSF albumin (mg/L)/serum albumin (g/L) and was used as a measure of the blood-brain barrier integrity.[22] CSF concentrations of interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor α (TNF-α) were measured using the Meso Scale Discovery 4-Plex Proinflammatory Panel II according to instructions from the manufacturer (Meso Scale Discovery, Rockville, MD) and have been published previously.[23] Laboratory technicians were blinded to the groups.

Statistical methods

Demographic and clinical characteristics were presented as mean (standard deviation), median (interquartile range [IQR]), or number (percentage).

Biomarkers were presented as median (IQR) and compared among groups as fold changes with 95% confidence intervals. Unadjusted analyses were performed using the Welch analysis of variance on log-transformed outcomes, and adjusted analyses were performed using the Welch analysis of covariance on log-transformed outcomes, adjusting for age, parity, gestational age (GA) at blood sampling, and time from eclampsia to plasma sample collection. Angiogenic biomarkers were further adjusted for time from delivery to plasma sample. Furthermore, we performed a separate analysis of angiogenic biomarkers on the subgroup of women with blood samples obtained before delivery.

In statistical evaluations with <6 observations per group, analyses were performed using nonparametric

TABLE 1
Background characteristics by subtype of preeclampsia

Characteristic	Preeclampsia[a]	Pulmonary edema	HELLP	Neurology
n	31	23	20	72
At baseline				
Maternal age (y)	24.9 (5.2)	30.4 (8.0)	28.6 (7.4)	22.8 (6.2)
Nulliparous	17 (55)	11 (48)	7 (35)	50 (69)
HIV	5 (16)	5 (22)	4 (20)	7 (10)
Smoking	2 (7)	1 (4)	2 (11)	12 (17)
Alcohol use	1 (3)	0 (0)	1 (5)	7 (10)
Methamphetamine use	0 (0)	0 (0)	1 (5)	2 (3)
Diabetes mellitus				
Pregestational	1 (3)	0 (0)	0 (0)	0 (0)
Pregnancy induced	0 (0)	1 (5)	0 (0)	1 (1)
Chronic hypertension	6 (19)	1 (5)	3 (15)	6 (9)
BMI (kg/m^2)	27.9 (7.8)	32.7 (8.7)	31.2 (5.7)	25.7 (5.0)
Missing	3 (10)	3 (13)	6 (30)	14 (19)
After inclusion				
GA at delivery (wk)	33.5 (4.2)	31.6 (4.5)	30.3 (5.4)	33.4 (4.4)
Sample taken before delivery	11 (36)	3 (13)	5 (25)	33 (46)
Sampling in relation to delivery (d)				
Antepartum samples	−0.5 (0.7)	−0.7 (0.6)	−0.2 (0.4)	−0.2 (0.6)
Postpartum samples	2.3 (1.8)	1.7 (1.2)	2.1 (1.3)	2.8 (5.3)
Mode of delivery				
Vaginal delivery	8 (26)	6 (26)	7 (35)	23 (32)
Elective CD	1 (3)	0 (0)	0 (0)	1 (1)
Emergency CD	22 (71)	17 (74)	13 (65)	48 (67)
Live-born infant	26 (84)	19 (83)	13(65)	60 (83)
Birthweight (g)	2014.1 (947.9)	1747.8 (997.3)	1366.3 (689.3)	2090.3 (901.5)
Angiogenic biomarkers				
PlGF (pg/mL)	17.5 (9.7–44.4)	18.6 (10.6–50.2)	9.5 (7.4–28.5)	18.0 (10.6–28.7)
sFlt-1 (pg/mL)	4617.0 (981.0–8099.0)	1929.0 (840.8–4297.0)	4663.5 (1170.5–12779.0)	4415.5 (2090.8–11197.8)
sFlt-1–to–PlGF ratio	117.5 (60.7–328.2)	70.2 (46.1–119.6)	162.6 (58.5–1636.0)	171.0 (100.3–561.0)
sEng (pg/mL)	183,516.3 (130,565.2–236,011.3)	152,344.6 (121,787.1–31,273.7)	287,394.2 (168,641.7–376,916.7)	228,487.8 (146,314.4–301,254.5)
Maternal complications				
Maternal death	0 (0)	0 (0)	0 (0)	2 (3)
ICU admission	0 (0)	1 (4)	2 (10)	9 (13)
OCCU admission	3 (10)	22 (96)	13 (65)	52 (72)
Eclampsia	0 (0)	0 (0)	0 (0)	68 (94)
Recurrent eclampsia	0 (0)	0 (0)	0 (0)	23 (32)
Stroke[b]	0 (0)	0 (0)	0 (0)	3 (4)

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TABLE 1
Background characteristics by subtype of preeclampsia *(continued)*

Characteristic	Preeclampsia[a]	Pulmonary edema	HELLP	Neurology
GCS<13	0 (0)	0 (0)	0 (0)	17 (24)
Cortical blindness	0 (0)	1 (4)	0 (0)	4 (6)
Pulmonary edema	0 (0)	23 (100)	6 (30)	2 (3)
Inotropic support	0 (0)	0 (0)	1 (6)	1 (1)
Renal impairment	0 (0)	3 (13)	9 (45)	14 (19)
Dialysis	0 (0)	1 (4)	1 (6)	0 (0)
HELLP syndrome	0 (0)	1 (4)	20 (100)	17 (24)
Increased INR (>1.2)	0 (0)	3 (13)	3 (15)	9 (13)
Severe hypertension	8 (26)	16 (70)	16 (80)	29 (40)
Sepsis	0 (0)	4 (15)	2 (13)	8 (11)
Venous thromboembolism	0 (0)	0 (0)	0 (0)	2 (3)
Placental abruption	1 (3)	1 (4)	2 (10)	4 (6)

Data are presented as number (percentage), unless otherwise indicated. For continuous variables, values are presented as mean (standard deviation). For angiogenic biomarkers, values are presented as median (interquartile range).

BMI, body mass index; *CD*, cesarean delivery; *GA*, gestational age; *GCS*, Glasgow Coma Scale; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count; *ICU*, intensive care unit; *INR*, international normalized ratio; *OCCU*, occlusion culling unit; *PlGF*, placental growth factor; *sEng*, soluble endoglin; *sFlt-1*, soluble fms-like tyrosine kinase 1.

[a] Preeclampsia without pulmonary edema, HELLP syndrome, or neurologic complications; [b] Intracranial hemorrhage or ischemic lesion.

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permutation tests. Corresponding confidence intervals were calculated by test inversion.[24] Comparisons were performed on both unadjusted and adjusted for GA at blood sampling.

Correlations between biomarkers in plasma and neuroinflammatory markers in CSF were analyzed using Pearson correlations between log-transformed variables. Because of small sample sizes, *P* values were calculated nonparametrically using exact permutation tests.

In all hypothesis tests, a 2-sided *P* value of <.05 was considered statistically significant. Data and statistical analyses were performed using SPSS (version 26.0; SPSS; PASW Statistics, Chicago, IL), Stata/MP (version 16.0; StataCorp, College Station, TX) for Mac software package, and SAS software (version 9.4; SAS Institute, Cary, NC).

Sample size

Previous studies comparing women with normotensive pregnancies with women with preeclampsia used a sample size of 10 in each group to detect a difference in plasma concentrations of NfL with an alpha error of 0.05 and a power of 0.8.[13] To study the subgroups and to study preeclampsia with neurologic complications, the sample size was set to at least 20 in each group and at least 60 in the group with preeclampsia and neurologic complications.

Ethics approval and registration details

Ethics approval was obtained (protocol number N18/03/034; Federal Wide assurance number 00001372; Institutional Review Board approval number IRB0005239). All participants or their guardians signed informed consent. The biobank is registered (ISRCTN10623443) and the protocol is published.[18]

Data availability

Anonymized data will be made available on request from any qualified investigator after approval.[18]

Results

We included women from April 2018 to March 2020. A total of 177 plasma samples were available for analysis: 28 were normotensive pregnancies and 146 had preeclampsia. Of note, 31 women had preeclampsia without pulmonary edema, HELLP syndrome, or neurologic complications, 23 women had pulmonary edema, 20 women had HELLP syndrome, and 72 women had severe neurologic complications. We had CSF samples for 8 women with preeclampsia or eclampsia and for 7 women with normotensive pregnancies (Figure 1).

Background characteristics

Maternal characteristics and pregnancy outcomes are presented in Table S1. Women with preeclampsia were younger, more often nulliparous, more often used alcohol and/or methamphetamine, and had a higher body mass index. They delivered at an earlier gestation, had more low birthweight infants, and experienced more stillbirth than women with normotensive pregnancies (Table S1). Women with preeclampsia were divided into subgroups as presented in Table 1.

Circulating cerebral biomarkers

Plasma concentrations and fold change of cerebral biomarkers between

TABLE 2
Fold changes of cerebral biomarkers among subgroups, crude and adjusted for time point for blood sampling, maternal age, and parity

		NfL		Tau		GFAP	
Reference	Subgroup	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Normotensive	Normotensive (n=28)	1.00	1.00	1.00	1.00	1.00	1.00
	Preeclampsia (n=146)	2.47 (1.90–3.20) P<.0001	2.18 (1.64–2.88) P<.0001	1.90 (1.35–2.68) P<.001	2.17 (1.49–3.16) P<.001	2.61 (2.02–3.37) P<.0001	2.77 (2.06–3.72) P<.0001
Preeclampsia[a]	Preeclampsia[a] (n=31)	1.00	1.00	1.00	1.00	1.00	1.00
	Pulmonary edema (n=23)	1.01 (0.69–1.50) P=.94	0.90 (0.59–1.35) P=.59	1.01 (0.64–1.61) P=.95	1.00 (0.61–1.63) P=1.00	1.27 (0.89–1.80) P=.18	1.21 (0.84–1.75) P=.29
	HELLP syndrome (n=20)	1.74 (1.13–2.68) P=.013	1.64 (1.06–2.55) P=.029	4.46 (1.89–10.52) P=.001	4.44 (1.85–10.66) P=.002	1.89 (1.41–2.53) P<.0001	1.82 (1.32–2.50) P<.001
	Neurologic complications (n=72)	1.16 (0.86–1.55) P=.32	0.85 (0.59–1.23) P=.39	2.09 (1.47–2.96) P<.0001	2.99 (1.92–4.65) P<.0001	2.49 (1.83–3.39) P<.0001	3.22 (2.06–5.02) P<.0001
Eclampsia only	Eclampsia only (n=25)	1.00	1.00	1.00	1.00	1.00	1.00
	Several neurologic complications (n=47)	1.50 (0.94–2.41) P=.088	1.36 (0.89–2.07) P=.15	1.62 (1.07–2.45) P=.024	1.81 (1.20–2.73) P=.006	2.09 (1.28–3.39) P=.004	2.24 (1.37–3.67) P=.002

Data are presented as fold change (subgroup vs reference) with 95% confidence interval. Unadjusted analyses were performed using the Welch analysis of variance on log-transformed variables. Adjusted analyses were performed using the Welch analysis of covariance on log-transformed variables, adjusting for gestational age at blood sampling, time from eclampsia to plasma sample, maternal age, and parity.

GFAP, glial fibrillary acidic protein; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count; *NfL*, neurofilament light.

[a] Without pulmonary edema, HELLP syndrome, or neurologic complications.

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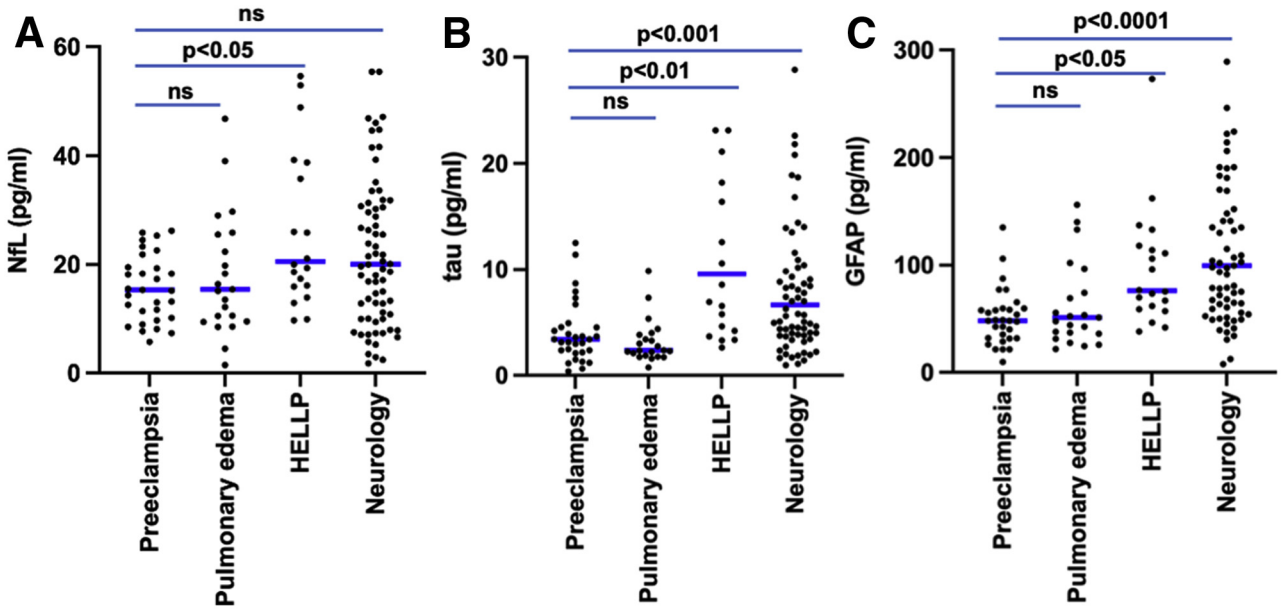
normotensive women and women with preeclampsia are presented in Table 2 and Table S2. After adjustments for GA at sampling, time from seizures to sampling, maternal age, and parity, plasma concentrations of NfL and tau were 2.2-fold higher (2.18 [95% CI, 1.64−2.88] and 2.17 [95% CI, 1.49−3.16]) in women with preeclampsia than in women with normal BP. Furthermore, plasma concentrations of GFAP were 2.8-fold higher (2.77; 95% CI, 2.06−3.72) in women with preeclampsia than in women with normal BP. Plasma concentrations and fold change of cerebral biomarkers within subgroups of women with preeclampsia are presented in Figure 2, Table 2, and Tables S3 and S4. Compared with women with preeclampsia without pulmonary edema, HELLP syndrome, or neurologic complications after adjustments, plasma concentrations of NfL, tau, and GFAP were increased in women with HELLP syndrome (1.64-fold change [95% CI, 1.06−2.55], 4.44-fold change [95% CI, 1.85−10.66], and 1.82-fold change [95% CI, 1.32−2.50]). Women with preeclampsia with neurologic complications demonstrated a 3-fold increase in plasma concentrations of tau and GFAP (2.99 [95% CI, 1.92−4.65] and 3.22 [95% CI, 2.06−5.02]) compared with women with preeclampsia without pulmonary edema, HELLP syndrome, or neurologic complications. Women with pulmonary edema did not demonstrate differences in plasma concentrations in any of the cerebral biomarkers compared with women with preeclampsia without pulmonary edema, HELLP syndrome, or neurologic complications.

In adjusted analyses for women with neurologic complications, women with several neurologic complications had increased plasma concentrations of tau and GFAP compared with women with eclampsia only (1.81-fold change [95% CI, 1.20−2.73] and 2.24-fold change [95% CI, 1.37−3.67]), but there was no difference among groups for NfL (Figure 3 and Table 2).

Circulating angiogenic biomarkers

Angiogenic biomarkers drop rapidly after delivery; therefore, we adjusted for

FIGURE 2
Differences between women with different phenotypes of preeclampsia



The *scatterplots* show the plasma concentrations with medians for NfL (**A**), tau (**B**), and GFAP (**C**). The outliers were removed from the figure but included in the statistical analyses: preeclampsia (n=31; preeclampsia without pulmonary edema, HELLP syndrome, or neurologic complications), pulmonary edema (n=23), HELLP syndrome (n=20), and neurologic complications (n=72).

GFAP, glial fibrillary acidic protein; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count; *NfL*, neurofilament light; *ns*, nonsignificant.

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days from delivery to sampling and GA at sampling in addition to time from seizures to sampling, maternal age, and parity. Compared with women with normotensive pregnancies, women with preeclampsia demonstrated 50% lower plasma concentrations of PlGF (95% CI, 0.25−0.99), 2.58-fold higher plasma concentrations of sFlt-1 (95% CI, 1.84−3.62), 4.98-fold higher plasma concentrations of the sFlt-1−to−PlGF ratio (95% CI, 2.75−9.00), and 1.67-fold higher plasma concentrations of sEng (95% CI, 1.38−2.02) (Table S5).

When women with preeclampsia without pulmonary edema, HELLP syndrome, or neurologic complications were compared with other subtypes of preeclampsia, women with neurologic complications had 2.48-fold higher plasma concentrations of sFlt-1 (95% CI, 1.49−4.14), 2.46-fold higher plasma concentrations of sFlt-1−to−PlGF ratio (95% CI, 1.45−4.17), and 1.34-fold higher plasma concentrations of sEng (95% CI, 1.11−1.63). There was no significant difference for angiogenic biomarkers for women with HELLP syndrome. Women with pulmonary edema had a lower sFlt-1−to−PlGF ratio (0.46-fold change; 95% CI, 0.26−0.83) and no significant difference in sFlt-1, sEng, or PlGF (Table S5). There was no difference in angiogenic markers when women with eclampsia only were compared with women with several neurologic complications (Table S5).

A subgroup analysis of women with samples available before delivery showed similar results, but the numbers were very small for HELLP syndrome and pulmonary edema (Table S6).

Correlation between biomarkers in plasma with blood-brain barrier integrity and neuroinflammatory markers in cerebrospinal fluid

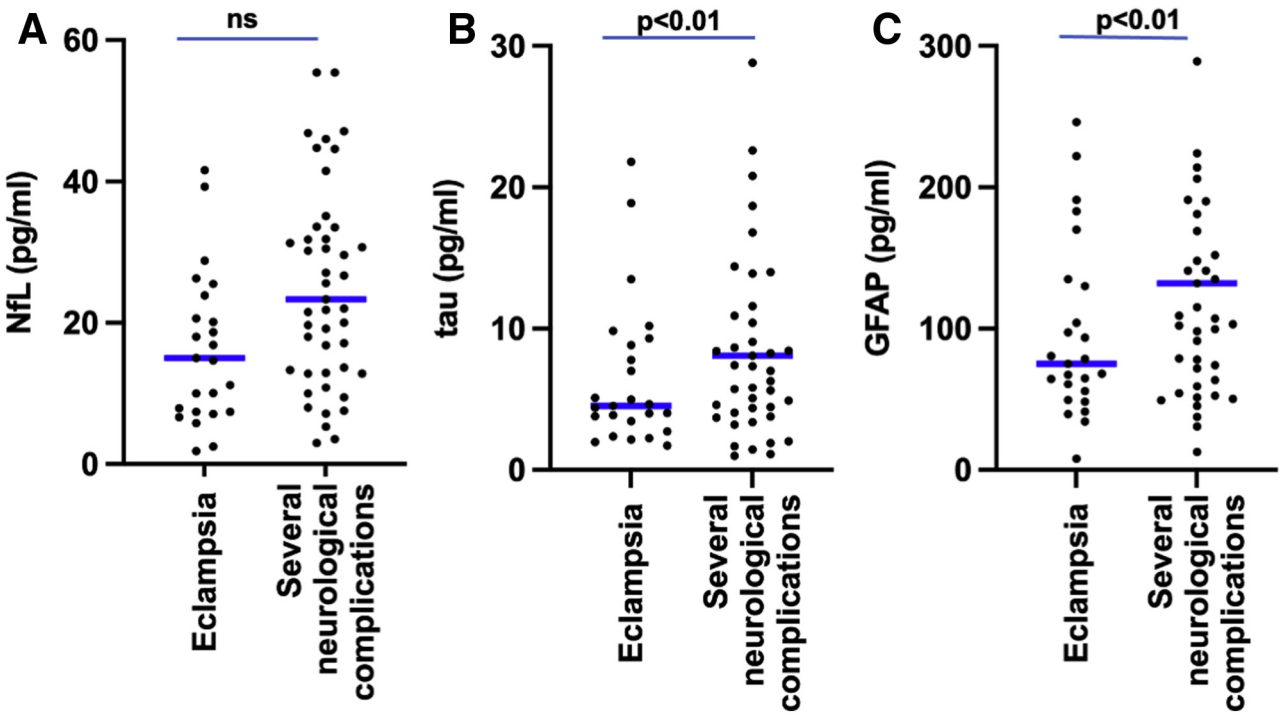
There was a positive correlation between circulating concentrations of GFAP and neuroinflammatory markers IL-6 (r=0.96; *P*=.004), IL-8 (r=0.93; *P*=.010), and TNF-α (r=0.98; *P*<.001) and between circulating concentrations of tau and TNF-α (r=0.77; *P*=.029) in women with preeclampsia or eclampsia (n=8). There was no correlation between angiogenic biomarkers and neuroinflammatory markers or CSF to plasma albumin quotient in women with preeclampsia or eclampsia. In women with normotensive pregnancies, a negative correlation between albumin ratio and tau (−0.74; *P*=.29) was found, but no other correlation was seen (n=7) (Table S7).

Comment

Principal findings

Circulating cerebral biomarkers were increased in preeclampsia with neurologic complications and HELLP syndrome but not in pulmonary edema. These biomarkers could play a role in increasing the diagnostic and/or prognostic accuracy of cerebral complications in preeclampsia, alone, or together with angiogenic biomarkers.

FIGURE 3
Differences within the group of neurological complications between women with one neurolog complication compared to women with several neurologic complications/other organ complications



The *scatterplots* show the plasma concentrations with medians for NfL (**A**), tau (**B**), and GFAP (**C**). Eclampsia only (n=25) indicate 1 generalized tonic-clonic fit without complications. Several neurologic complications (n=47) indicate ≥2 complications, including recurrent eclampsia, Glasgow coma scale of <13, intubation, or other organ complications. Outliers were removed from the figure but included in the statistical analyses.

GFAP, glial fibrillary acidic protein; *NfL*, neurofilament light.

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Results in context

Our study assessed plasma concentrations of cerebral biomarkers among women with preeclampsia and severe complications. NfL, tau, and GFAP were increased in women with preeclampsia with neurologic complications and/or HELLP syndrome compared with women with preeclampsia without pulmonary edema, HELLP syndrome, or neurologic complications. Women with HELLP syndrome have a higher risk of eclampsia, and treatment with magnesium sulfate to prevent eclampsia is warranted.[19] Thus, increased plasma concentrations of cerebral biomarkers may reflect neurologic impairment in these cases.

The underlying pathophysiology of eclampsia and cerebral edema in preeclampsia is not fully understood. Disturbed cerebral blood flow autoregulation in combination with injury to the blood-brain barrier and neuroinflammation play a role.[25] Increased plasma concentrations of cerebral biomarkers could originate from an increased release through an impaired blood-brain barrier, an increased production in the central nervous system, or a combination.

Angiogenic biomarkers are established predictors for preeclampsia and disease severity.[6,7,26] Circulating concentrations of sFlt-1 increase and concentrations of PlGF decrease in women with eclampsia compared with women with normotensive pregnancies.[8] We have previously shown that angiogenic biomarkers are altered in preeclampsia with neurologic complications and HELLP syndrome compared with preeclampsia without severe features.[9] Here, we observed equal or stronger associations between cerebral biomarkers and neurologic complications than angiogenic biomarkers. Furthermore, tau and GFAP were increased in women with more severe forms of neurologic complications compared with women with eclampsia only, a finding not present for angiogenic biomarkers. We did not demonstrate altered plasma concentrations of angiogenic biomarkers in women with HELLP syndrome. Although we corrected for GA at sampling and date of sampling concerning date of delivery, some of the blood samples were drawn 1 to 4 days after delivery, and as angiogenic markers drop dramatically after delivery, this may have impacted our results. When only antepartum samples were analyzed, the results remained similar for neurologic complications. Because of small antepartum sample numbers in women with HELLP syndrome and pulmonary edema, it is difficult to draw any conclusions for these groups.

Plasma GFAP showed a positive correlation to CSF concentrations of neuroinflammatory markers that reflect the degree of neuroinflammation. This was not seen for angiogenic biomarkers. These results from CSF measurements should be interpreted with caution because of the small sample size and multiple testing.

In neurologic diseases, such as stroke, traumatic brain injury, hypoxia owing to cardiac arrest, and neurodegenerative disease, NfL, tau, and GFAP are promising biomarker candidates for both the prediction and diagnosis of the disease and long-term outcome.[27–30] NfL and tau are both axonal proteins, and GFAP is a protein present in glial cells. All are used as central and peripheral biomarkers for neurodegenerative disease and can be useful in both diagnosis and prognosis.[21,31] In patients with traumatic brain injury, increased concentrations of NfL have been detected in both CSF and plasma.[11] In addition, plasma concentrations of NfL have proven to predict stroke in a population of patients with diabetes mellitus.[27] Similarly, tau has been identified in increased concentrations in plasma and CSF in stroke,[28] and tau has also been shown to predict a 6-month outcome regarding cerebral symptoms after cardiac arrest.[32] GFAP and tau have both been shown to be increased in plasma several months after traumatic brain injury, indicating a persisting injury.[30] Preeclampsia predisposes women to acute neurologic complications, such as eclampsia, cerebral edema, and intracerebral hemorrhage,[25] and long-term complications, such as dementia, epilepsy, and stroke.[2–4] Cerebral biomarkers, reflecting both axonal and glial injury, could potentially serve as acute diagnostic and prediction tools and perhaps predictors for long-term outcomes.

Clinical implications

Cerebral biomarkers may be of value when evaluating a woman with preeclampsia for the risk of neurologic complications and HELLP syndrome. Cerebral and angiogenic biomarkers could be combined to improve the detection of severe complications. Early detection and intervention for women at risk could improve prognosis and decrease the incidence of maternal morbidity and mortality.

Research implications

Our findings need to be confirmed in further studies. Prospective studies should be performed to assess if these cerebral biomarkers are increased before the onset of neurologic complications. If these biomarkers can accurately reflect the degree of neurologic injury, they could be examined for their prognostic significance in long-term neurologic morbidity.

Strengths and limitations

This study included a large number of women with severe preeclampsia, enabling us to assess different phenotypes. We used well-established analyses with the potential to detect very low concentrations of analyzed biomarkers in plasma that have previously not been possible.[33]

Study limitations included that biosamples were obtained after the onset of complications and that less than half of the biosamples were antenatal samples.

Conclusions

Circulating cerebral biomarkers NfL, tau, and GFAP were increased among women with preeclampsia and neurologic complications and HELLP syndrome. The circulating cerebral biomarkers may be useful diagnostic tools and could potentially be predictors for degree of neurologic involvement. ■

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H.Z. has served at scientific advisory boards and/or as a consultant for AbbVie, Alector, Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, NervGen, AZTherapies, Cognition Therapeutics, and Red Abbey Labs and has given lectures in symposia sponsored by Cellectricon, Fujirebio, AlzeCure, and Biogen. Furthermore, H.Z. is a cofounder of Brain Biomarker Solutions in Gothenburg AB, which is a part of the GU Ventures Incubator Program. K.B. has served as a consultant or has served at advisory boards for Abcam, Axon, Biogen, Lilly, MagQu, Novartis, and Roche Diagnostics. Furthermore, K.B. is a cofounder of Brain Biomarker Solutions in Gothenburg AB, which is a part of the GU Ventures Incubator Program, all unrelated to the work presented in this article. L.B. is a part of a steering group in a study investigating first-trimester prediction of preeclampsia, where Roche Diagnostics, Thermo Fischer Scientific, and PerkinElmer provide free reagents for placental growth factor. The remaining authors report no conflict of interest.

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