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Cerebrospinal fluid levels of tau and phospho-tau-181 proteins during pregnancy

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ABSTRACT

Objectives: During pregnancy various interactions occur between structural alterations of the maternal brain and placental metabolism. The aim of the present study was to investigate whether cerebrospinal fluid concentrations of tau and phospho-tau-181 protein vary during normal pregnancy and in women with preeclampsia and HELLP syndrome.

Study design: We measured cerebrospinal fluid biomarkers, tau and phospho-tau-181 protein levels in 90 pregnant women electively assigned for regional anaesthesia during pregnancy or for cesarean section using enzyme-linked immunosorbent assays.

Results: Cerebrospinal fluid concentrations for tau and phospho-tau-181 in 66 women with normal pregnancy were 308.5 ± 117.3 pg/mL and 50.5 ± 16.7 pg/mL, respectively. Blood pressure, liver function, clotting activity and kidney function were significantly different in eleven women with preeclampsia and HELLP syndrome. The weight of the newly born ($p < 0.001$; HR: 0.998), the weight of the placenta ($p = 0.018$) and concentrations for phospho-tau-181 ($p = 0.043$; HR: 1.211) correlated significantly with the disease.

Conclusion: Mean concentrations of cerebrospinal fluid tau and phospho-tau-181 protein during pregnancy were evaluated. Phospho-tau-181 protein concentrations correlated with placental function supporting the hypothesis that altered expression of neuronal factors during pregnancy may affect development of the placenta.

1. Introduction

Pregnancy, birth, and lactation are characterized by numerous specific alterations in several systems of the maternal body [1]. Adaptive mechanisms of the maternal brain occur during pregnancy to maintain physiologic conditions and proper fetal and neonatal development [2]. Structural alterations of the maternal brain include volume changes, receptor, synaptic and neuronal plasticity, changes in adult neurogenesis, functional and structural synaptic plasticity, and dendritic remodeling in different brain regions [1].

D'Souza et al. reported that neurotrophic factors influence development of the materno-feto-placental unit during pregnancy [3]. Furthermore, alterations in the levels of neurotrophic factors during pregnancy may be associated with abnormal development of the placenta [3]. Placental disorders due to impaired trophoblast invasion and spiral artery remodeling in the second trimester is common in preeclampsia [4]. Pathogenetic mechanisms implicated in preeclampsia include defective deep placentation, platelet and thrombin activation, intravascular inflammation, endothelial dysfunction and imbalanced angiogenesis [5]. Preeclampsia is a multisystemic disorder that affects several organ systems, including the maternal brain [4]. Effects on the cerebrovasculature may alter cerebral blood flow autoregulation and cause disruption of the blood-brain barrier [6].

Tau and phospho-tau-181 protein in cerebrospinal fluid (CSF) can reflect biological activity and are usually associated with neurodegenerative processes. Results from animal research indicated that tau and phospho-tau expression also change in a tissue-dependent manner throughout pregnancy and the beginning of lactation in the rat brain [7]. González-Arenas et al. concluded that

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pregnancy involves changes in brain function that imply a reorganization in the neuronal cytoskeleton.

The aim of this study was to evaluate CSF concentrations of tau and phospho-tau-181 protein in pregnant women undergoing regional anaesthesia during pregnancy or for cesarean section and determine whether preeclampsia and HELLP syndrome affect concentrations of either biomarker.

2. Materials and methods

The study was approved by the Ethics Committee of the Medical University of Innsbruck and was conducted in accordance with the Declaration of Helsinki [8]. Written informed consent was obtained from all patients before participation. Elective gynecological operations during pregnancy including cesarean section were performed under spinal block. All pregnant women undergoing spinal anaesthesia with direct access to the CSF at the Department of Gynecology, Innsbruck Medical University Hospital, were eligible participants.

Inclusion criteria were: pregnant women with preeclampsia and HELLP syndrome and women with normal pregnancy, 18 years of age or older, nonsmokers in good health. Also, women had no history of past or present major psychiatric disorders except depression during pregnancy, and did not suffer from major neurological, renal or hepatic disease. Cases lacking written consent were not to be included.

2.1. Study protocol

Medical history, blood chemistry (blood sugar, hemoglobin, protein), liver and kidney function parameters (blood urea nitrogen, creatinine, glomerular filtration rate, proteinuria) were obtained from the patient's records. Chronic medications other than multivitamins, magnesium and iron supplementation were recorded. Circulatory and respiratory status (systolic and diastolic blood pressure, pulse rate and oxygen saturation) were measured non-invasively prior to spinal anaesthesia. Demographics, clinical characteristics and laboratory findings of the study participants were recorded in a working chart. Women with second trimester pregnancy, third trimester pregnancy and women with preeclampsia and HELLP syndrome were investigated. Second trimester pregnancy was defined from week 13 to week 28 and third trimester pregnancy from week 29–40 according to U.S. Department of Health and Human Services [9]. Preeclampsia is a disorder of pregnancy with hypertension and proteinuria. Preeclampsia can be complicated by severe HELLP syndrome, characterized by hemolysis, elevated liver enzymes and low platelet count [10]. Post-hoc subgroup analysis focused on women with diminished uteroplacental blood flow detected by uterine artery Doppler ultrasound.

2.2. Collection and processing of samples

Spinal anaesthesia was performed according to standard operation procedures of the Department of Anesthesiology and Critical Care Medicine. After disinfection and draping a 20-gauge introducer needle was inserted in the mid-line lumbar region. A 25-gauge needle was inserted through the introducer into the subarachnoid space. Then the trocar was removed. When CSF fluid started to drip from the needle, one milliliter was collected in a sterile polypropylene tube [11]. Samples were immediately transported to the Psychiatry Laboratory and stored at −80 °C prior to processing. Following delivery of the newly born and removal of the placenta, umbilical cord blood was analysed for pH and base excess.

For detection of total tau and phospho-tau-181 protein CSF samples were thawed. Biomarker concentrations were measured by ELISA according to the manufacturer's instructions (Innotest Tau and Phospho-Tau, Fujirebio Europe N.V., Ghent, Belgium), as reported previously by us [12].

2.3. Physical activity, estimated stress and increase in body weight

Degree of physical activity and estimated stress were expressed on a 5-point Likert scale (1 = very much, 2 = much, 3 = moderate, 4 = poor, 5 = very poor). Grading of physical activity follows the WHO-recommended levels of physical activity for adults aged 18–64 years with 150 min of moderate-intensity aerobic physical activity minimum throughout the week [13]. Consequently, we defined daily activities >30 min = very much, up to 30 min = much, 20 min = moderate, 10 min = poor, and <10 min = very poor. Body mass index (BMI) was calculated as body weight divided by the square of the body height. Increase in body weight BMI (delta) was calculated as BMI (current) minus BMI (before pregnancy) in kg/m^2 [14].

2.4. Statistical analysis

Calculations were conducted with SPSS 21.0 (IBM SPSS Statistics Standard). Epidemiologic data were reported as mean and standard deviation. Non-parametric analysis was made with the Mann-Whitney *U* test. *T* test was used for comparison of means in independent samples when data was normally distributed. For analysis of categorical or ordinal variables we used Fisher's exact test. Spearman rank correlation coefficients (two-tailed) were calculated between CSF marker levels and individually estimated stress and degree of physical exercise during pregnancy. For other ordinal and continuous data either Pearson or Spearman correlation was calculated as appropriate. Logistic regression analysis was used for estimating the relationships between CSF biomarkers, placental weight and preeclampsia/HELLP. Statistical significance was deemed given when $p < 0.05$.

3. Results

3.1. Patient characteristics

A total of 90 pregnant women between second trimester and term who underwent spinal anaesthesia were consecutively enrolled in a prospective research cohort. Nine women in second trimester pregnancy were treated for cervical incompetence (6), for dysplastic lesions of the transformation zone (2) and for amnion prolapse (1). Preeclampsia was diagnosed in nine women and HELLP syndrome in two women. In third trimester pregnancy six women (two women with preeclampsia/HELLP syndrome and four women of the control group) had diminished uteroplacental blood flow as detected by uterine artery Doppler ultrasound.

Demographic data including age, body height, current body weight, BMI and BMI gain during pregnancy, number of previous pregnancies, abortions and deliveries are shown in Table 1. No age-related differences were found.

3.2. Preeclampsia/HELLP syndrome

We compared eleven women with preeclampsia/HELLP syndrome to 66 controls with no evidence of impaired uteroplacental perfusion in third trimester pregnancy. The two groups were similar in demographic data (Table 1). Stress was scored higher than physical activity but the two criteria did not significantly differ between the groups. Hepatic function, clotting system activity

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Table 1
Demographic data of eleven women with pre-eclampsia/HELLP and 66 controls at delivery. Numerical data are expressed as mean and standard deviation and were analysed with *t*-test or Mann-Whitney *U* Test as appropriate. Ordinal data are presented as frequencies and were analysed with Fisher's exact test.

	Preeclampsia/HELLP ($n = 11$)	Control ($n = 66$)	p value
Characteristics			
Age (years)	31.8 ± 7.8	32.7 ± 5.4	0.625
Height (cm)	165.2 ± 7.4	165.9 ± 6.6	0.953
Weight (kg)	78.4 ± 12.4	81.4 ± 14.0	0.616
BMI (kg/m^2)	28.6 ± 3.2	29.7 ± 5.0	0.665
Index gain[a] (kg/m^2)	5.6 ± 2.0	5.7 ± 1.9	0.994
Gravidity	1.8 ± 0.9	2.5 ± 1.2	0.076
Deliveries	0.4 ± 0.5	0.8 ± 0.7	0.092
Abortions	0.4 ± 0.7	0.7 ± 1.1	0.469
Physical activity	2.1 ± 0.8	2.2 ± 0.9	0.787
Stress	2.8 ± 1.4	3.5 ± 1.2	0.087

[a] Index gain is the increase in BMI from onset of pregnany to current BMI.

and renal function differed significantly between the groups (Table 2). Platelet count was significantly lower ($p = 0.003$) and proteinuria was more frequently observed ($r_s = 0.638$; $p < 0.001$) in women with preeclampsia/HELLP syndrome. Systolic and diastolic blood pressure was significantly higher in women with preeclampsia/HELLP. Health status of the newly born after 5 min was worse in women with preeclampsia/HELLP syndrome ($p = 0.031$); pH and base excess in umbilical cord blood were comparable to controls (Table 3). Preeclampsia/HELLP syndrome correlated significantly with placenta weight ($r_s = 0.274$; $p = 0.017$) and with baby weight ($r_s = 0.459$; $p < 0.001$). In a post hoc subgroup analysis of six women with reduced placental perfusion as detected by uterine artery Doppler sonography birth weight ($p < 0.001$) was significantly diminished as well (Table 2).

Table 2
Blood chemistry, liver function, clotting system, kidney function and urinalysis in eleven women with preeclampsia/HELLP and 66 controls at delivery. Numerical data are expressed as mean and standard deviation and were analysed with *t*-test or Mann-Whitney *U* Test as appropriate. Nominal data were expressed as frequencies and analysed with Fisher's exact test.

	Preeclampsia/HELLP ($n = 11$)	Control ($n = 66$)	p value
Blood chemistry			
Platelets (10^3/mL)	157.2 ± 49.6	217.4 ± 60.5	**0.003**
Hemoglobin (mg/dL)	12.4 ± 1.0	12.1 ± 1.1	0.278
Glucose (mg/dL)	102.0 ± 29.1	95.7 ± 27.6	0.703
Protein (mg/dL)	6.0 ± 0.5	6.6 ± 0.6	**0.025**
Liver function			
Glutamate oxalate transaminase (mg/dL)	49.9 ± 72.5	21.5 ± 11.0	**0.018**
Lactate dehydrogenase (mg/dL)	237.6 ± 64.3	197.1 ± 73.5	**0.045**
Clotting system			
Fibrinogen (mg/dL)	393.0 ± 81.6	435.0 ± 63.1	**0.030**
Prothrombin time (%)	112.3 ± 10.5	108.1 ± 8.0	0.082
Partial thromboplastin time (sec)	27.4 ± 4.0	26.4 ± 2.2	0.571
Kidney function			
Urea (mg/dL)	22.0 ± 10.3	16.1 ± 4.9	0.285
Blood urea nitrogen (mg/dL)	10.2 ± 4.2	7.5 ± 2.3	0.140
Creatinine (mg/dL)	0.8 ± 0.2	0.6 ± 0.1	**0.009**
Urinalysis			
Haematuria N (%)	5 (45.4)	12 (18.2)	0.123
Proteinuria N (%)	7 (63.6)	3 (4.5)	**0.000**

Significant p values ($p < 0.05$) are given in bold.

Table 3
Cardiorespiratory parameters, health status of the newly born and analysis of umbilical cord blood in eleven women with preeclampsia/HELLP and 66 controls at delivery. Values are expressed as mean and standard deviation and were analysed with *t*-test or Mann-Whitney *U* Test as appropriate.

	Preeclampsia/HELLP ($n = 11$)	Control ($n = 66$)	p value
Cardiorespiratory parameter			
Systolic blood pressure (mmHg)	158.2 ± 15.0	121.7 ± 9.5	**0.000**
Diastolic blood pressure (mmHg)	97.6 ± 13.6	77.1 ± 9.8	**0.000**
Heart rate (1/min)	91.6 ± 18.7	87.4 ± 13.9	0.380
Oxygen saturation (%)	97.4 ± 2.7	97.6 ± 1.4	0.543
Newly born health status			
Apgar 1 min	8.3 ± 0.6	8.5 ± 1.1	0.072
Apgar 5 min	8.8 ± 0.9	9.4 ± 0.8	**0.031**
Apgar 10 min	9.6 ± 0.5	9.8 ± 0.5	0.077
Birth weight	2055.0 ± 783.7	3161.9 ± 581.3	**0.000**
Placenta weight	424.6 ± 110.4	506.0 ± 118.7	**0.018**
Umbilical cord blood			
pH	7.3 ± 0.0	7.3 ± 0.1	0.180
Base excess	1.1 ± 1.7	1.0 ± 2.1	0.953

Significant p values ($p < 0.05$) are given in bold.

3.3. CSF biomarkers

CSF concentrations of tau and phospho-tau-181 protein in 90 pregnant women ranged from 131 to 816 pg/mL and from 25 to 112 pg/mL, respectively (Table 4). Concentrations of biomarkers did not differ significantly among the groups, but concentrations for phospho-tau-181protein ($p = 0.043$; HR: 1.211) correlated significantly with preeclampsia/HELLP syndrome in eleven women.

CSF concentrations of tau and phospho-tau-181 protein were not significantly lower in nine women with second trimester pregnancies and in six women with diminished uteroplacental perfusion (Table 4). Phospho-tau-181/tau ratio ranged from 0.111 to 0.204 and did not differ significantly between the groups.

4. Discussion

This is, to the best of our knowledge, the first study in which tau and phospho-tau-181 concentrations were measured in CSF of pregnant women. Mean levels of the two biomarkers were high with peak values for tau protein of 816 pg/mL and for phospho-tau-181 protein of 112 pg/mL. In pregnant rats González-Arenas A. et al. [7] found that tau and phospho-tau expression change in a tissue-dependent manner. In particular, tau was increased in the hypothalamic region. The authors concluded that CSF biomarkers may directly reflect an adaptive physiological response to the metabolic demands of pregnancy. In our study concentrations for phospho-tau-181 protein ($p = 0.043$; HR: 1.211) correlated significantly with evidence of preeclampsia/HELLP syndrome. At this point we cannot explain the pathophysiology behind our findings. Presumably, changes in neuronal plasticity during pregnancy are more pronounced in preeclampsia/HELLP syndrome.

There is a variety of hypothalamic neurohormones expressed in the placenta and fetal and placental metabolism regulates maternal, placental and fetal physiology [2]. In addition, neurotrophic factors influence the development of the materno-feto-placental unit [3]. Moreover, preeclampsia may adversely affect the maternal brain, including cerebral blood flow autoregulation and blood–brain barrier disruption [6]. At this point we cannot tell from our results whether altered blood–brain barrier can influence concentrations of tau and phospho-tau-181 protein.

Artunc-Ulkumen et al. [15] found that increased levels of S100B protein indicating brain injuries in perinatal medicine may also be

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Table 4
CSF tau and phospho-tau-181 levels in eleven women with preeclampsia/HELLP, six women with hypoperfusion of the placenta, nine women in 2nd trimester and 66 controls at delivery. Values are expressed as mean and standard deviation and were analysed with Kruskal-Wallis test.

	Preeclampsia/HELLP (*n = 11*)	Hypoperfusion (*n = 6*)	2nd trimester (*n = 9*)	3rd trimester (*n = 66*)	p value
Biomarker					
Tau (pg/mL)	296.3 ± 109.7	248.3 ± 105.8	290.7 ± 124.6	308.5 ± 117.3	0.455
P-tau-181 (pg/mL)	50.9 ± 20.1	42.3 ± 14.3	47.4 ± 18.1	50.5 ± 16.7	0.286
P-tau/tau ratio	0.173 ± 0.024	0.177 ± 0.024	0.167 ± 0.020	0.166 ± 0.014	0.276

a potential marker in preeclampsia, indicating severe hypoperfusion in placenta and maternal brain. Van Dijk et al. reported that pre-eclampsia susceptibility gene STOX1 controls a conserved pathway shared between placenta and brain and that it is functionally involved in late-onset Alzheimer's disease [16]. However, it is unlikely that placental disorders result only from impaired neurotrophic factor pathways.

Excessive stress was reported to be associated with impairment of the placental adaptive response [2]. In our study, stress levels were not significantly higher in women with preeclampsia/HELLP syndrome and did not correlate with biomarker concentrations in the CSF. Impaired maternal uterine vasculature was reported in women with gestational hypertension and preeclampsia [17]. Whether hypertension during pregnancy is sufficient to alter tau and phospho-tau-181 expression or whether responsiveness is modulated by placental disorders warrants further investigation. Not surprisingly, proteinuria was more frequent as this finding is among the leading symptoms of preeclampsia/HELLP syndrome. Thrombocytopenia was more common in women with preeclampsia/HELLP syndrome but a platelet count below 100,000 per microliter was not observed in our study [18].

Limitations arise from the fact that in this preliminary study the number of pregnant women with preeclampsia/HELLP was low. In the absence of human studies we had no information on normal values of tau and phospho tau protein during pregnancy.

5. Conclusions

In summary, our data indicate that phospho-tau-181 protein may respond to placental development during pregnancy. Larger trials focusing on placental morphology and function in preeclampsia and HELLP syndrome are needed to draw definitive conclusions.

Disclosures

The authors have no competing interests to declare including financial, personal or relationships with other persons or organizations that could inappropriately influence, or be perceived to influence, the work.

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