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Levels of serum copeptin in preeclampsia and association with maternal echocardiographic and doppler ultrasound parameters

Asparuh NIKOLOV [1,*], Nikola POPOVSKI [2]

[1]Department of Pre-clinical and Clinical Sciences, Faculty of Pharmacy, Medical University – Pleven, Pleven, Bulgaria
[2]Department of Obstetrics and Gynaecology, University Hospital Pleven, Medical University-Pleven, Pleven, Bulgaria

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Abstract

Copeptin is a peptide that has been reported as a valuable tool in monitoring major cardiovascular diseases such as myocardial infarction and heart failure. Echographic examinations are useful in assessing alterations in cardiovascular structure and function during pregnancy. Having in mind the role of copeptin in cardiovascular abnormalities and the subtle changes in heart and spiral arteries that can be detected by echography, the present study aimed to evaluate copeptin concentrations in preeclampsia (PE) and to investigate the existence of an association between copeptin and maternal echocardiographic and Doppler ultrasound parameters. The current research was a case-control study. Fifty-five women with PE were examined. The mean age of patients was 24.9±6 years, and the mean age of the control group of 35 women with normal pregnancies was 24.7±5.4 years. The enzyme-linked immunosorbent assay (ELISA) was used to determine copeptin concentrations. An echocardiographic assessment of all subjects was performed. In addition, uterine (UtA) artery pulsatility indices (PI) were evaluated. Levels of serum copeptin in preeclamptic women were statistically insignificantly lower than these in women with normal pregnancy: 142.2 (131.4÷146.7) vs. 144.8 (138.5÷149.4) ng/l ($p>0.05$). Copeptin correlated with systolic blood pressure ($r=-0.41$; $p=0.0001$), diastolic blood pressure ($r=-0.30$; $p=0.004$), UtA PI ($r=-0.36$; $p=0.0005$), IVS ($r=-0.23$; $p=0.03$) and LVPWD ($r=-0.21$; $p=0.05$). We report the existence of a relationship between serum copeptin and maternal echocardiographic and Doppler ultrasound parameters in preeclampsia. The present study argues for a potential copeptin implication on maternal cardiac structures and spiral arteries. Our results also confirm that copeptin is associated with increased blood pressure in preeclampsia.

Keywords: copeptin, blood pressure, echography, preeclampsia, serum levels

1. Introduction

Preeclampsia (PE) is a pregnancy-associated hypertensive disorder after 20 weeks of gestation, characterized by the development of new-onset hypertension (140/90 mmHg) and either proteinuria (0.3g in a 24-hour urine sample) or end-organ dysfunction. Current evidence shows that PE complicates nearly 2–8% of all pregnancies worldwide (1). It's one of the leading causes of maternal and perinatal morbidity and mortality (2). It has been assumed that preeclampsia involves generalized vascular injury commonly associated with endothelial alteration (3). Significant pathways contribute to abnormal hemodynamic state, including increased circulating plasma volume and fine regulation of vascular tone (4).

Copeptin is a peptide also known as C-terminal of pre-pro-hormone of arginine vasopressin (CT-proAVP) (5). The molecule of copeptin involves 39 amino acid chains, derived by C-terminal of pre-pro-hormone of arginine vasopressin, neurophysin II, and copeptin. Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), plays a key role in many cardiovascular and renal conditions. Its abnormal levels have been associated with different myocardial and kidney abnormalities (6). Unfortunately, AVP measurement has not been incorporated into routine clinical practice because of its short half-life (7, 8). Contrary to that, immunoassays can easily detect copeptin and are also used as vasopressin secretion surrogate indicators (9, 10). Copeptin has been reported as a valuable tool in monitoring cardiovascular pathologies such as myocardial infarction, left ventricular hypertrophy, cardiogenic shock, and heart failure (11, 12). Its expression correlated with survival, severity, and disease prognosis (13, 14). For instance, copeptin also significantly correlates with 6MWD and New York Heart Association (NYHA) class (15-17) as well as with kidney function in pulmonary hypertension (18-21). Interestingly, data about maternal circulatory copeptin in preeclampsia are insufficient yet.

Echocardiography is a safe, noninvasive method for evaluating changes in cardiac structure and function in

*Correspondence: a_nicoloff@yahoo.com

pregnancy (22-25). Uterine and umbilical Doppler ultrasound assessments are fast, harmless, and easily applicable diagnostic techniques to identify the compromised fetus and examine placental perfusion. It has been proposed that Doppler flow studies of the maternal uterine vessels could be used to detect women at higher risk for developing preeclampsia (26-31). Hence, these echographic methods allow the evaluation of the heart and vessels of pregnant women without exposition to X-rays and give valuable data referring to abnormal cardiovascular and hemodynamic changes during a healthy and complicated pregnancy. However, there are no data in the literature on a parallel examination of copeptin concentrations and maternal echocardiographic and Doppler ultrasound measurements in preeclampsia.

Having in mind the role of copeptin in cardiovascular abnormalities and the subtle changes in heart and spiral arteries that can be detected by echography in preeclampsia, this study aimed to: 1-) determine circulating copeptin levels in sera of women with preeclampsia and normal pregnancy; 2-) to investigate a possible relationship between copeptin and maternal echocardiographic and Doppler ultrasound parameters.

2. Materials and Methods

2.1. Study design

The current research was a case-control study**.**

2.2. Study setting

The current study was a part of the university scientific project N1/2020. The project was approved by the Ethics Committee of Medical University-Pleven with Protocol N51/2020. All participants signed informed consent. Study procedures followed all guidelines for ethical standards of the responsible committee on human experimentation as well as the Helsinki Declaration of 1975, as revised in 2000.

2.3. Study population

All patients were residing in the Clinic of Obstetrics and Gynecology, University Hospital "G. Stranski" Pleven. Sera of subjects were taken from October 2019 to March 2021. The study group consisted of 55 women with preeclampsia, the mean age of patients was 24.9±6 years, and the mean age of the control group of 35 women with normal pregnancies was 24.7±5.4 years.

2.4. Inclusion and exclusion criteria

The following criteria applied to inclusion in the study: Pregnant women with clinical symptoms who also met the laboratory criteria for preeclampsia [According to the European Society of Cardiology 2018 Guideline for the management of cardiovascular diseases during pregnancy was used for the diagnostic criteria of preeclampsia: gestational hypertension with significant proteinuria (>300mg/24h urine collection or the extrapolated amount from a timed collection)] (32); maintaining a regular diet and exercise routine throughout the research; signed informed consent form to take part in the investigation; dysfunction of mother's organ such as HELLP syndrome, kidney failure, neurological involvement, hepatic involvement, and fetal growth retardation. The following criteria applied to exclusion in the study: diabetes mellitus, renal and heart disease, signs of chorioamnionitis, and the presence of a fetus with a chromosomal abnormality.

2.5. Outcome measures and methods

Enzyme-linked immunosorbent assay (ELISA)

ELISA was used for the determination of copeptin levels. Copeptin was measured in serum samples using an ELISA kit (RJ-HUFI02359 Human Copeptin/CPP ELISA Kit- Reagent Genie) according to the manufacturer's instructions.

Echocardiography

Echocardiography was performed with General Electric (Vivid S5) with a 4-MHz transducer. All measurements were obtained according to the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) criteria for Cardiac Chamber Quantification by Echocardiography (33)

Doppler ultrasound of umbilical and uterine artery

Flow velocity waveforms of the uterine artery were performed by ultrasound apparatus using an AB 2–7 MHz convex abdominal probe. The mean pulsatility index (PI) was calculated. An abnormal Doppler of uterine artery result was diagnosed as a mean PI> the 95th percentile for each gestational age (34).

2.6. Statistical analysis

In order to analyze the research data following computer programs were used: Excel (Microsoft Corporation, Redmond, WA), SPSS, and Statgraphics Plus (Manugistics, Rockville, MD) for Windows. The level of significance was determined as ($p<0.05$). Stnd. Skewness and Stnd. Kurtosis tests were used to check the normality of distribution and equality of variances. To discover significant differences between groups, Student's t-test, and ANOVA with mean±SD were used in cases with normal distribution (LSD, Tukey HSD, Scheffe, Bonferroni, Newman-Keuls, Duncan). $\chi 2$ and Kruskal–Wallis H tests with median (M) value were used in cases with different from normal distribution, together with first and third quartile Q1 and Q3; (twenty-fifth and seventy-fifth percentile P25 and 75P). Pearson type of correlation was used. To confirm the existence of a significant relationship between the variables, linear regression analysis was carried out. All the linear regression assumptions were checked.

3. Results

Clinical data of women with preeclampsia and healthy pregnant women are presented in Table 1. Echocardiographic data of healthy pregnant women and patients with preeclampsia are described in Table 2. Levels of serum copeptin in preeclamptic women were statistically insignificantly lower than these in women with normal pregnancy: 142.2 (131.4÷146.7) vs. 144.8 (138.5÷ 149.4) ng/l

(p>0.05) (Fig. 1). Copeptin correlated with systolic blood pressure (SBP) (r=-0.41; p=0.0001) (Fig. 2), diastolic blood pressure (DBP) (r=-0.30; p=0.004) (Fig. 3), uterine artery pulsatility index (UtA PI) (r=-0.36; p=0.0005) (Fig. 4), interventricular septal thickness (IVS) (r=-0.23; p=0.03) and left ventricular posterior wall thickness (LVPWD) (r=-0.21; p=0.05).

Table 1. Clinical data of women with preeclampsia and healthy pregnant women

	Normal pregnant women	Preeclampsia	p
Maternal age	24.7±5.4	24.9±6	>0.05
BMI	26.7±4.2	34±7.3*	0.001*
Gravida	2(2) **	2 (2)**	
Parity	1(2) **	1(2) **	
SBP (mmHg)	116.1±9.55	157.8±22*	0.001*
DBP (mmHg)	75.3±7.76	100.5±10*	0.001*
Past history of PE	0/35	23/55	
Family history of AH	1/35	26/55	
AH before pregnancy	0/35	15/55	
Uterine artery PI	0.79±0.12	1.19±0.44*	0.001*
PP	40.8±7.32	57.3±16.1*	0.001*
MAP	88.8±7.69	119.7±13.1*	0.001*
Urea	2.96±0.78	3.75±1.63*	0.01*
Creatinine	75.78±14.45	73.33±15.33	>0.05
Uric acid	205.6±40.2	326.8±105.93*	0.001*
Total protein	68.89±3.16	58.71±8.78*	<0.01*
Albumin	37.31±2.78	31.67±4.98*	<0.01*
ASAT	8.43±2.33	20.67±7.82*	<0.01*
ALAT	9.83±2.50	27.76±8.25*	<0.01*
LDH	369±70.78	435.25±80.74*	0.04*
PLT	237.26±61.12	228.74±88.53	>0.05
Copeptin	144.8 (138.5÷149.4) **	142.2 (131.4÷146.7) **	>0.05
CPK	83.1±23.77	130.5±46.8*	<0.05*
CK-MB	15.3±3.3	24.3±7.9*	<0.05*
Number	(n=35)	(n=55)	

Abbreviations: BMI- body mass index; SBP- systolic blood pressure; DBP- diastolic blood pressure; PE-preeclampsia; AH-arterial hypertension; PI- pulsatility index; PP- pulse pressure; MAP- mean arterial pressure; ASAT- aspartate aminotransferase; ALAT-alanine aminotransferase; LDH-lactate dehydrogenase; PLT-platelets; CPK-creatine phosphokinase; CK-MB- creatine phosphokinase isoenzyme MB. Data are shown as the mean±SD; *p<0.05; **Data are expressed as median (interquartile range)

Table 2. Echocardiographic data of healthy pregnant women and patients with preeclampsia

	Healthy Pregnancy	Preeclampsia	p
LVEDD	46.06±1.51	47.67±2.83*	0.001*
LVESD	28.23±1.48	29.84±2.43*	<0.001*
IVS	9.47±0.86	10.74±0.93*	<0.01*
LVPWD	9.03±1.04	10.4±1.31*	<0.001*
EF%	68.28±1.98	64.69±5.14*	<0.001*
E/e'	9.64±1.02	11.76±0.77*	0.001*
Count	**35**	**55**	

Abbreviations: LVEDD- left ventricular end-diastolic diameter, LVESD-left ventricular end-systolic diameter, IVS- interventricular septal thickness, LVPWD- left ventricular posterior wall thickness, EF%- left ventricular ejection fraction, *p<0.05, Data are expressed as mean±SD

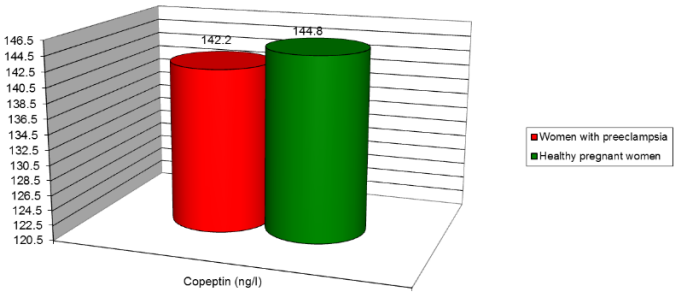

Fig. 1. Serum copeptin levels in preeclampsia and healthy pregnant women determined by ELISA

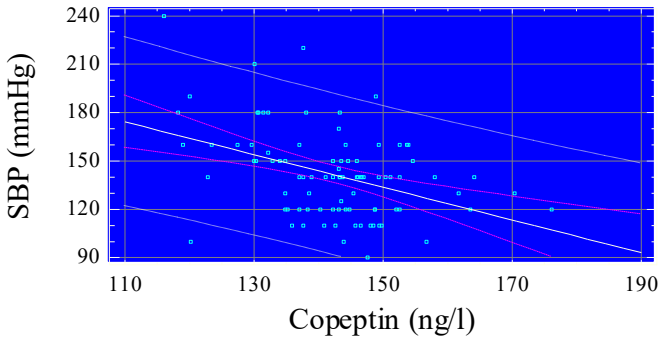

Fig. 2. Linear regression analysis, showing the results of fitting a linear model to describe the relationship between copeptin and SBP

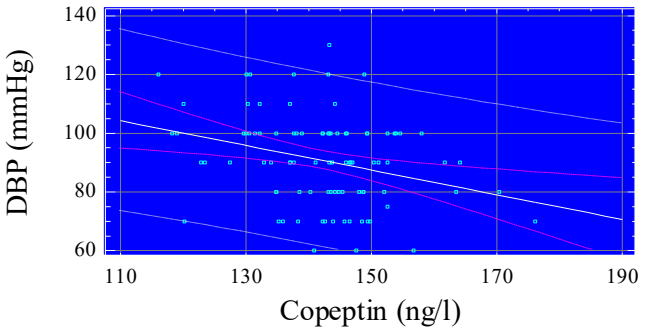

Fig. 3. Linear regression analysis, showing the results of fitting a linear model to describe the relationship between copeptin and DBP

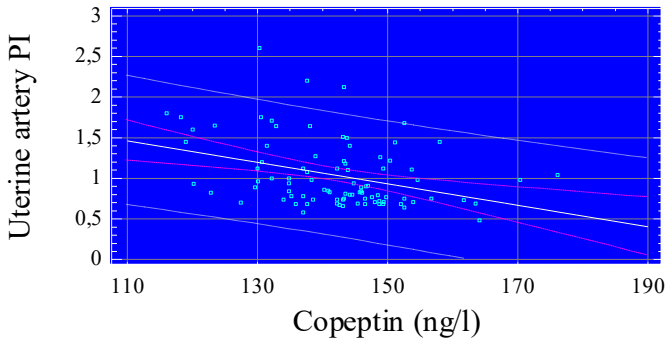

Fig. 4. Linear regression analysis, showing the results of fitting a linear model to describe the relationship between copeptin and Uterine artery pulsatility index

4. Discussion

Preeclampsia is one of the most common pregnancy disorders. It is a major cause of maternal and perinatal morbidity and mortality. According to the current understanding, preeclampsia is a systemic disease with generalized endothelial cell injury/dysfunction and multi-organ involvement. It has been reported by several studies that echocardiographic assessment of patients with preeclampsia indicates major findings such as increased ventricular mass, left ventricular hypertrophy, left atrial enlargement, and diastolic dysfunction (35-41).

Copeptin is a glycopeptide that forms the C-terminus of prepro-arginine vasopressin, which is the precursor protein of AVP, a vasoactive neuro pituitary hormone (42). Therefore, copeptin levels are used as a surrogate measurement for vasopressin secretion (43). Moreover, copeptin has also been previously investigated as a potential diagnostic and prognostic biomarker for various cardiovascular diseases (44-46). It has been theorized that copeptin is involved in the pathophysiology of preeclampsia. However, a possible relationship between copeptin and maternal echocardiographic and Doppler ultrasound parameters has not been explored.

A few researchers have assessed copeptin concentrations in healthy and complicated pregnancies so far. For example, Yeung et al. (2014), in the longitudinal study "Calcium for Preeclampsia Prevention trial," determined via BRAHMS Immunoluminometric Assay serum copeptin levels in 136 control subjects, 169 preeclampsia cases, 92 women with gestational diabetes, 101 with gestational hypertension and 86 with preterm birth. Authors found increased copeptin concentrations in pregnant women before the diagnosis of preeclampsia with "elevation specific to this pregnancy complication rather than hypertension alone"(47).

In 2015, Akinlade et al. considered the role of copeptin in PE and reported elevated maternal copeptin levels in preeclampsia. Moreover, copeptin concentrations increased with disease severity. Furthermore, the authors concluded that copeptin levels in the third trimester "could predict preeclampsia, and its elevation is associated with adverse perinatal outcome"(48).

In another research, Tuten et al. (2015) used ELISA and investigated serum copeptin levels in 80 pregnant women divided into the following subgroups: early-onset preeclampsia, late-onset preeclampsia, and two control groups of similar gestational ages for both preeclamptic groups. The mean copeptin levels in the early-onset and late-onset preeclampsia groups were higher compared with the control groups, but the difference was only statistically significant in the early-onset preeclampsia group. Copeptin levels were associated only with gestational age and systolic-diastolic blood pressure. The investigators suggested that "copeptin levels might be useful in evaluating the severity of preeclampsia." Based on their findings, authors concluded that copeptin could be involved in early- rather than late-onset preeclampsia (49).

Zulfikaroglu et al. (50) evaluated plasma levels of copeptin in preeclampsia patients and healthy pregnant women in 2011. Researchers used ELISA and measured higher plasma levels in mild and severe PE compared with normotensive pregnant women. Similarly, Santillan et al. (51) assessed copeptin levels throughout pregnancy in maternal plasma of women with preeclampsia and healthy controls in 2014. Authors reported that maternal plasma copeptin was significantly higher in preeclamptic pregnancies compared to control pregnancies. The researchers found that as early as the sixth gestational week, elevated maternal plasma copeptin concentration is an extremely important predictor of preeclampsia throughout pregnancy. Although these data suggest AVP as a novel predictive biomarker for preeclampsia very early in pregnancy, further larger clinical studies should be performed to confirm the prediction of preeclampsia by copeptin. Furthermore, new studies are needed to determine the reasons for the increased AVP production in these patients.

Recently, Hagras et al. (52) applied BRAHMS Immunoluminometric Assay in 2018 and reported that serum copeptin is higher as early as 13 weeks gestation in women who later developed preeclampsia than in cases who remained normotensive till full term and delivery and is higher in severe cases than mild cases of preeclampsia. In the same year, Mohamed et al. (53) found that serum copeptin level could be used as an important biomarker for the early diagnosis of preeclampsia.

To the best of our knowledge, the current research was one of the few in the literature to explore maternal serum copeptin concentrations in preeclampsia. In the present study, we reported statistically insignificantly lower serum copeptin levels in preeclamptic patients than in women with normal pregnancies. Our data demonstrated for the first time a relationship exists between serum copeptin and maternal echocardiographic and Doppler ultrasound parameters in preeclampsia. The current investigation argues for a potential copeptin implication on maternal cardiac structures and spiral arteries. These data were also validated by linear regression

analysis. The results obtained from our research also confirmed the findings of Tuten et al. (49) that copeptin is associated with increased blood pressure in preeclampsia. The relationship between copeptin levels and blood pressure implicates a possible copeptin role in the pathophysiology of hypertension in pregnancy and the development of preeclampsia.

Analyzing the results mentioned above, we can deliberate that the present findings agree with the findings of Tuten et al. (49), who represented that serum copeptin is associated with blood pressure in preeclampsia and might contribute to the diagnostic process of PE as for the measuring of copeptin levels in PE and healthy pregnancy, current data was not fully consistent with the reports of Yeung et al. (47), Zulfikaroglu et al. (50), and Santillan et al. (51), who demonstrated higher copeptin levels in PE vs. normal pregnancies. This difference can be explained by the usage of various laboratory methods (Yeung et al. [47] and Hagras et al. [52] used BRAHMS Immunoluminometric Assay, while our study, Akinlade et al. [48], Tuten et al.[49], Zulfikaroglu et al. [50] and Santillanet al. [51] used ELISA). Another explanation can be related to the usage of different sample types. For example, Zulfikarogluet al. (50) and Santillan et al. (51) used plasma while we investigated serum probes. The smaller sample size and measurement timing can also be important factors influencing the determination of circulating copeptin. Noteworthy, we explored blood samples after 20 gestational weeks, while Hagras et al. (52) analyzed probes before 20 weeks of gestation, and Mohamed et al. (53) collected samples in the third pregnancy trimester. It should also be highlighted that preeclampsia severity also impacts copeptin concentrations.

It has been reported by several studies that echocardiographic assessment of patients with preeclampsia indicates major findings such as increased ventricular mass, left ventricular hypertrophy, left atrial enlargement, and diastolic dysfunction (35-41). Our investigation found a relationship between copeptin and specific echocardiographic measurements such as interventricular septum thickness and left ventricular posterior wall diameter. This result assumes a possible interplay between copeptin and the above-mentioned heart structures. In addition, the relationship between copeptin and Doppler ultrasound parameters as uterine Doppler pulsatility index might reflect vascular changes responsible for abnormal remodeling and pathologically increased vascular resistance in preeclampsia. However, more specific methods like immunohistochemistry or immunocytochemistry with tissue samples analysis and evaluation of copeptin expression might be required to detect the exact structural alterations. This would help to assess exactly which tissues derive copeptin in serum during preeclampsia.

The current investigation demonstrated compelling evidence. To our knowledge, this is the first study reporting a significant relationship between serum copeptin and maternal echocardiographic and Doppler ultrasound parameters in preeclampsia. Another key finding is the association between serum copeptin concentrations and blood pressure values. The present results were validated by linear regression analysis. Our findings confirmed that copeptin might play an important role in blood pressure elevation in pregnancy. The presented data also demonstrate a potential copeptin effect on specific cardiac structures, such as the left posterior ventricular wall and interventricular septum. This might favor abnormal cardiovascular remodeling, the development of hypertension in pregnancy, and subsequent preeclampsia. Hereby, copeptin is proposed to be related to the process of altered spiral arteries' remodeling. All the factors mentioned above take part in the central pathways in the development and progression of preeclampsia.

Considering the correlation between copeptin and blood pressure found in the present investigation, we confirm that copeptin might be involved in the pathogenic mechanisms of the increase of blood pressure and the development of hypertension in pregnancy. The current study argues for a potential implication on maternal cardiac structures and spiral arteries based on the demonstrated relationship between copeptin and maternal echocardiographic and Doppler ultrasound parameters. However, larger-scale and longitudinal studies with more specific methods, such as immunohistochemistry or immunocytochemistry analysis of tissue samples, would allow a more precise assessment of the copeptin's role in the pathogenesis of PE and its interaction with the maternal heart and spiral arteries. This could provide a deeper understanding of the structural alterations and help identify the tissues involved in copeptin production during preeclampsia.

The present research had limitations. Firstly, it was a case-control study, and we could not perform serial measurements of copeptin. Secondly, the relatively small sample size also constituted a study design limitation. Thirdly, the variations in copeptin levels reported in different studies might be due to a lack of consistent laboratory methods and standardized timing of copeptin measurements. Using successive laboratory methods and validated determination timing would contribute to the comparability and reliability of copeptin level results across future studies.

Ethical Statement

The project was approved by the Ethics Committee of Medical University- Pleven with Protocol N51/2020.

Conflict of interest

The authors declare no conflict of interest.

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None to declare.

Authors' contributions

Concept: A.N., N.P., Design: A.N., N.P., Data Collection or Processing: N.P., Analysis or Interpretation: A.N., N.P., Literature Search: N.P., Writing: A.N., N.P.

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