Electroneuropathological patterns of EEG mapping in hypertensive disease associated with pregnancy

PhD THESIS
SUMMARY

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PhD thesis contains:
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- 106 figures;
- 170 bibliographical references;
- annexes;
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In this summary, the table of contents, the tables, the figures and the references retain the numbering of the thesis.

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Introduction

Currently, about 0.2-4% of all pregnancies are complicated by cardiovascular diseases, and the number of patients who develop these conditions associated with pregnancy is increasing. Hypertensive disorders associated to pregnancy, including here preeclampsia and eclampsia, remain a major cause of maternal, fetal and neonatal morbidity and mortality. Preeclampsia produces multiple systemic derangements that can involve a diversity of organ systems including hematologic, hepatic, renal, and cardiovascular systems as well as the central nervous system (3,4). Perhaps the most feared complication of preeclampsia is eclampsia itself, defined by the occurrence of one or more generalized convulsions and/or coma in the setting of preeclampsia and in the absence of other neurologic conditions (5). To better understand the cerebrovascular mechanism(s) involved, a number of neuroimaging techniques have been used that include angiography, computed-tomographic (CT) scanning, magnetic resonance imaging (MRI), positron emission tomography (PET/sPET) and Doppler velocimetry (6). These tests are used to measure brain anatomy or structure, but many of them are costly and, in some cases, there are risk factors associated with the procedures. By contrast, the EEG (Electroencephalogram) does not assess the structure of the brain, but evaluates the manner in which a particular person’s brain functions. In this context, QEEG (Quantitative EEG) is a quantitative recording of cortical electrical activity, evidenced by different type of brain waves, based on the processing of EEG recordings. Convert characteristics of brain wave such as amplitude (shape), frequency, spatial coordinates in numbers, and their subsequent representation as statistical topographic maps of the brain (brain mapping) is achieved via a suitable software (5). This creates the premises of using QEEG, also known under the acronym BEAM (Brain Electrical Activity Mapping) as an neurometric tool in the diagnosis and monitoring therapeutic efficacy. These findings constitute a base of using EEG brain mapping, for the first time, in quantification of brain damage in hypertension associated with
pregnancy, a noninvasive neuroimaging method with a real impact in the study of focal or diffuse brain lesions of diverse etiology. We also try to identify the patterns by which we can distinguish pathological groups from normals, the premise of implementation of this technique in study of neurological damage associated with hypertension in pregnancy.

Chapter I. Hypertensive syndromes in pregnancy

Hypertension is the most common medical disorder associated to pregnancy, complicating up to 15% of all pregnancies, with an average of 6-8%. The hypertensive syndromes complicating pregnancy are still responsible for 5-30% of maternal deaths, occurred due to cardiac failure, cerebral hemorrhage, hepatic or acute renal failure, and over 20% of fetal and neonatal deaths, explained by prematurity, neurological deficits, vascular disorders, and hypoxia (7,8). In hypertensive pathology associated with pregnancy, preeclampsia (PE) is a multisystem disorder that complicates approximately 3-14% of all pregnancies (1.8), with a recurrence rate up to 13-18%, being responsible for approximately 60,000 deaths/year (9,10). Eclampsia, defined as seizures at a woman with preeclampsia, that can not be attributed to other causes, is another formidable complication of hypertension associated with pregnancy. The global incidence of eclampsia is 0.3 - 0.6 ‰ in Europe and the U.S., ranging up to 6-100 cases/10.000 live births in developing countries.

In the hypertensive disorders associated with pregnancy, it is essential to identify high-risk pregnancies. Epidemiological studies describing a number of common characteristics of these patients. Schematically, the main risk factors are: maternal personal and medical factors associated with fetal / placental factors. One of the difficulties of interpreting studies about hypertensive disorders in pregnancy, is the inconsistency of terminology. The currently used classification is based on defining the following clinical and laboratory entities:
• Chronic hypertension
• Preeclampsia-eclampsia
• Preeclampsia superimposed on chronic hypertension
• Gestational hypertension (transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy)

Hypertension associated with pregnancy is considered to be a multisystemic disease, in which environmental and genetic factors seem to play an important role. Among the factors currently considered to be the most important in disease pathogenesis are: maternal immunologic intolerance, abnormal placentation, cardiovascular and inflammatory changes, genetic, nutritional, and environmental disorders (37).

Chapter II. Brain damage in hypertension associated with pregnancy

The pathological changes revealed in women died from eclampsia or biopsies taken from preeclamptic women, have clearly demonstrated that preeclampsia is not an manifest hypertension, or a variant of malignant hypertension, and increasing blood pressure is not primary pathogenic mechanism(30). Neurological complications are represented mainly by brain hemorrhage, hemiparesis, seizures, coma. Major cerebrovascular changes in eclampsia were found to be similar to those described in hypertensive encephalopathy, including overcoming self-regulating mechanism of cerebral blood flow with cerebral edema - a common neuroimaging finding (CT, MRI) at these patients (54.55).

The lesional complexes of cortical and subcortical white matter in the form of edema, infarction and hemorrhage (petechial and parenchymal intracerebral hemorrhage) is a common finding in patients who died from eclampsia. Another finding is the post-mortem cortical petechial hemorrhages, which are arranged in strips of 2-4 cm, with radial distribution in the cerebral cortex, most commonly in the occipital lobes (13,61,62). Over the years, clinical, pathological and neuroimaging findings have led to the issuance of two theories to
explain the brain abnormalities associated with hypertension in pregnancy. The first theory is centred on cerebral vasospasm, that could be the etiopathogenic basis of ischemic stroke associated with eclampsia. According to other theories, an acute and excessive elevation in mean arterial pressure causes forced dilatation of the cerebral arteries and arterioles, loss of cerebral blood flow autoregulation, with increasing hydrostatic pressure and hyperperfusion.

**Chapter III. EEG Brain Mapping**

EEG refers to the recording of the brain's spontaneous electrical activity over a short period of time, as recorded from multiple electrodes placed on the scalp. EEG is a major investigation to analyze one of the most complex and unknown systems in nature. Lately, digital electroencephalography is increasingly used. The signal is continuously represented online on a computer screen and stored in electronic form.

Digital electroencephalography techniques have grown rapidly in popularity due to the benefits in terms of recording, reviewing and storing the EEG traces. Also, digital EEG recordings are flexible, because they allow display of EEG traces, unlike conventional recording on paper, using analog electrical signal. EEG brain mapping or BEAM (Brain Electrical Activity Mapping) is a noninvasive neuroimaging investigation, in which the recording of biocurrents emitted spontaneously from the scalp is converted to an digital format, resulting in numerical series that quantifies the principals characteristics of wave highlighted.

EEG spectral analysis methods is based on Fourier analysis of frequency information (temporal, spatial or otherwise), and is extremely useful in signal processing of various types, including EEG. By using spectral analysis of traces, within the brain's EEG mapping technique, we try to highlight different aspects of pathological brain activity in hypertensive pregnant women, their location and their interpretation in the clinical and paraclinical context.
Chapter IV. Objectives

The main objective of this study was the analysis and quantification of brain events in hypertensive syndromes associated with pregnancy, using EEG brain mapping. Also, a topographic distribution analysis of EEG abnormalities was performed. The principal criteria for evaluation were considered evidence of abnormal patterns of brain electrical activity for patients with hypertension associated with pregnancy. The results were compared with those of a control group represented by normotensive pregnant. Another objective was the possibility of identifying the pathophysiological mechanisms involved in the pathogenesis of cerebral damage in hypertensive syndromes of pregnancy. Another objective of this study was the possibility of integrating the anomalies highlighted by EEG brain mapping, in the clinical and paraclinical context of hypertensive syndromes associated with pregnancy. It was also considered the predictive nature of EEG anomalies, and the possibility of including brain mapping in clinical protocols of monitoring hypertensive pathology associated with pregnancy, to evaluate high-risk pregnancies.

Chapter V. Materials and Methods

To achieve these objectives, we chose to perform an analytical case–control study. The factor studied in our project was an diagnostic test, namely, the EEG brain mapping. The evaluation criteria were considered the evidence of abnormal patterns of brain electrical activity in patients with hypertension associated with pregnancy. We have based both on classical and quantitative analysis of EEG traces, and the results were compared with those of a control group represented by normotensive pregnant without any inclusion criteria in high-risk pregnancies. This study was carried out at the Department of Obstetrics, Second Clinic of “Cuza Voda” University Hospital in Iasi, a state facility specialized in high-risk pregnancies serving as a tertiary referral center, and was conducted from November 2009 to October 2012.
Eligible women were identified by the research coordinator and/or the medical staff involved in project.

**V.1 Groups studied**

The study group was represented by 50 patients hospitalized in the Second Clinic of "Cuza Voda" University Hospital, representing high-risk pregnancies through hypertension associated with pregnancy (gestational / preeclampsia) with or without specific therapy. To determine statistically significant correlations, the study group was subdivided according to: age, socio-economic conditions of life and work, the motifs of admission, history and evolution of pregnancy, specific therapy used.

Criteria for inclusion in the study were represented by:
- patients included in the group of high-risk pregnancies, diagnosed with hypertension associated with pregnancy;
- age between 18-40 years;
- gestational age between 20-39 weeks;

Diagnosis of hypertension of pregnancy was performed according to the protocols, in correlation with clinical and paraclinical medical records generated during hospitalization.

Exclusion criteria were represented by: age under 18 and over 40 years, neurological pathology with or without signs of cerebral focalization, history of head trauma, stroke history, family history of early degenerative disease, cerebral arteriovenous malformation, mental disorders with or without specific medication, history of comatose state by diverse etiology, neurologic acute intoxication, history of acute and chronic alcohol/drugs abuse, chronic hypertension, claustrophobia.

The control group was represented by 50 pregnant women admitted in the Second Clinic of "Cuza Voda" University Hospital. The inclusion criterion was the age between 18-40 years old, represented normotensive pregnant without any inclusion criteria in high-risk pregnancies. Exclusion criteria were the same as for the study group, based on identifying those pregnant with history of neurological pathology associated. EEG/BEAM recordings were performed in
Ambulatory Care Unit (Functional Exploration Laboratory) of Sf. Spiridon Hospital, Iasi, Romania. Only one measurement was performed for each subject in both groups. Subjects were seated in a comfortable reclining chair in a dimly-lit, sound-attenuated room. Each patient was informed about the type of EEG recording used in our study, which unlike other types of brain investigations is completely safe, and not requiring injections or taking any substances. Throughout the recording period, patients were continuously monitored by medical specialists, including the obstetrician, which was able at any time to provide expert advice and help urgently in case of apparitions of any inconvenience and discomfort of the pregnant woman or fetus.

Analysis of the EEG consisted of four stages: (1) removal of artifacts (2) preliminary visual analysis (3) calculation of power spectra, and (4) determination of the statistical significance of differences between conditions/groups. Spectral analysis of EEG included a FFT transformation in which the absolute power (the total amount of brain activity at each electrode; µV²) of four different EEG frequency bands (alpha, beta, theta, delta) was estimated. Frequency components of EEG (amplitude and frequency) could be displayed as a DSA (Density Spectral Array) (Fig. 41):

![EEG recording with DSA (Density Spectral Array) analysis](image)
QP-150AK software includes an advanced analytics platform that allows viewing topographic mapping in the 6:15 standard series of positions, including dynamic 3D shape (Fig.45):

![Topographic Distribution](image)

**Fig. 45. Topographic distribution of wave amplitude in several series of position.**

The platform QP-220AK available for analysis, has enabled to display up to eight map of frequency and power spectral bands studied according to the location of the electrodes (Fig.50):

![Spectral Analysis](image)

**Fig 50. Spectral analysis based on the location of the electrodes**
Maternal monitoring included clinical/neurological evaluation, blood pressure measurements, blood and urine tests to check liver and kidney function, and blood cell counts. Fetal monitoring included a combination of nonstress tests and ultrasound examination. Differences between groups were investigated by using t-tests. Data were expressed as mean ± SD. Mean, standard error of the mean, and standard deviation were determined for quantitative variables. Relative risks with the 95% CIs were also determined. A P value of < 0.05 was considered statistically significant.

Chapter VI. EEG quantitative analysis

VI.1 Objectives
The purpose of this study was the quantification of brain damage in hypertension associated with pregnancy, by quantitative analysis of electroencephalographic traces, in terms of the main types of EEG abnormalities highlighted.

VI.2 Results
The groups did not differ by mean years of age (hypertension associated with pregnancy 27.74; control group 27.74) or parity (percent multiparous: hypertension associated with pregnancy 25.7%; control 27.74%) at index pregnancy. There were no statistically significant differences in weight and body mass index (BMI) in patient profiles between groups. By definition, systolic and diastolic blood pressures were elevated in the preeclamptic group compared with the healthy pregnant control groups. A preliminary visual inspection and analysis was carried out in order to establish the objectives. The whole group of hypertensive patients shows EEG abnormalities in 32 cases, without any abnormal EEG in control group. Generalized slowing with dominant frequency of rhythmic background activity below 8 Hz or anteriorly prominent delta waves was highlighted (9 cases). We found focal slowing of the dominant posterior background activity-namely, parietooccipital lobes-with right hemisphere location in 12 cases.
Intermittent slowing was also present (6 cases), consisted in bursts of generalized slowing (2-4 sec), especially polymorphic delta. In 4 cases EEG shows sudden bursts of electrical activity (spikes) and slow-wave complexes in left temporo-occipital region associated with background attenuation. DSA analysis platform (Density Spectral Array) showed in the specific lesional area, a sudden increase in activity in the frequency of analyzed bands. Brain mapping allowed us to obtain a complete and a better interpretation of the topography of EEG abnormalities, a digital mapping of brain electrical activity, especially in parieto-occipital regions.

**VI.3 Discussions**

Generalized slowing is generally nonspecific, an abnormal pattern appearing as an indicative of diffuse brain dysfunction, representing the most common finding in encephalopathies of various etiologies. In this context, the EEG slowing of background activity in the hypertensive group may be related to metabolic and hypertensive encephalopathy. It has been generally assumed that neurologic complications of hypertension associated with pregnancy are thought to be similar to posterior reversible encephalopathy syndrome (PRES), a variant of hypertensive encephalopathy (88). Focal slowing activity seen in EEG recordings in preeclamptic patients, is also nonspecific as to etiology, and is the most common abnormality associated with focal lesions of any type, including vascular (hypertension), neoplastic subdural collections, traumatic, and infectious (85). Another finding in the present study was intermittent rhythmic delta activity, usually occurs at frequencies of 2-2.5 Hz with relatively sinusoidal, stereotypic, bilaterally synchronous waveforms appearing in short bursts. Although the mechanisms for production are understood incompletely, intermittent rhythmic delta activity has many etiologies, including vascular, metabolic, toxic, hypoxic, or various diffuse or focal intracranial diseases (91-93). These findings may be another argument in favor of the fact that an etiological mechanisms involved in the pathogenesis of neurological complications in hypertension associated
with pregnancy is cerebral vasoconstriction. The EEG recording shows spikes and slow-wave complexes, that are considered as epileptiform patterns, associated with epilepsy or other neurologic conditions. However, the term epileptiform is only descriptive and does not necessarily imply that the pattern is epileptogenic (94,95). We found no EEG abnormalities after visual inspection in healthy controls. The findings of the current study are consistent with those of Brussé (95) and Keunen et al. (98) who found no significant differences during third trimester pregnancy and six month postpartum in healthy women, an argument that EEG is normal in the third trimester pregnancy. According to these studies, it appears that EEG changes seen during normal pregnancy indicate a pre-existing or more recent brain's unknown injury. EEG abnormalities regarding topographic distribution, were more frequent in the posterior cerebral region, explained by the pathophysiology of PRES.

VI.4 Conclusions

EEG abnormalities revealed in our study, appear to confirm that brain damage in hypertensive syndromes associated with pregnancy is based on the existence of hypertensive encephalopathy. In this context, changes in electrical activity may be associated with hypertensive and metabolic encephalopathy. Some of the etiologic mechanisms involving can be represented by cerebral vasospasm with ischemia and necrosis, or by cerebral hyperperfusion, loss of cerebral blood flow autoregulation, blood-brain barrier disruption, and vasogenic edema.

Chapter VII. EEG spectral analysis

VII.1 Objectives

In this study, we considered both the possibility of functional brain activity analysis, complex analysis computerized EEG signal in the brain's mapping, and correlations already highlighted in other brain disorders between EEG changes and several etiopathogenic theories.
VII. 2 Results

This study included 32 patients with primary EEG abnormalities and spectral analysis results were compared with a control group. The brain topography of power spectra along the antero-posterior (A-P) axis was studied in the group of hypertensive woman with EEG abnormalities (in the preliminary analysis) compared with control group. Absolute alpha power was reduced for the majority of the electrodes for the hypertensive group, and that the differences were statistically significant over parietal (P3,P4) and occipito-temporal regions (O1,O2,T5,T6). Absolute beta power, was reduced over parietal (P3,P4) and occipital (O2) regions in the hypertensive group. Patients with hypertensive syndromes associated with pregnancy showed, as compared with controls, a significant increase in absolute delta power over parietal (P3,P4) and occipital (O2) regions. Absolute delta power was also increased for the majority of the electrodes over frontal (FP2,F3,F4,F7) regions. No statistically significant differences were found between groups for the absolute theta power.

VII. 3 Discussion

The current results showed a decrease of power in the high frequency EEG bands. Also, it had been established that alpha band activity can be used as an index of cortical activity, implying a negative correlation with cerebral blood flow (103). Sadato et al.(104) analyzed the existence of correlations between the cerebral blood flow and alpha wave power using PET. Therefore, reduction of alpha power may be an indicator of increased cerebral blood flow in the parieto-occipital bilateral cortex, according with the concept that hypertension in pregnancy is a state of over-perfusion, associated with the syndrome of reversible posterior leukoencephalopathy (PRES). Beta power spectrum reduction found in our study can be an indicator of cortical integrity in hypertension associated with pregnancy, because loss of beta activity, whether diffuse or focal, indicates compromised cortical function (37). Furthermore, decreases in beta activity was associated with reductions in cerebral blood flow (113). For delta frequency, increases in activity
occurred in absolute power in hypertensive patients. In addition, in brain imaging studies, delta activity recorded at the scalp was shown to correlate negatively with cerebral blood flow in the thalamus, cerebellum or orbito-frontal cortex (115). Put together, reduction of beta power and delta's increase in hypertensive syndromes associated with pregnancy can be attributed to cerebral blood flow reductions.

**VII.4 Conclusions**

EEG spectral analysis for hypertensive pregnant women in our study suggests that both mechanisms seem to play a role in disruption of brain electrical activity, and the genesis of neurological manifestations. However, the essential problem remains the sequence of these vasoactive phenomena's. Regional differences in the distribution of EEG abnormalities, indicates that hypertension associated with pregnancy is not only a global phenomenon, but also local, with the regional involvement of different neuronal populations.

**Chapter VIII. Correlations between EEG mapping abnormalities and clinical aspects**

**VIII. 1 Objectives**

Objective of this study was the possibility of integrating EEG brain mapping anomalies highlighted in the clinical/paraclinical context of hypertensive syndromes associated with pregnancy.

**VIII.2 Results**

Neurological symptoms were present in 23 patients with primary EEG abnormalities, represented by subjective complaints such as frontal – occipital headache, auditive disorders (tinnitus), visual disorder (transient amaurosis, phosphenes), confusion, hyperreflexia, myoclonus, nausea and vomiting. Regarding the distribution and type of the main symptoms presented during hospitalization in hypertensive pregnant women with abnormal EEG, we observed prevalence of headache (11 cases), followed by visual disturbances (7 cases). The
mean value of SBP in patients with abnormal EEG's was 152 mmHg, and the value of DBP was 99.9 mmHg. No significant statistically correlations were found between the severity of hypertension and EEG abnormalities.

**VIII. 3 Discussion**

One explanation of the absence of correlation between the severity of hypertension and EEG abnormalities, is that posterior reversible encephalopathy syndrome is a variant of hypertensive encephalopathy with diverse causes including pregnancy. The difference between hypertensive encephalopathy and PRES is that PRES can develop without a significant elevation in blood pressure. It is clear that the change in blood pressure needed to promote brain hyperperfusion and cerebral edema is considerably lower during pregnancy, an "normal" increase of blood pressure being pathological, based on impairment of cerebral autoregulation (41,46). Headache is the most common symptom that creates discomfort, stress and anxiety. This findings is consistent with the concept that headache in a woman with hypertension in pregnancy are associated with an abnormality in cerebral perfusion pressure, causing EEG abnormalities. It also highlighted an increase in cerebral blood flow at hypertensive pregnant with severe headache, which seems to indicate the hyperperfusion as an crucial pathophysiological mechanism (54). Visual symptoms, such as blurred vision, double vision, photophobia, reported by women with hypertension, can be associated with an abnormality in cerebral perfusion pressure and PRES (*posterior reversible encephalopathy syndrome*). Evidence of hypertensive vasculopathy were clearly highlighted in PRES, as well as a number of features that reflect the presence of vasoconstriction/vasodilation and reduced cerebral perfusion. In the past, these events were attributed to retinal abnormalities, including edema and vascular changes such as vasospasm or thrombosis of the central retinal artery or retinal detachment. If original visual disturbances were attributed to retinean arteriolar vasospasm or microthrombosis, they are now recognized to
be associated with vasogenic cerebral edema as a result of PRES (143-146).

VIII. 4 Conclusion

The association between neurological symptoms and EEG abnormalities in hypertensive pregnant women, may suggest that the presence of neurological complaints may represent a predictive factor and at the same time a manifestation of disturbance of brain electrical activity. The fact that the pathophysiologic mechanisms involved in the genesis of both the neurological manifestations and EEG abnormalities seem to overlap, it strengthen this association.

References: