Associations of affective temperaments with arterial stiffness and Brain-derived Neurotrophic Factor in hypertension

Ph.D. Thesis

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1. INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality in most industrialized countries worldwide, despite highly effective preventive treatments. In addition to elevated blood pressure, arterial stiffening – integrating the damage of risk factors on the aortic wall over a long period – is increasingly recognized as a marker and mediator of CVDs. Accordingly, carotid-femoral pulse wave velocity (PWV), an accepted non-invasive measure of arterial stiffness, is recommended for cardiovascular (CV) risk prediction among hypertensive patients in European Guidelines.

Mood disorders, especially depression, are also a common public health problem in the Western world and their connections with CVDs are already recognized. While specific affective temperament types (depressive, cyclothymic, hyperthymic, irritable and anxious) are regarded as an inherited part of personality and represents the biologically stable core of emotional reactivity; these are the subclinical, trait-related manifestations and commonly the antecedents of minor and major mood disorders. On the other hand, they are associated with CVDs: dominant cyclothymic temperament was connected with hypertension and with acute coronary events in hypertensive patients.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophic factor family, playing a central role in the regulation of neuronal growth, maintenance, and survival, but it has proangiogenic features as well. Its involvement in psychiatric conditions is well described: in major depressive disorder the decreased serum BDNF (seBDNF) level was elevated following a course of antidepressant treatment. The importance of BDNF was suggested also in high risk CV conditions, such as obesity, metabolic syndrome and coronary atherosclerosis. It is hypothesized to play a protective role in CV pathophysiology as its higher serum level was found to be associated with decreased risk of CVD. In different animal models, BDNF was shown to be vasorelaxant not only on pulmonary arteries but also on rat aortic rings. Based on these data, a possible association between the seBDNF level and different arterial stiffness parameters can also be supposed in humans.

2. OBJECTIVES

1. In the first study, our aim was to measure arterial stiffness and serum BDNF levels in hypertensive patients with and without dominant affective temperaments. We hypothesised that hypertensive patients with dominant affective temperaments score higher depression and anxiety values and have impaired arterial stiffness, central blood pressure or serum BDNF compared with hypertensive patients without dominant affective temperaments, forming a high-risk subgroup patient population.

2. In the second study, our aim was to explore the associations of affective temperaments with blood pressure and arterial stiffness in hypertensive patients. We hypothesized that individual affective temperament scores may be related to brachial blood pressure as well as arterial stiffness in chronic hypertensive patients. We speculated a positive association in instances of depressive, cyclothymic, irritable or anxious temperaments and an inverse association in instances of hyperthymic temperament. We also hypothesized the presence of sex differences in relation to these studied associations.

3. In our third study, our aim was to measure BDNF serum levels in hypertensive patients and in healthy controls to discover the associations of BDNF with affective temperaments, depression, anxiety and arterial stiffness. We hypothesized that as hypertension is a risk factor for cardiovascular diseases and BDNF is protective in cardiovascular pathology, seBDNF can be altered in hypertension. We also presumed that seBDNF is associated with different affective temperaments, depression, anxiety, and arterial stiffness parameters providing a new bridge of psychosomatic processes.

3. PATIENTS AND METHODS

3.1. Study 1.

Caucasian patients were selected from two primary care practices in Budapest, Hungary. Out of the 183 patients 175 completed the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A), Beck Depression Inventory (BDI) and Hamilton Anxiety Scale (HAM-A) questionnaires in order to evaluate the presence of affective temperaments, depression and anxiety, respectively. Exclusion criteria were the presence of atrial fibrillation or uncontrolled hypertension (>145/95 mmHg in repeated office measurements), the history or ongoing treatment of depression or anxiety (as with arterial stiffening the associations are clarified) or bipolar disorder, schizophrenia, dementia posing an obstacle to completing questionnaires or denial of consent. Following the initial screening, 29 hypertensive patients with dominant affective temperaments (DOM) were identified and 24 of them continued to participate in our study. 24 hypertensive controls without DOM, matched in age, gender and presence of diabetes, were selected from the initial hypertensive patient cohort and included in the arterial stiffness and seBDNF measurements. During the initial visit patients completed the questionnaires. Physical examination (blood pressure, heart rate, height, weight and waist circumference) were completed and data on medical history (with special attention to CV risk factors, complications and depression) as well as on current medication was collected.

3.1.1. Questionnaires

3.1.1.1. Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire

The TEMPS-A was used to assess affective temperaments on depressive, cyclothymic, hyperthymic, irritable and anxious subscales, requiring ‘yes’ (score 1) or ‘no’ (score 0) answers. This autoquestionnaire is used to assess the point scores of each subscale and also to measure the presence of the dominant form of affective temperaments: subjects reaching the mean+2 SD level or higher in each subscale are considered to have dominant affective temperaments.

3.1.1.2. The Beck Depression Inventory

The BDI is a 21-question multiple-choice self-report questionnaire, one of the widely used instruments for measuring the severity of depression. The cut-off values might differ in various populations, but there are generally accepted thresholds. Participants are asked to make ratings on a four-point scale, where a higher score correlates with more severe depression.

3.1.1.3. Hamilton Anxiety Scale

HAM-A was evaluated by the examiner. The scale consists of 14 items, each defined by a series of symptoms. Higher scores correlate with more severe anxiety.

3.1.2. Clinical measurements

3.1.2.1. Arterial stiffness recordings

Arterial stiffness parameters were evaluated with the gold-standard tonometric method (PulsePen, DiaTecne, Milan, Italy). In each subject two sequences of arterial stiffness measurements were performed and their mean was used for statistical analysis. The main arterial stiffness parameters, PWV and augmentation index (AIx) were investigated. Higher PWV indicates increased arterial stiffness and the recent cut-off value of PWV>10 m/s is considered a conservative estimate of significant alterations of aortic function in middle-aged hypertensive patients. Negative AIx values indicate elastic large arteries and positive AIx with growing values indicate increased wave reflection.

3.1.2.2. Measurement of serum BDNF concentrations

Peripheral blood samples of patients were collected in anticoagulant-free tubes, right after the measurement of arterial stiffness. After centrifugation at 3600 revolutions per minute for 6 minutes, the serum was stored at -20 °C. SeBDNF was measured using commercially available sandwich enzyme-linked immunosorbent assay (R&D Systems, Minneapolis MN, USA) according to the manufacturer's protocol, and seBDNF level was determined in pg/ml.

3.1.3. Statistical analysis

Differences in variables between controls and DOM patients were analyzed using unpaired Student's t-tests or Mann-Whitney rank-sum tests for data failing tests of

normality. Blood pressure medications were calculated and compared using equivalent doses, differences were analysed with unpaired Student's t-tests or Mann-Whitney rank-sum tests. Data were expressed as mean±SEM and medians, significance was accepted at $p<0.05$. Statistical analysis was performed using the SigmaStat for Windows Version 3.5 (SPSS) program package.

3.2. Study 2.

The difference in patients selection compared to the first study was here that not only well-controlled but also grade 1 chronic (on medication for more than 3 months) hypertensive patients were investigated from three primary care practices in Budapest. A total of 173 subjects were included. Moderate use of the anxiolytic alprazolam (less than 0.5 mg/day) was neither a restrictive criterion. The methods regarding to the questionnaires and arterial stiffness measurement were the same like in the first study, but seBDNF was not investigated.

3.2.1. Statistical analysis

Normality of continuous parameters was tested with the Kolmogorov-Smirnov test. Pearson correlation coefficients were calculated to study the relationship between affective temperament scores and demographic, hemodynamic or arterial stiffness parameters. Multiple linear regression analysis was used to study the determinants of these hemodynamic or arterial stiffness parameters which were associated in univariate analysis with affective temperaments. Based on literature data, sex differences in the association between affective temperaments and the studied hemodynamic or arterial stiffness parameters were expected, and therefore sex and its interaction with the given affective parameter was included into all regression models and where an interaction was found, such interaction was further studied. Descriptive data were expressed as mean±SD or median with interquartile ranges or percentages. A two-sided $p<0.05$ was considered to be significant. SPSS 13.0 for Windows was used for all calculations.

3.3. Study 3.

The difference in patients selection compared to the first study was that besides chronic (>12 months medication) well-controlled and grade 1 hypertensive patients (HT), age-matched healthy controls (CONT) were also involved from three primary care practices

in Budapest. 151 HT and 32 CONT subjects were investigated. Moderate use of the anxiolytic alprazolam (less than 0.5 mg/day) was neither a restrictive criterion. In the case of CONT the denial of consent was the only exclusion criterion. Data of the subjects were analysed for the relationship between the seBDNF level, routine laboratory parameters, affective temperaments, anxiety, depression, and arterial stiffness parameters. The methods were the same like in the first study.

3.3.1. Statistical analysis

Normality of the parameters was tested with the Kolmogorov-Smirnov test. Descriptive characteristics, laboratory, arterial stiffness parameters and TEMPS-A, BDI, HAM-A scores were compared between CONT and HT groups using unpaired Student's t-tests or Mann-Whitney rank sum test for data failing tests of normality. The equality of variances was studied with Levene's test. Pearson correlation coefficients were calculated to study the relationship between seBDNF and all other factors measured. Hierarchic linear regression analysis was used to study the determinants of seBDNF in the whole population with a stepwise entry of variables with either previously described association with seBDNF or with a significant univariate correlation with seBDNF in the present data set. As a bidirectional association can be hypothesized between affective temperaments and hypertension, predetermined interaction analysis was performed to investigate moderation between hypertension and affective temperament scores on seBDNF level. Data were expressed as mean±SD or mean with interquartile ranges, and $p<0.05$ was considered to be significant. SPSS 13.0 for Windows was used in calculations.

4. RESULTS

4.1. Study 1.

In this cross-sectional case-control study well-treated chronic (>12 months medication) hypertensive patients were investigated. The arterial stiffness and seBDNF of altogether 48 hypertensive patients was evaluated: 24 DOM and 24 control subjects matched in age, gender and presence of diabetes. Among the DOM patients, six subjects were found to have a depressive, five an irritable and four an anxious dominant temperament. In the other patients, combinations of dominant temperaments were present: three patients had cyclothymic and depressive, two had cyclothymic and irritable, two had cyclothymic, depressive and anxious, one had cyclothymic, irritable and anxious temperaments and one patient was dominant for cyclothymic, irritable, anxious and depressive affective temperaments. No patient with a dominant hyperthymic temperament was found in our cohort.

4.1.1. Demographic, anthropometric, laboratory parameters and antihypertensive medication

No differences were found among the groups studied in baseline demographic, anthropometric or routine laboratory parameters. Comparing the control and DOM patients seBDNF level was significantly decreased in DOM patients [27290 (24200-30350) vs. 20100 (14740-27110) pg/ml, respectively, $p<0.05$]. The median number of the used antihypertensive compounds was 2 (IQR: 2–3). Beta-blockers were prescribed more frequently and in higher dose in the DOM group [0.63 (0-5) vs. 5 (0.63-6.88) mg, calculated for bisoprolol, respectively, $p<0.05$], but in the other antihypertensive medicaments there were no differences.

4.1.2. TEMPS-A, depression and anxiety scores

Compared with controls, in DOM patients depressive, cyclothymic, irritable and anxious scores were higher [6 (4.25-8.75) vs. 12.5 (7-13.75); 3 (1-5) vs. 9.5 (7-13.75); 2 (1-4.75) vs. 9.5 (5-11) and 5.08±0.81 vs. 14.67±0.88, respectively, $p<0.05$], while hyperthymic scores were equal [12.13±0.73 vs.10.46±0.99]. Both BDI and HAM-A scores were markedly higher in DOM patients [5 (2-7.75) vs. 14.5 (8.5-19.75) and 7±1.27 vs. 16.67±1.68, respectively, $p<0.05$].

4.1.3. Hemodynamic parameters

Compared with controls in DOM patients brachial systolic blood pressure [130.8 (122-137.1) vs. 122.6 (116.4-129.7] mmHg, respectively, $p<0.05$], brachial and central diastolic blood pressure [71.2±1.5 vs. 66.6±1.71 and 71.2±1.5 vs 66.5±1.71, respectively, $p<0.05$] and brachial and central mean blood pressures [91.9±1.53 vs. 86.6±1.94, 94.1±1.55 vs. 88.9±1.96 mmHg, respectively, $p<0.05$] were lower. Compared with controls PWV and AIx did not differ [9.32 (8.02-11.25) vs. 8.74 (8.32-9.87) m/s and 16.04±2.24 vs. 14.54±2.66 %, respectively].

4.2.Study 2.

4.2.1. Independent predictors of brachial systolic blood pressure and augmentation index

Cyclothymic temperament score – after adjustment for age, sex, diastolic brachial blood pressure, triglyceride and cholesterol level, BDI and HAM-A scores and the use of alprazolam – was an independent covariate of brachial systolic blood pressure (B=0.529, SE=0.258, p=0.042). Hyperthymic temperament score – after adjustment for age, sex, smoking, heart rate, uric acid, BDI and HAM-A scores and the use of alprazolam – was an independent covariate of AIx (B=-0.612, SE=0.243, p=0.013). In the final model adjusted for all potential confounders a one-unit increase in cyclothymic score was associated with 0.529 mmHg (95% CI: 0.019-1.040) higher brachial systolic blood pressure while a one-unit increase in hyperthymic score was associated with -0.612 % (95% CI: -1.092-0.132) lower AIx.

4.2.2. Further predictors of hemodynamic or arterial stiffness parameters

Although, in univariate models, affective temperament scores were associated with hemodynamic or arterial stiffness parameters in many cases, however, upon further correction for age and sex, certain temperaments failed to be independent covariables of these parameters, notably irritable temperament score of brachial systolic blood pressure (p=0.056) and depressive temperament score of AIx (p=0.595).

The correlation between PWV and irritable temperament score still remained significant (p=0.012) after adjustment for age, sex, brachial systolic blood pressure, GFR-EPI, blood glucose and duration of hypertension, although became nonsignificant after

further adjustment for BDI and HAM-A scores and the use of alprazolam (p=0.078). The same results were also found for anxious temperament score and PWV: the significant association (p=0.043) that was present after adjustment for age, sex, brachial systolic blood pressure, GFR-EPI, blood glucose and duration of hypertension disappeared after further adjustment for BDI and HAM-A scores and the use of alprazolam (p=0.475).

When studying the interaction between cyclothymic temperament score and sex in predicting brachial systolic blood pressure, a significant association was found (p=0.025). There was a positive association between cyclothymic temperament score and brachial systolic blood pressure in men (B=1.012, SE=0.392, p=0.011) which was absent in women (B=0.294, SE=0.311, p=0.346). After adjustment for age, brachial diastolic blood pressure, cholesterol and triglycerides, this interaction became nonsignificant (p=0.090; in men B=0.680, SE=0.347, p=0.052 and in women B=0.279, SE=0.272, p=0.307).

There was also a significant interaction between irritable temperament score and sex in predicting PWV (p=0.021). There was a positive association between irritable temperament score and PWV in men (B=0.154, SE=0.060, p=0.012) which was absent in women (B=0.076, SE=0.064, p=0.235). After adjustment for age, blood glucose, brachial systolic blood pressure and GFR-EPI, the interaction p-value was attenuated (p=0.037), however the strength of the association remained similar (in men B=0.104, SE=0.050, p=0.039 and in women B=0.082, SE=0.052, p=0.116). The interaction became nonsignificant (p=0.168) after further adjustment for BDI and HAMA-A scores and the regular use of alprazolam (in men B=0.091, SE=0.051, p=0.078 and in women B=0.054, SE=0.061, p=0.375).

Similarly to irritable temperament, there was also a significant interaction between the anxious temperament score and sex in predicting PWV (p=0.023). There was a positive association between anxious temperament score and PWV in men (B=0.106, SE=0.043, p=0.015) which was absent in women (B=0.047, SE=0.036, p=0.189). After adjustment for age, blood glucose, brachial systolic blood pressure and GFR-EPI, the interaction p-value was attenuated (p=0.046), however the strength of the association remained similar in men (in men B=0.088, SE=0.036, p=0.017 and in women B=0.021, SE=0.030, p=0.484). The interaction became nonsignificant (p=0.135) after further

adjustment for BDI and HAMA-A scores and the regular use of alprazolam (in men B=0.070, SE=0.039, p=0.075 and in women B=-0.017, SE=0.037, p=0.656). An interaction with borderline significance (p=0.052) was found between sex and hyperthymic affective temperament in predicting AIx. An inverse association was found in women (B=-0.754, SE=0.326, p=0.022) which was absent in men (B=-0.305, SE=0.370, p=0.411). This interaction became weaker (p=0.064) after further adjustment for age, smoking, heart rate and uric acid (in women B=-0.678, SE=0.312, p=0.032 and in men B=-0.327, SE=0.352, p=0.325).

4.3. Study 3.

4.3.1. Baseline demographic, anthropometric and laboratory parameters, current medication

Differences between CONT and HT were found in body weight (72.4±12.1 vs. 79.7±14 kg, p<0.05) BMI (24.5±5.4 vs. 28.6±4.5 kg/m^2, p<0.05), serum glucose [5.36 (4.88-5.81) vs. 6.15 (5.11-6.7) mmol/l, p<0.05], cholesterol [5.57 (4.97-6.05) vs. 5.18 (4.37-5.98) mmol/l, p<0.05], LDL (3.46±0.91 vs. 3.07±1.04 mmol/l, p<0.05) and HDL [1.68 (1.31-1.98) vs. 1.40 (1.15-1.61) mmol/l, p<0.05]. In the demographic, other anthropometric and routine laboratory parameters there were no differences. The median number of the used antihypertensive compounds was 2 (IQR: 2–3).

4.3.2. TEMPS-A, depression and anxiety scores

Compared with the CONT group, BDI and HAM-A scores were significantly higher in the HT population [2.8 (1-4) vs. 6.3 (3-9) and 3.9 (1-6) vs. 7.4 (2-10), respectively, p<0.05]. Compared with CONT there were no differences in the affective temperaments scores [depressive: 5.9 (4-7) vs. 7.1 (5-9), cyclothymic: 2.9 (0-4) vs. 3.9 (1-6), hyperthymic: 11.2±4 vs. 11 (4.2), irritable: 3.2 (2-4) vs. 4.3 (2-6), anxious: 4.1 (1-6) vs. 6.3 (2-9)].

4.3.3. Hemodynamic parameters

In the HT group compared with CONT increased brachial and central systolic blood pressure [125.5±9.3 vs. 133.0±12.3 and 117 (111.2-122.3) vs. 124.1 (113.4-131.6) mmHg, respectively, p<0.05] and brachial pulse pressure [51.5 (46.4-56.7) vs. 56.7

(46.4-63) mmHg, $p<0.05$] were found. Other hemodynamic and arterial stiffness parameters – compared with controls – showed no significant differences between the two groups [PWV: 8.6 (7.4-9.2) vs. 9.3 (7.8-10) m/s; AIx: 13.2 (5.75-23) vs. 17.8 (8.5-25.1) %].

4.3.4. SeBDNF

Compared with CONT seBDNF was elevated in the HT population [21202.6±6045.5 vs. 24880±8279 pg/ml, $p<0.05$]. In the analysis of simple correlations, the following parameters were found to be associated significantly with seBDNF: hypertension ($r=0.174$, $p=0.018$), serum cholesterol ($r=0.194$, $p=0.009$), LDL ($r=0.208$, $p=0.015$) and HDL level ($r=0.204$, $p=0.006$), platelet count ($r=0.188$, $p=0.011$), pulse pressure amplification ($r=0.157$, $p=0.037$) and hyperthymic temperament score ($r=0.189$, $p=0.010$). Tendencies of inverse correlations were found with the presence of diabetes or the use of alprazolam, but these were not significant ($r=-0.114$, $p=0.12$ and $r=-0.103$, $p=0.16$, respectively).

In the final hierarchical linear regression model – adjusted for all potential confounders like age, sex, the presence of diabetes, cholesterol, HDL level, platelet number, BDI and HAMA-A scores, the use of alprazolam and pulse pressure amplification – one unit increase in the hyperthymic score was associated with a 405.8 pg/ml higher seBDNF and the presence of hypertension was associated with a 6121.2 pg/ml higher seBDNF. We found an interaction ($p=0.002$) between hypertension and hyperthymic temperament score on seBDNF in the whole study population: there was no significant association between hyperthymic score and seBDNF in CONT ($p=0.545$) and a unit increase in hyperthymic score was associated with a 533.3 (95 %CI 241.3–825.3) pg/ml higher seBDNF level in HT ($p<0.001$).

5. CONCLUSIONS

Although similar arterial stiffness parameters were found in hypertensive patients with depressive, cyclothymic, anxious and irritable dominant affective temperaments, their increased depression and anxiety scores, the decreased brachial and central diastolic blood pressures as well as the decreased seBDNF might refer to their higher vulnerability regarding the development not only of major mood disorders, but also of CV complications.

On the other hand, since the ratio of those subjects who score high on different temperament directions while having a dominant affective temperament is relatively low, the evaluation of the continuous association between affective temperament scores and blood pressure or arterial stiffness parameters are meaningful. We have found elevated blood pressure among subjects (analysing also sex differences) with high cyclothymic temperament as well as an increased level of arterial stiffening in subjects with low hyperthymic scores, suggesting that affective temperaments scores are associated with hypertension and arterial stiffening and may thus represent markers of CV risk.

Since the pathophysiological background of our findings is complex we tried to clarify the possible role of BDNF, as a potential psychosomatic mediator between affective temperaments and CV risk. We have found significantly higher seBDNF levels in hypertensive patients compared with controls. Hyperthymic temperament score and the presence of hypertension were independent determinants of seBDNF.

Our results suggest, that with further supporting data the evaluation of affective temperaments can be beneficial both for psychopathological and CV preventive interventions. In these processes the mediator role of neurotrophins, especially BDNF is highly suggested.

6. PUBLICATION SUMMARY

6.1. Publications related to the thesis

László A, Babos L, Kiss-Igari Z, Pálfy A, Torzsa P, Eőry A, Kalabay L, Gonda X, Rihmer Z, Cseprekál O, Tislér A, Lénárt L, Hodrea J, Fekete A, Nemcsik J. Identification of hypertensive patients with dominant affective temperaments might improve the psychopathological and cardiovascular risk stratification: a pilot, case-control study. Ann Gen Psychiatry, 2015;14:33. *IF: 1.411*

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