LETTER TO THE EDITOR

Plasma brain natriuretic peptide levels in children with idiopathic epilepsy treated with long-term sodium valproate and oxcarbazepine monotherapy

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Received March 8, 2021 – Accepted June 29, 2021

To the Editor,

Brain natriuretic peptide (BNP) was first discovered in hypothalamus but it is mainly secreted by the heart in response to increased ventricular wall stress associated with heart failure and it is recognized as an important and reliable biomarker for cardiac dysfunction (1, 2). BNP has been studied extensively in adults and has been shown to increase significantly in relation to cardiovascular, renal and pulmonary disorders (3). Children and infants with structural cardiac defects, dilated cardiomyopathy, pulmonary hypertension and sepsis, have all been found to have increased levels of BNP (2, 4).

Recent studies postulate that epileptic activity may trigger BNP secretion in the short term, either directly by the cerebral tissue or indirectly by the heart, as a result of the cardiovascular overactivity that accompanies epileptic seizures (5-8). Nevertheless, several aspects of BNP concentrations in epileptic patients remain unanswered such as their long-term changes after the seizures or the possible effects of antiepileptic drug treatment. Antiepileptic drugs may have an impact on autonomic cardiac function and/or cardiovascular risk factors and, therefore, a possible effect on BNP secretion (9).

This prospective study aimed to evaluate BNP plasma concentrations in children with idiopathic epilepsy, during long-term treatment with sodium valproate (VPA) or oxcarbazepine (OXC) monotherapy.

MATERIALS AND METHODS

The study was carried out in a tertiary pediatric referral center in Athens, Greece. Subjects were derived from patients treated for idiopathic epilepsy. Written informed consent was obtained from all parents before participation and the study was approved by the local ethics committee.

Inclusion criteria were age between 4 and 15 years with a diagnosis of idiopathic epilepsy (focal or generalized). Exclusion criteria were previous use of any antiepileptic medication, chronic illness, history of cardiac disease, chronic use of other medication during the study period, developmental deficits and abnormal MRI findings. All patients underwent a brain MRI apart from those with a certain diagnosis of epileptic syndromes (childhood absence, juvenile myoclonic and epilepsy with centrotemporal spikes). All patients who required at some point add-on therapy with a second antiepileptic drug (AED) were also excluded from the study.

After applying the exclusion criteria, the final study population comprised 59 children (29 boys),

Key words: anti-epileptic drugs; brain natriuretic peptide; children; convulsions.

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0393-974X (2021)

aged 4 to 15 years (mean age 8.9±2.9 years, median age 8.8 years). Patients were treated with VPA (n=32) or OXC (n=27) monotherapy based on clinical and electroencephalographic criteria. The maintenance dose was gradually titrated to the usual therapeutic doses (25-40 mg/kg/day for VPA and 25-35 mg/kg/day for OXC). Patients were followed for a period of 20 months. One hundred and forty three healthy children (70 boys, 4 to 15 years, mean age 10.9±2.8 years, median age 10.8 years) were used as controls.

In all children, Body Weight (BW), Height (H) and Blood Pressure (BP) were measured and Body Mass Index (BMI) was calculated using the standard Quetelet formula [BMI = BW (Kg) /H^2 (m^2)]. For the classification in normal weight, overweight and obese, international growth charts were used and Standard Deviation Scores (SDS-BMI, z-scores) were derived for the study population.

Complete blood count and basic chemistry panel were investigated in fasting morning blood venous samples. For the assessment of BNP levels, venous blood samples were collected in EDTA tubes and were placed in ice and immediately centrifuged at 4000 rpm for 10 min at 4°C. The extracted plasma was stored at -60° C until measurement. Brain natriuretic peptide fragment was investigated by enzyme immunoassay (EIA) using a commercially available kit ("Biomedica Gruppe", Austria). The Intra Assay and Inter Assay Variations were 4% CV and 3.8% CV, respectively and the Detection Limit 5 fmol/ml.

In the epileptic group the investigations were performed

Table I. *Study population characteristics*

mean±SD, median (range)	overall	patients (n=59)	controls (n=143)	
age	10.29±2.96, 10.25 (4.16, 16.83)	8.83±2.98, 8.8 (3.7, 15.25)	10.89±2.75, 10.83 (5.83, 16.83)	P<0.001*
Gender (boys/girls)	99/103	29/30	70/73	
SDS BMI (z-scores)	0.56±1.06, 0.48 (-1.69, 3.21)	0.80±1.25, 0.94 (-1.54, 3.21)	0.47±0.97, 0.34 (-1.69, 2.62)	P=0.031*

**ANOVA between patients and controls. BMI: Body Mass Index*

Table II. *Plasma brain natriuretic peptide (BNP) levels (mean±SD) in children receiving OXC or VPA (group A) and in healthy controls (group B)*

	BNP1 (8 months) fmol/ml	BNP2 (20 months) fmol/ml	BNP1 *vs* BNP2
Group A (n=59)	545.62±191.91	645.01±227.64	p=0.0019*
Group B (n=143)	694.58±273.82		
Group A *vs* Group B	p=0.001*	p=0.12*	

**ANCOVA adjusted for gender, age and BMI effect. BNP: Brain Natriuretic Peptide; OXC: Oxcarbazepine; VPA: Valproate*

at 8 and 20 months (time 8 and time 20, respectively) of VPA (n=32) and OXC (n=27) monotherapy. In the control group, the investigations were performed once. At the time of testing, all subjects were free of acute illness and at least 2 months seizure-free.

Statistical analysis

Data analysis was performed using STATA for Windows v 11.2, (Stata Corp, Texas, USA, 2009). Age, SDS-BMI and BNP values exhibited normal distribution, so parametric analysis was performed. SDS-BMI and age values were compared with analysis of variance (ANOVA), while BNP values between groups were compared with analysis of covariance (ANCOVA), adjusted for the effect of gender, age and SDS-BMI with Bonferroni correction for multiple comparisons. A value of $P<0.05$ was considered statistically significant.

RESULTS

During the 20-month period all patients had an absolu te response to the treatment, remaining seizure-free after 6 months of therapy.

Study population characteristics and SDS-BMI distribution are described in Table I. Patients differed when compared with controls, regarding age and SDS-BMI. No correlation was found between BNP levels and gender (p=0.44), age (p=0.45), SDS-BMI (p=0.56) or pubertal status (p=0.6) of the subjects. Since previous studies reported differences in BNP values after gender, age and BMI stratification, we performed analysis of BNP levels with gender, age and BMI as covariates.

When compared with controls, epileptic children had significantly lower BNP levels at time 8 (p=0.001), but similar levels to controls at time 20 (p=0.12). Compared to levels at 8 months, BNP levels were significantly increased at 20 months of therapy (p=0.0019) (Table II). There were no significant differences in BNP levels between the VPA and OXC group at any time during the study (8 and 20 months, respective p values 0.21 and 0.32) (Table III). BNP levels had no significant correlation with BMI in healthy children and children with epilepsy at 8 and 20 months of treatment. Twenty month post-therapy BNP levels were lower in children with generalized epilepsy compared to those with focal seizures (p=0.01) (Table IV).

DISCUSSION

In the present study, plasma BNP levels were lower than controls at the 8th month of OXC or VPA monotherapy after adjustment for gender, age and BMI. However, the long-term use of the above antiepileptic drugs was associated with an increase of BNP levels at 20th months of treatment, similar to control group levels. There were no significant differences in BNP levels between the VPA and OXC group at 8 or 20 months of treatment. Moreover,

Table III. *Plasma brain natriuretic peptide (BNP) levels (mean±SD) in children receiving OXC, VPA*

	BNP1 (8 months) fmol/ml	BNP2 (20 months) fmol/ml	BNP1 *vs* BNP2
OXC (n=27)	566.8±168.8	628.4±202.6	p=0.06*
VPA (n=32)	527.17±211.0	657.58±247.6	p=0.0024*
OXC *vs* VPA	p=0.21*	p=0.32*	

**ANCOVA adjusted for gender, age and BMI effect. BNP: Brain Natriuretic Peptide; OXC: Oxcarbazepine; VPA: Valproate*

Table IV. *Plasma brain natriuretic peptide (BNP) levels (mean±SD) in children regarding seizure type, generalized or focal*

	BNP1 (8 months) fmol/ml	BNP2 (20 months) fmol/ml	BNP1 *vs* BNP2
Generalized epilepsy (n=29)	500.7±119.0	558.2±164.9	p=0.036*
Focal epilepsy (n=30)	558.4±176.5	672.4±173.2	p=0.009*
Generalized *vs* Focal epilepsy	p=0.07*	p=0.01*	

**ANCOVA adjusted for gender, age and BMI effect. BNP: Brain Natriuretic Peptide*

children suffering from generalized seizures had significantly lower BNP levels at 20 months post-therapy, compared to those with focal seizures.

BNP secretion after convulsive seizures has been related to transient myocardial ischemia and/or brain dysfunction that returns to normal after 24-48 hours to 7 days (5-8, 10). The lower BNP levels 8 months after the initiation of VPA or OXC monotherapy, the elevation of BNP in the epileptic group at 20 months of treatment at levels similar to the ones of controls, and the differences in BNP levels between children with generalized compared to focal seizures, indicate a possible role of antiepileptic drugs and/or epilepsy itself. Antiepileptic drugs may have an impact on autonomic cardiac function and/or cardiovascular risk factors and, therefore, a possible effect on BNP secretion (9). Considering the controversies that exist in respect to the paradox of low BNP levels in individuals with metabolic cardiovascular risk factors (11), the transient decrease in BNP levels at 8 months of VPA or OXC monotherapy might be associated with the cardiometabolic effect of antiepileptic drug treatment. On the other hand, optimized seizure control may be related to lower BNP levels, since epileptic activity in the brain can activate BNP secretion in both the heart and the brain (5-8).

Limitations of our study are the small number of patients enrolled, the absence of BNP measurement in the first hours after the seizure attack and the absence of a group with uncontrolled seizures. The advantages are the prospective design and the homogeneity of the study groups.

In conclusion, long term use of VPA or OXC monotherapy in children with idiopathic epilepsy was associated with an increase of BNP at levels similar to the ones of controls. Further long-term prospective studies are required in order to clarify the clinical significance of the above observation and whether this is the direct result of the antiepileptic medication or the result of epilepsy itself and/or the optimized seizure control.

ACKNOWLEDGEMENTS

This study was funded by the "Kapodistrias Research Program" of the National and Kapodistrian University of Athens special account for research grants. There was no involvement in the design of the project.

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