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Alterations in lipid profile and enzymes paraoxonase and butyrylcholinesterase in CBS-deficient patients.

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Introduction:

Homocystinuria is an inborn error of metabolism most frequently caused by cystathionine β-synthase (CBS) deficiency. Homocysteine (Hcy), methionine (Met) and other metabolites of Hcy accumulate in the body of affected patients, leading to clinical manifestations such as dislocation of the optic lents, osteoporosis, mental retardation, and thromboembolism. Despite the fact that thromboembolism represent the major cause of morbidity and the most frequent cause of death in CBS-deficient patients, the cause of cardiovascular changes found in homocystinuria remain unclear. In this work, we evaluated the lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol, oxidized LDL cholesterol, apolipoprotein A-1) and the activities of the enzymes paraoxonase (PON1) and butyrylcholinesterase (BuChE) in plasma of CBS-deficient patients, at diagnosis and during the treatment.

Materials and Methods:

CBS-deficient patients were recruited from the Medical Genetic Service of Hospital de Clínicas de Porto Alegre, Brazil. Patients were divided in two groups: group A consisted of 9 patients with CBS deficiency at diagnosis (median age:10 years; range: 4 – 27 years) and group B consisted of 9 patients with CBS deficiency under treatment (median age:19 years; range: 12 – 32 years). All patients were diagnosed after the neonatal period by identification of abnormal elevated concentrations of tHcy and Met in plasma. The treatment consisted of a protein-restricted diet supplemented by pyridoxine (median dose: 500mg/day; range: 100 – 750mg/day), folic acid (median dose: 5mg/day; range: 2 – 5mg/day), betaine (median dose: 6g/day; range: 2 – 6g/day) and vitamin B12 (median dose: 1mg IM /month). The average duration of treatment was 10 years (range: 5 – 20 years). Plasma samples were obtained from and 12 healthy individuals with comparable age and sex (median age:25 years; range: 4 – 34 years). The present study was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre, Brazil. Informed consent was obtained according to the guidelines of the committee.

Results:

It was verified a significant decrease in HDL cholesterol and apolipoprotein A1 levels in the both groups of CBS-deficient patients (at diagnosis and under treatment) when compared to controls. PON1 activity was also significantly lower in the both groups of CBS-deficient patients when compared to controls, which may be related with an Hcy-dependent oxidation of any group important to catalytic activity of the enzyme that favors the atherogenesis. BuChE activity was significantly increased only in CBS-deficient patients at diagnosis and it is known that this enzymatic activity is positively associated with cardiovascular risk factors.

Table 1. Lipid profile and Hcy levels in CBS-deficient patients at diagnosis (Group A), CBS-deficient patients under treatment (Group B) and controls.

	Controls	Group A	Group B
Total cholesterol (mg/dl)	185,62 ± 56,53	118,75 ± 38,48*	125,78 ± 28,36*
HDL cholesterol (mg/dl)	59,35 ± 19,43	38,98 ± 9,62**	33,27 ± 9,99**
LDL cholesterol (mg/dl)	106,65 ± 53,95	71,14 ± 30,45	78,76 ± 29,21
Oxidized LDL cholesterol (U/L)	19,15 ± 7,44	14,77 ± 4,76	13,12 ± 5,75
Apolipoprotein A (mg/dL)	200,98 ± 29,57	156,32 ± 33,81**	141,34 ± 20,79**
Hcy (µmol/L)	5,84 ± 2,52	266,5 ± 66,71***	137,8 ± 104,3*

Data represent mean ± standard deviation
*p < 0.01 statistically different from controls (ANOVA, followed by the Duncan multiple range test).
**p < 0.001 statistically different from controls (ANOVA, followed by the Duncan multiple range test).
***p < 0.0001 statistically different from controls (ANOVA, followed by the Duncan multiple range test).

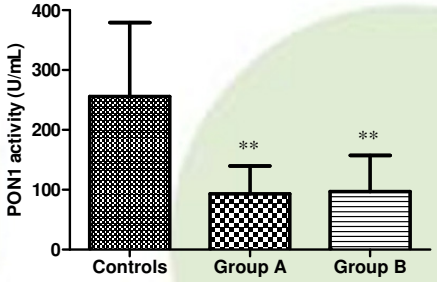

Fig. 1. PON1 activity in CBS-deficient patients at diagnosis (Group A, n=9), CBS-deficient patients under treatment (Group B, n=9) and controls (n=12). Data represent mean ± standard deviation, **p<0.001 statistically different from controls (ANOVA, followed by the Duncan multiple range test).

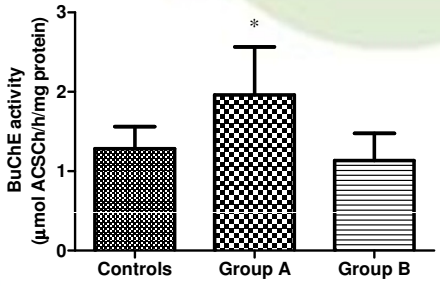

Fig. 2. BuChE activity in CBS-deficient patients at diagnosis (Group A, n=8), CBS-deficient patients under treatment (Group B, n=8) and controls (n=11). Data represent mean ± standard deviation, *p<0.01 statistically different from controls and from group B (ANOVA, followed by the Duncan multiple range test).

Conclusion:

Evaluated together, our results demonstrated that treated or not CBS-deficient patients presented important alterations in lipid metabolism. This work contributes to the understanding of the responsible mechanisms of vascular lesions in CBS-deficient patients.

Apoio: CNPq, FAPERGS, CAPES, FIPE/HCPA