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Short Communication

Homocysteine, an indicator of methylation pathway alternation in Down syndrome and its regulation by folic acid therapy

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Abstract

BACKGROUND: Down syndrome (DS) is a complex genetic disease. Some clinical features of patients with this syndrome could be related to functional folate deficiency. The purpose of this study was to evaluate the total homocysteine (T-Hcy) metabolism in DS children and to determine whether the supplementation with folic acid therapy would shift the genetically induced metabolic imbalance or not.

METHODS: Thirty-five infants with DS, with the mean age of 17.66 ± 12.24 months were included in this study. They were selected from those attending the Genetic Outpatients Clinic in Children hospital.

RESULTS: Our results revealed that Down syndrome children had a significant decrease in serum plasma T-Hcy level after the treatment with folic acid [11.79 ± 0.92 vs. 14.41 ± 4.93 μmol/L]. A significant negative correlation was found between T-Hcy and folic acid serum levels [r = -0.112; P<0.05].

CONCLUSIONS: We concluded that the regulation of methylation pathways in Down syndrome patients becomes important in the light of possible normalization of the metabolic imbalance and the detection of increased sensitivity to therapeutic interventions.

KEY WORDS: Down syndrome, hyperhomocysteine, folic acid, vitamin B-12.

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Down syndrome (DS) or trisomy 21 is a complex genetic disease. Some clinical features of patients with Down syndrome could be related to the functional folate deficiency. These features include enhanced methotrexate sensitivity [1], elevated mean corpuscular volume, and gastrointestinal malabsorption [2]. Impaired folate function may explain deoxynucleotide-pool imbalance and elevations in folate sensitive fragile sites and DNA strand breaks. Impaired S-adenosylmethionine dependent transmethylation reaction may have diverse effects including dysfunction of the central nervous system [3]. Fetuses and neonates are in a state of rapid cell turnover that require a high rate DNA synthesis. This high rate of DNA synthesis is associated with a great need for vitamin B-12 and folate. Early detection of deficiencies is important. However, the neurologic changes that take place after pronounced vitamin B_{12} deficiency in infant may be irreversible. Megaloblastic anemia and neurologic disorders such as hypotonia and delay in psychomotor development in infants occur at later stages of the deficiency and are evident only in severe cases of folate and vitamin B-12 deficiencies [4]. Metabolites, such as methylmalonic acid, total

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homocysteine [T-Hcy] and cystathionine, involved in enzymatic reactions depend on vitamin B-12. Folate and vitamin B-6 have been found to be sensitive in estimations of both functional and intracellular deficiencies of these vitamins [5]. Homocysteine especially is widely regarded as a reliable indicator for this purpose [6]. The dual purpose of the present study was to evaluate the total homocysteine metabolism in DS children and to determine whether the supplementation with folic acid therapy would shift the genetically induced metabolic imbalance.

Methods

Thirty-five infants with DS (17 male and 18 female], with the mean age of 17.66 ± 12.24 months were included in this study. They were selected from those attending the Genetic Outpatients Clinic, Children hospital at Cairo University. All patients were subjected to full clinical examinations. All patients received a daily dose of folic acid, equivalent to 5 mg for a month. Plasma T-Hcy, folic acid and vitamin B-12, were also estimated before and after the treatment. After the venous blood was taken, Plasma was separated by centrifugation and was stored at -30°C until analyzed. Plasma T-Hcy was estimated by competitive immunoassay method according to the manufacture's instructions [Axis-Cheild As, Axis-Homocysteine, Bickbeerngrund 4, D-29614 Solute, Germany]. Plasma folic acid and vitamin B-12 were estimated by the radioimmunoassay [RIA] method using kits which were obtained from Diagnostic Product Corporation (DPC).

Statistical analysis

SPSS version 7.0 was used for the statistical analysis. All numeric data were expressed as the mean ± SE. Data were analyzed using the student t-test to compare means before and after the treatment. Pearson's correlation coefficient was used to determine the relationships between different values. For all the tests a probability of <0.05 was considered significant.

Results

Our results revealed that children who suffered from DS had the mean value of plasma folate of 11.95 ± 1.55 ng/ml and vitamin B-12 of 358.36 ± 57.43 pg/ml which within the normal international values. There was a significant increase of mean plasma folic acid after the treatment with folic acid therapy (18.91 ± 3.59), while no significant changes in mean vitamin B-12 (323.17 ± 38.42) was observed. There was a significant decrease in plasma T-Hcy level after the treatment with the folic acid therapy (11.79 ± 0.92) (figure 1). In figure 2, a significant negative correlation was found between the plasma T-Hcy and the folic acid levels (r = -0.112; P<0.05) while there was a negative significant correlation between the plasma T-Hcy and the vitamin B-12 levels (r = -0.593; P<0.05).

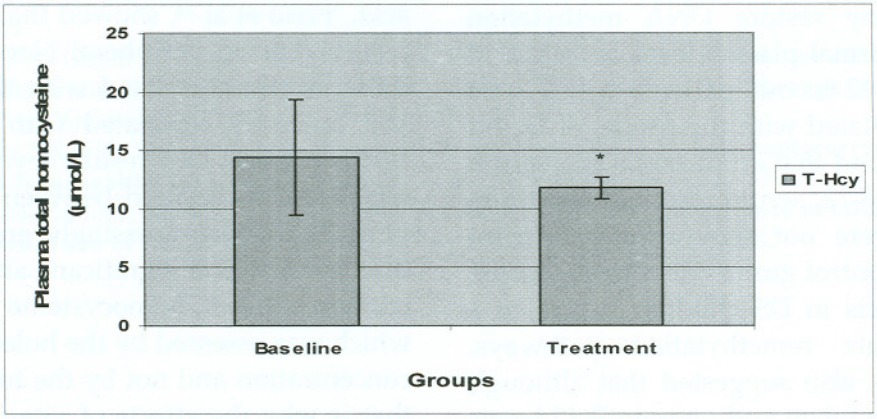

Figure 1. Plasma total homocysteine level in children with Down syndrome before and after folate therapy.

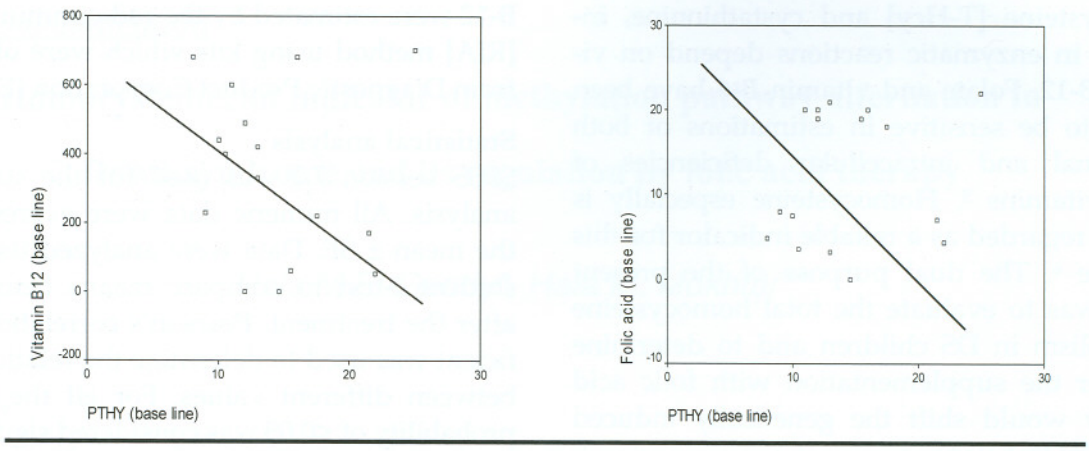

Figure 2. Spearman correlation between plasma total homocysteine, folate and vitamin B-12.

Discussions

Individuals suffering from DS exhibit significant disturbances in methylation pathways. The overexpression of cystathionine beta-Synthase (located on the 21 chromosome) causes homocysteine to convert into cysteine at an accelerated rate [7]. Many micronutrients and vitamins are critical for DNA synthesis, the repair and the maintenance of DNA methylation patterns. Folate has been most extensively investigated in this regard. Deficiency of folate induces disruption of DNA as well as alterations in DNA methylation status [8]. Folate and/or methyl group dietary supply provides the most compelling data for the interaction of nutrients and DNA methylation,. Not only dietary folate depletion decreases genomic DNA methylation in both human and animal models but it also may restore DNA methylation status [9]. The normal plasma level of folic acid and vitamin B-12 in our patients with Down syndrome correlated with the results of David et al [10], who found that erythrocyte and serum folate, vitamin B-12, serum iron and ferritin in DS children were not significantly different from those of control group. He also suggested that macrocytosis in DS children is due to a defect in folate remethylation pathways. Gericke et al [11], also suggested that although the mean serum folate and vitamin B-12 levels were normal in DS individuals, red cell folate values were very low in this group.

An increase in the mean value for plasma T-Hcy level in our patients may be due to the deficiency of intracellular folate levels. This observation correlates with Ueland et al [12], who reported that a mild hyperhomocysteinemia appears as an indicator of altered one carbon metabolism. Despite the results of many studies which show low serum level of T-Hcy in DS children, some studies report that low T-Hcy level is due to the increase of cystathionine β-synthase which leads to increase in homocysteine degradation through the transsulfuration pathway [2,7]. Decrease in T-Hcy level after folate therapy in our study is compared with Pullin et al [13] study, which reported that there was a decrease in homocysteine concentration after the supplementation of folic acid.. Friso et al [14], showed that genomic DNA methylation in peripheral blood mononuclear cells directly correlated with the folate status and inversely correlated with plasma homocysteine levels. Our results revealed a negative significant correlation between T-Hcy and vitamin B-12. Wickramasinghe and Fida [15], found that there was a significant and independent relation between homocysteine and B-12 status which was assessed by the holotranscobalamin concentration and not by the total serum B-12; that is why the effects of vitamin B-12 on homocysteine concentrations are frequently masked by the folate status. Quinlivan et al [16],

found that after folate therapy, the inverse association between plasma homocysteine and plasma vitamin B-12 was strengthened.

Conclusions

The methylation may be important for the function of myelin sheaths and for the synthesis of neurotransmitters. Therefore, the study of the regulation of methylation pathways in Down syndrome becomes important in the light of possible normalization of the metabolic imbalance and the detection of increased sensitivity to therapeutic interventions.

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